Review article

Extracorporeal Membrane Oxygenation Therapy - A review

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Abstract

Since the first successful case of Extracorporeal Membrane Oxygenation (ECMO) in early 1970's till date, there has been quite a change in clinical approach and technology. The recent H1N1 flu pandemic led to a wider use of ECMO therapy worldwide, proving its superiority in supporting respiratory failures with better outcomes. More over centres applied it as a rescue therapy for refractory hypoxaemia and refractory circulatory failures understanding its benefits and limitations. Understanding and execution of the ECMO therapy can be quite challenging and may have a greater learning curve. Initiating the ECMO program in the hospital with an organised and planned approach may shorten the learning curve and improve outcomes. Multiple factors are responsible for successful and smoother functioning of the ECMO program, which should be identified and worked upon. There are many indications where ECMO therapy can be applied and understanding its potential in the hospital is of utmost importance. Along with this, forming an ECMO team with trained members, forming policies and protocols, and taking the right decisions at the right time are important. An in-depth review of every aspect of its successful institution has been discussed in this article.

Keywords: Cardiac failure, extracorporeal membrane oxygenation, respiratory failure

Introduction

Extracorporeal membrane oxygenation (ECMO) is a modified form of cardiopulmonary bypass (CPB) used to treat patients with life-threatening cardiac and/or lung failure. ECMO must be considered when the patient's condition starts to deteriorate and fails to respond to conventional therapy. This condition is often named as refractory and can have reversible or irreversible organ injury. This refractory situation is usually associated with <20-30% survival chances. Instituting ECMO therapy at the right time with right management can have increased survival outcomes to >50 to 70%.Thus mortality risk can be halved if the patient is supported well with ECMO therapy.

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The journey of extracorporeal membrane oxygenation started in early 1970's. The first successful long term support was initiated by D. Donal Hill in a patient with severe respiratory failure after undergoing surgery for repair of aortic rupture due to polytrauma in an automobile accident.[1-2] After a few years, Dr Bartlett and colleagues, from University of California successfully treated a neonate with severe respiratory failure due to meconium aspiration using ECMO.[1-3] The initial positive outcomes of this newer therapy led to a randomised, controlled trial supported by National Institute of Health which compared the venoarterial ECMO support *versus* conventional ventilation for patients with severe ARDS.[4] After randomisation of 90 patients, the study was stopped due to mortality exceeding 90% in both the groups. At that time, the main concern about mechanical ventilation was the use of high inspired oxygen fraction, beyond physiological range rather than the unphysiological volumes and pressures. The only difference in the study and control arms was that the inspired

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fraction of oxygen (FiO_2) was kept lesser in study group. Furthermore, the CPB components available then were used for ECMO but for a longer period. Hence, there was a greater chance of system failures, increased bleeding due to systemic anticoagulation and increased systemic inflammation due to larger circuits and continuous contact of blood with unphysiological surface. The limitations and results of this trial led to the abandon of the use of ECMO on patients. At the same time, Kolobow developed a membrane oxygenator which consisted of silicon membrane sheets, rolled over and spaced with proper spacers, preventing the sticking of membranes to each other.[5-7] This was introduced initially to remove the excess carbon dioxide from blood for patients having chronic obstructive pulmonary disease. Later, due to its superior gas exchange capabilities and lower failure rates, the membrane oxygenator became a standard component of longer term ECMO procedures.

Since then ECMO has been applied on patients with various indications but the main feature of the clinical conditions are either hypoxemic respiratory failure, hypercarbic respiratory failure or circulatory failure, mainly due to cardiac dysfunction or failure. A recent study named CESAR trial (Conventional ventilatory support *versus* ECMO for severe adult respiratory failure) clearly showed an improvement in mortality rate and severe disability 6 months after randomisation. All the patients in the study arm were treated with extracorporeal membrane oxygenation in an expert referral centre. Around 63% of the patients (57/90) were considered to be treated with ECMO support survived to 6 months without disability when compared with 47% (41/87) of those considered for conventional management. Also an actual difference of 25% in survival at 28 days was observed in patients treated with ECMO.[8] The main reason for resurgence of interest in ECMO was its use as rescue therapy in patients with H1N1 influenza pandemic, mostly in Australia and New Zealand.[9] The increase in usage was also due to improvement in the ECMO systems, making the procedure simpler and safer for the patients, helping in improving outcomes.

