Initiating an Adult and Paediatric Extracorporeal Membrane Oxygenation (ECMO) Program in a Developing Country: Challenges, Successes, Opportunities and Road Ahead

Abstract
In developing countries, there is a growing number of patients with complex heart and lung disease (both adults and pediatric population) which is coupled with an environment