Factors affecting outcome

Unlike other therapies applied in the intensive care unit, extracorporeal membrane oxygenation therapy needs a multidepartmental approach in the hospital.The outcomes are completely dependent on the organisation of ECMO program and success depends on a systematic approach. The important factors for successful outcomes after ECMO include formation of an ECMO team, selection of right patient indication at right time, standardising operating protocols and policies, selection of the correct ECMO system and ECMO disposables. These factors, if properly followed will shorten learning curves, ease implementation of the therapy and improve outcomes in patients receiving ECMO. A deeper insight into all these factors will be required to have an organised ECMO program in the hospital.

Formation of ECMO team

As described before, extracorporeal membrane oxygenation needs a multidisciplinary approach and requires different skilled professionals to treat patients and also work as a team. It is quite challenging sometimes to have all the team members with different expertise to come together and work as a team. Representative members of a mechanical circulatory support team are listed in *Table 1*.

***Table 1*:** ECMO team composition

- Decision makers: Cardiothoracic surgeon, cardiologist, intensivist, pulmonologist or cardiothoracic anaesthesiologist
- Program organisers: ECMO Director/ECMO co-ordinator
- Managers: Perfusionist/Nursing staff/Operating room staff/General ward staff/Cardiac anaesthesiologist
- Support staff: Financial, billing counsellor, dietician, consultants such as nephrologist, neurologist, infectious disease specialist, pathologist, microbiologist, haematologist, blood bank, psychiatrist, psychologist, cardiac rehabilitation, physical therapist.

The role of ECMO program director is to lead the ECMO program and coordinate with the ECMO

coordinator for forming policies and protocols. The role of an ECMO program coordinator can be taken by a qualified perfusionist, certified respiratory therapist, registered nurse or certified physician assistant. The ECMO coordinator is an important manager involved in complete functioning and execution of an ECMO program. His/her responsibilities include routine circuit check management, crew resource management, situation awareness to the team members, standardising operating procedures, policy management for intrahospital transport and interhospital transport, patient data management and review of statistics, troubleshooting management/ coordination, initiation, maintenance and weaning coordination.

The managers (perfusionist, nursing staff, intensivist, anaesthesiologist) provide *'round the clock'* support to the ECMO patient, with their respective roles. Other support function members will be required whenever the necessity arises for their role.[10]

Indications

The indications for ECMO are now wide spread and can be utilisedby various departments of the hospital. ECMO started initially as a therapy for cardiac failure rather than for respiratory failure. With growing number of indications, ECMO can be utilised by almost every major department of the hospital.

Indications based on the type of department involved to initiate ECMO therapy on patients are listed in *Table 2*.

Criteria for selection

There are no clearly defined selection criteria for institution of ECMO so far. In cardiac or respiratory failure, according to the guidelines of Extracorporeal Life Support Organization (ELSO), ECMO should be considered when there is a 50% risk for death and is definitely indicated when the death risk exceeds 80%. In practice, the indications are often determined by the institutional experience. A large experience with ECMO systems leads to a more liberal diagnosis and better results.

Table 2: Indications for ECMO support

Neonates/Infants/Children

- Respiratory distress syndrome
- Meconium aspiration
- Persistent foetal circulation
- Congenital diaphragmatic hernia
- Refractory cardiogenic shock
- Sepsis

Adults

- Respiratory distress syndrome
- Infections: Septicemia, Septic shock syndromes, influenza H_1N_1 pneumonia (Swine flu).
- Refractory cardiogenic shock (myocardial infarction, right ventricular failure)
- Failure to wean from cardiopulmonary bypass after cardiac surgery
- Bridge to cardiac transplantation or placement of a ventricular assist device
- Procedural support - Abdominal aortic graft replacement, Donor organ preservation
- Cardiomyopathy
- Cardiotoxicity
- Thoracic trauma involving lung contusion, cardiac trauma
- Post-resuscitation: Cardiac arrest, cardiogenic shock, drug overdose, hypothermia, pulmonary oedema, pulmonary embolism

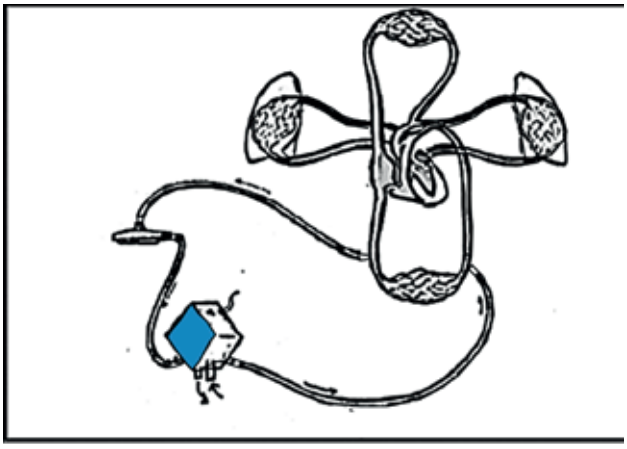

Figure 1: VA ECMO Support (Courtesy Maquet Cardiopulmonary AG)

Indications for venoarterial (VA) ECMO

Patients with severe cardiac and/or lung failures who deteriorate in spite of volume therapy, vasoconstrictors, inotropes and intra-aortic balloon pump therapy (IABP), and fail in providing adequate systemic perfusion are candidates for VA ECMO support *(Table 3)*. Usually the time frame to initiate ECMO support on these patients is minimal as it is often used in conditions of cardiac arrest, post-cardiotomy ventricular dysfunction or cardiopulmonary failure where ECMO support should be initiated at the quickest time possible.

Table 3: Selection criteria for V-A ECMO support [11]

Urgent
• Cardiac Index <2.0 L/min/m^2 (unresponsive to therapy including catecholamine support, Intra-aortic balloon pump counter pulsation)
Emergency
• Resuscitation without adequate cardiac pump function

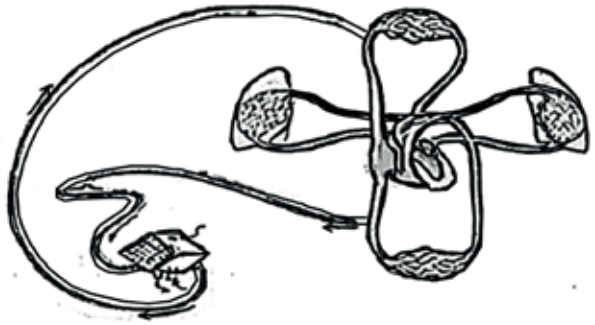

Figure 2: VV ECMO Support (Courtesy Maquet Cardiopulmonary AG)

Indications for VV ECMO

Potentially reversible acute severe lung failure that fails to respond to conventional ventilation with low tidal volumes and plateau pressures or rescue therapies such as prone ventilation, nitric oxide, high frequency oscillatory ventilation is an indication for ECMO therapy. ECMO should be considered before irreversible injury or multiple organ failure develops in the patient *(Table 4)*.

Table 4: Indications for VV ECMO[11]

Urgent
• PaO_2/FiO_2 < 100 mm Hg (FiO_2 = 1.0)
• Oxygenation Index - 20
• Lung Protective Ventilation is not possible.
• Murray Score - 2 to 3
Emergency
• PaO_2/FiO_2 < 60 mm Hg (FiO_2 = 1.0, PEEP = 20 cm H_2O)
• Uncontrollable Respiratory Acidosis: pH < 7.15
• Oxygenation Index - 40
• Murray Score - 3 to 4

Contraindications

It is already described that depending on the indication, ECMO can be utilised as a Bridge to Transplant, Bridge to Recovery, Bridge to Decision and Bridge to Bridge (any mechanical assist device). Contraindications to ECMO therapy vary accordingly with respect to the purpose of the therapy indicated *(Table 5)*. Exclusion criteria for ECMO are given below. In an emergency setting, it may not be possible to identify all the conditions that would normally exclude patients from ECMO. At the discretion of the consultant intensivist or cardiothoracic surgeon, ECMO may be commenced emergently and if contraindications become obvious at a later time, ECMO should be withdrawn.

Standardising operating protocols and policies

The purpose of forming standard policies and protocols is to standardise the procedures done during ECMO support to facilitate better patient outcomes by more organised and planned approach to any of the clinical or technical condition. Qualified ECMO team members are responsible for giving their inputs to form standard protocols to ECMO coordinator and ECMO program director.

ECMO protocols for initiation, selection of components, management, weaning, follow up and data management will be set by the ECMO coordinator along with ECMO director in discussion with other ECMO team members.

Table 5: Contraindications for ECMO

Relative
• Prolonged aggressive Mechanical ventilation for > 7 days (Mechanical ventilation with FiO_2 > 0.9 and Pplat > 30 cmH_2O for > 7 days)
• Severe chronic lung disease
• Unwitnessed arrest or CPR for 30 minutes
• Uncontrollable metabolic acidosis
• Pulmonary fibrosis
• Severe coagulopathy
• Age > 75 years
• Gestational age of < 35 weeks.
• Body weight: > 140 kg
• Trauma with multiple bleeding sites
• Significant immunosuppression
• Recent diagnosis of haematological malignancy
Absolute
• Significant neurological injury
• Active bleeding/coagulation disorder
• Terminal disease with short life expectancy
• Progressive nonrecoverable lung disease, not amenable to transplantation
• Chronic severe pulmonary hypertension with right ventricular failure
• Advanced malignancy
• Chronic organ dysfunction
• Lung Failure associated with Bone Marrow transplantation
• Contraindication to anticoagulation therapy
• Progressive non-recoverable cardiac disease, not amenable to transplantation or Ventricular assist device
• Aortic valve regurgitation
• Aortic dissection
• Unwitnessed cardiac arrest

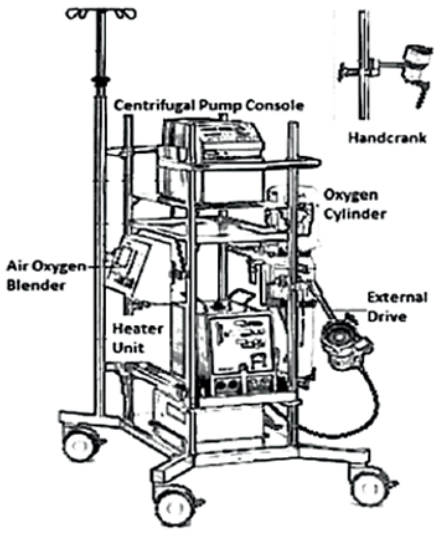

Figure 3: ECMO System (Courtesy Maquet Cardiopulmonary AG)

The initiation protocol should include policies for patient selection, cannulation, activation of ECMO team and centre-specific requirements to get the team members and materials required for initiation of ECMO support on an urgent basis, for quicker and smoother initiation of ECMO support. Selecting the appropriate equipment and disposables for ECMO support is necessary for getting the desired outcomes. The learning curve may involve 10 to 15 ECMO cases initially to understand the best suitable way of managing a patient supported with ECMO support. Management of a patient on ECMO should be standardised to prevent confusions and better patient outcomes. Follow-up of patients who received ECMO should be done to understand the progress in the patient's condition and also to understand the outcomes of the procedures done on the patient during the support. Data recording and retrieval system should be standardised to ensure better tracking of procedures and outcomes for improvement and statistical analysis.

Selection of the correct ECMO system and ECMO disposables

Selection of the right ECMO system and circuit components is the one of the important factors for successful ECMO support initiation. A recent article retrospectively compared different ECMO systems used in their hospital. Initially, the circuits included roller pumps with silicone membrane oxygenators. This was followed by circuits with Medtronic Biomedicus centrifugal pump and silicone membrane oxygenator. Presently, Maquet Quadrox D oxygenators with Rotaflow centrifugal pump are being used. A comparison of these equipment showed that the amount of mechanical related complications were almost one third in respiratory ECMO group and two third in cardiac ECMO group. Use of newer equipment was associated with improved outcomes.[11]

Attention must be paid to the following points while choosing equipment and components. All components should be well suited to handle required amount of blood flows. The initial preparation, assembly, priming and de-airing should take minimum time. The circuit should be reduced to its basic components, with no dead spaces and stagnant areas. All components should be approved by CE/ FDA and studied for longer term use. The circuit should have provisions for pressure monitoring, blood sampling and connecting other extracorporeal components. It should require lesser anticoagulation and should generate lesser Systemic Inflammatory Response Syndrome.

The components used in ECMO system are as mentioned below:

Equipment: Pump unit, heater unit, air-oxygen blender, trolley/ cart, holder for oxygen cylinder

Disposables: Pump disposables, oxygenator, heat exchanger, tubings with connectors, cannulae

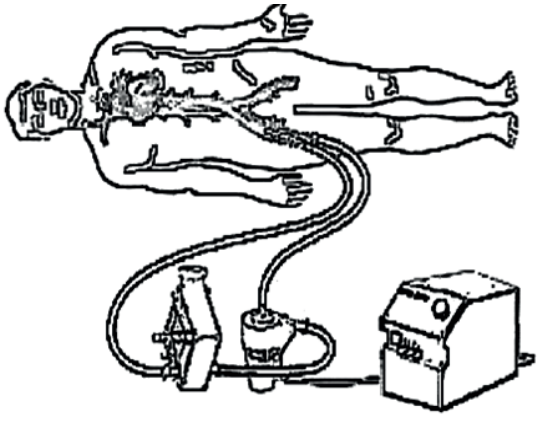

Figure 4: ECMO Circuit (Courtesy Maquet Cardiopulmonary AG)

All components should be well suited to handle required amount of blood flows: The blood flow rates are decided based on the cardiac index (CI) and body surface area (BSA) and depending on the need and condition of the patient, the required blood flow rates are established. A cardiac index of around 2.0 - 2.4 l/min/m^2 is applied in both VA as well as VV ECMO. In cases where only carbon dioxide (CO_2) needs to be eliminated and extracorporeal CO_2 removals need to be established, lower blood flow rates are sufficient and CO_2 flush out is handled by increasing the sweep gas rate in the gas blender. Also the size, length and type of cannulae are important in handling the required amount of blood flow rates.

Initial preparation, assembly, priming and de-airing should take minimum time: ECMO initiation is mostly urgent and requires prompt initiation of ECMO support. Especially in the cases of extracorporeal cardiopulmonary resuscitation (ECPR), ECMO should be initiated in less than 37 minutes of effective CPR, to reduce neurological deficits.[13] The newer generation systems are miniaturised, limited to basic components that are required and are also available as pre-connected ECMO circuits, which help in quicker initiation of the support.

Circuit should be minimised to its basic components, with no dead spaces and stagnant areas: Circuit system components should be minimum and selected to its basic requirements. No additional dead spaces should exist in the circuit to prevent clotting and clogging of the circuit. Less components in the circuit will lessen the amount of shear stress and surface contact to the blood elements, haemolysis and systemic inflammatory response syndrome. Newer generation systems used for ECMO are miniaturised to its basic components and no dead spaces with much lesser pressure drops, improving patient outcomes.

All components should be approved by CE/FDA and studied for long term use: ECMO components or circuits must be CE or FDA approved based on its long term performance, blood handling and durability of circuit components. Maquet PLS/ HLS circuits (Maquet Cardioplumonary AG) are the only commercially available circuits currently which have usage approval of 30 days for all circuit components including the oxygenator, coatings, heat exchanger, cannulae and centrifugal pumps.

Circuit should have provisions for pressure monitoring, blood sampling and connecting other components

Various pressures in the ECMO circuit have to be monitored during ECMO support, such as pre-pump, pre-membrane, post-membrane and trans-membrane pressures (Δp). Possibilities of collecting blood for checking blood gases of pre-membrane and post-membrane blood should be available in the circuit. Possibility of connection of other extracorporeal circuits should be available in the circuits.

The circuit should require lesser anticoagulation: Continuous contact with extracorporeal circuit activates the coagulation system and requires suppressionor prevention. Continuous anticoagulation is required to prevent clotting of blood into the circuit. Heparin is used as an anticoagulant during ECMO support and adequacy of anticoagulation is checked using Activated clotting time (ACT), Activated Partial Thromboplastin Time (aPTT) or Thromboelastogram (TEG).[10] Anticoagulation also increases the chances of bleeding and may lead to hypovolaemia-related complications, leading to excessive blood transfusions. Need for greater amounts of blood transfusion requirements are a major concern during ECMO support. The major causes of the need for blood transfusion are bleeding and blood cell damage in the ECMO circuit. Mortality and morbidity are higher and patients often need larger amounts of blood transfusions when supported by ECMO therapy. Increased number of blood transfusions is an independent predictor of mortality.[11] Bleeding can be due to postsurgical trauma, during cannulation, improper fixation of the cannula at the cannulation site, injury while intubation, GI bleed due to hypoperfusion or direct injury caused by feeding tubes, *etc.* Bleeding can be managed by local compression, surgical correction and by improving haemostasis during ECMO supports. The need for greater anticoagulation aggravates the risks of

bleeding in ECMO supported patients. The newer circuit components have been improvised to minimise the risk of bleeding by having miniaturised circuits, less blood-surface contact surface area and heparin coated tubings. These tubings also have homogenous surface lining when compared to PVC uncoated tubings, reducing the chances of shear stress on the blood elements and clotting. These heparin or heparin with albumin bonded circuits also help in preventing platelet adhesion to the circuit surface, help in maintaining platelet counts and supporting haemostasis during ECMO supports.

Should generate lesser systemic inflammatory response syndrome: Along with activation of coagulation system, inflammatory cascade is also initiated with the immediate blood-foreign surface contact. This continuous contact activates the inflammatory mediators such as complement factors (C3, C5, C8), interleukins, tissue necrosis factor andleukocytes which have a detrimental effect on the organ function. Maximum measures should be taken to prevent excessive accumulation of inflammatory mediators.Some of these measures include haemofiltration for clearing out most of the inflammatory mediators, infusing steroids to prevent or suppress inflammation and coating the extracorporeal circuit components with a biocompatible coating. These biocompatible coatings mostly consist of heparin, which have shown to minimise the activation and release of inflammatory mediators, reduced the need for anticoagulation, reduce shear stress on blood elements and reduce blood cell adhesion.[13-16] This property makes the heparin coated or the newer generation heparin-albumin coated systems to be ideal for performing ECMO supports on patients, which helps in preventing organ injury and preserving organ function.

Regular practice

As it applies for every therapy, regular practice helps understand therapy initiation time, management, weaning and troubleshooting better. The team members get familiar with the ECMO physiology, its pathophysiology, initiation and troubleshooting. A recent article compared 40 paediatric ECMO centres in the U.S. which were categorised into low, moderate and high volume ECMO centres.[17] Odds ratios for mortality and morbidity were calculated for all the groups, and it was found that centres performing minimum of 22 ECMO supports per year had comparatively greater survival outcomes and lesser morbidities, when compared to centres performing lower number of ECMO cases annually.[17] For regular practice, understanding the ECMO indications is very important.To achieve this, all the concerned departments including cardiac surgery, cardiology, intensive care unit and emergency medicine should be well informed about the indications and patient selection for ECMO therapy in the hospital. If a patient qualifies to be supported by ECMO, the ECMO coordinator or ECMO team director is informed. After the decision is made, the ECMO team gets activated to initiate and support the patient with ECMO.

Various cross-sectional studies indicate that the incidence of ARDS in the hospital is 5% of ventilated patients.[18]Another larger prospective European study mentions that the incidence of ARDS in hospital is around 7.1% of ICU admissions and 16.1% of mechanically ventilated patients develop acute lung injury or acute respiratory distress syndrome.[19]More than 75% of ARDS patients are severe and might require greater support than conventional ventilation. Around one third of the patients with mild ARDS will go into moderate or severe ARDS condition.[20,21]

The incidence of post-cardiotomy acute right heart failure is 0.4 to 1.2%. Overall 1% of post- cardiotomy patients develop intractable ventricular failure. Most of these patients do not respond to inotropes or IABP, which might require ECMO support or individual ventricular mechanical support.[22,23]Cardiogenic shock in acute myocardial infarction is one of the most common causes of death[24,25] and contributes to 7 to 10% of patients.[24,26] It is seen that almost 7.5% of the patients with ST-segment elevation myocardial infarction (STEMI) develop shock[26,27] and in 2.5% of patients with nonST-segment elevation myocardial infarction (NSTEMI) develop cardiogenic shock.[28] In another study, 4.2% of patients with STEMI and 2.5% of patients with NSTEMI had cardiogenic shock.[29] A significant delay precedes shock

development in patients with NSTEMI.[29] This may be because STEMI is associated with rapid cell necrosis whereas it is slower in NSTEMI. Thus, the highest creatine kinase (CK) level is found in STEMI as compared to NSTEMI.[28] Mostly cardiogenic shock can be managed by vasopressor, inotropic and IABP support, but if the patients are unresponsive to conventional therapy, then ECMO support should be considered.[30]

Primary graft failure after lung transplantation contributes to around 13% to 35% of patients undergoing lung transplantation.[31,32]Almost every patient waiting for lung transplantation is a candidate for ECMO support due to remote organ dysfunction and higher mortality rates.[33]

Conclusion

ECMO can be applied for various types of indications such as hypoxaemic respiratory failure, hypercarbic respiratory failure or circulatory failure, mainly due to cardiac dysfunction or failure. Approach to the patient to be supported by ECMO starts from patient selection and includes initiation, maintenance, weaning and till hospital discharge. These should be well organised and well planned for better patient outcomes. The systematic institution of ECMO program helps in reducing confusion amongst ECMO team members, promotes coordinated protocolised approach and helps build structure to the program. Believing in the potential of ECMO indications in the hospital and application of ECMO support on them, will help in regular use of ECMO support. Careful selection of ECMO system and its componentswill help prevent system related complications to the patient. Every factor required for successful initiation of ECMO program should be borne in mind, worked upon and continued to establish ECMO in the hospital.

References

1. Bartlett RH, Fong SW, Burns NE, Gazzaniga AB. Prolonged partial venoarterial bypass: physiologic, biochemical and haematologic responses. *Ann Surg* 1974; **180**: 850-6.
2. Hill JD, O'Brien TG, Murray JJ *et al.* Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N Engl J Med* 1972; **286**: 629-34.
3. Bartlett RH, Gazzaniga AB, Jeff eries MR, Huxtable RF, Haiduc NJ, Fong SW: Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Trans Am Soc Artif Intern Organs* 1976, **22**:80-93.
4. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG Jr: Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979, **242**:2193-6.
5. Kolobow T, Gattinoni L, Tomlinson T, White D, Pierce J, Iapichino G: The carbon dioxide membrane lung (CDML): a new concept. *Trans Am Soc Artif Intern Organs* 1977, **23**:17-21.
6. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE: Control of breathing using an extracorporeal membrane lung. *Anesthesiology* 1977, **46**:138-41.
7. Drummond M, Braile D, Paula A. Technological evolution of membrane oxygenators. *Braz J Cardiovasc Surg* 2005; **20**: 432-7.
8. Peek GJ, Mugford M, Tiruvoipati R *et al.* 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.
9. Davies A, Jones D, Bailey M *et al.* Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009, **302**:1888-95
10. Delius RE, Otto AM. Extracorporeal membrane oxygenation support (ECMO) for cardiorespiratory failure. *In:* Mechanical Circulatory Support. Ed. Richenbacher Wayne. LandesBioscience:Texas: 1999.p.53-75
11. Sivarajan VB, Best D, Brizard CP. Improved outcomes of paediatric extracorporeal support associated with technology change. *Interact Cardiovasc Thorac Surg* 2010; **10**: 400-5.
12. Park SB, Yang JH, Suh GY *et al.* Surviving factors of extracorporeal cardiopulmonary

resuscitation in adults with in-hospital arrest. *Crit Care Med* 2013;**41**:12

13. PalatianosGM, Foroulis CN, Vassili MI *et al.* A prospective, double blind study on the efficacy of the bioline surface heparinized extracorporeal perfusion circuit. *Ann Thorac Surg* 2003; **76**: 129-35.
14. Harig F, Feyrer R, Mahmoud FO *et al.* Reducing the post-pump syndrome by using heparin-coated circuits, steroids, or aprotinin. *Thorac Cardiovasc Surg* 1999; **47**: 111-8.
15. Wahba A, Philipp A, Behr R, Bimbaum DE. Heparin-coated equipment reduces the risk of oxygenator failure. *Ann Thorac Surg* 1998; **65**: 1310-2.
16. Feyrer R, Harig F, Cesnjevar R, *et al.* Bioline or safeline treatment of CPB circuits? *Cardiovascular Engineering* 2003; 8:79-84.
17. Freeman L C., Bennett D T, Casper C*et al.* Pediatric and neonatal extracorporeal membrane oxygenation: does center volume impact mortality? *Crit Care Med* 2014; **42**:512-9.
18. Esteban A, Ferguson ND, Meade MO, *et al.* Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;**177**:170-7.
19. Brun-Buisson C, Minelli C, Bertolini G, *et al.* ALIVE Study Group. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004;**30**:51-61.
20. Ranieri VM, Rubenfeld GD, Thompson BT *et al.* The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012; **307**: 2526-33.
21. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;**353**:1685-93.
22. Kaul TK, Fields BL. Postoperative acute refractory right ventricular failure: incidence, pathogenesis, management and prognosis. *Cardiovasc Surg* 2000;**8**:1-9.
23. Deng MC, Edwards LB, Hertz MI, Rowe AW, Keck BM, Kormos R, *et al.* International Society for Heart and Lung Transplantation. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report. *J Heart Lung Transplant* 2005;**24**(9):1182-7.
24. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967; **20**(4):457-64.
25. Menon V, Hochman JS. Management of cardiogenic shock complicating acute myocardial infarction. *Heart* 2002; **88**(5):531-7.
26. Goldberg RJ, Gore JM, Alpert JS, Osganian V, de Groot J, Bade J, Chen Z, Frid D, Dalen JE. Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community-wide perspective, 1975 to 1988. *N Engl J Med*; **325**:1117-22.
27. Holmes DR Jr, Bates ER, Kleiman NS, Sadowski Z, Horgan JH, Morris DC, Califf RM, Berger PB, Topol EJ. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol* 1995; **26**:668-74.
28. Jacobs AK, French JK, Col J, *et al.* Cardiogenic shock with non-ST-segment elevation myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularizeoccluded coronaries for cardiogenic shocK? *J Am Coll Cardiol* 2000; **36**:1091-6.
29. Holmes DR Jr, Berger PB, Hochman JS *et al.* Cardiogenic shock in patients with acute ischemic syndromes with and without ST-segment elevation. *Circulation* 1999; **100**:2067-73.
30. Khalid L, Dhakam SH. A review of cardiogenic shock in acute myocardial infarction. *Curr Cardiol Rev* 2008; **4**: 34-40.
31. Lee CJ. Intensive cardiopulmonary support for otherwise dying post-heart and lung transplant recipients with extracorporeal membrane oxygenation. *Artif Organs* 2001; **25**:597-8.
32. OtoT, Rosenfeldt F, Rowland M. Extracorporeal membrane oxygenation after lung transplantation: evolving technique improves outcomes. *Ann Thorac Surg* 2004; **78**:1230-5.
33. Cypel M, Keshavjee S. Extracorporeal life support as a bridge to lung transplantation. *Clin Chest Med* 2011; **32**:245-51.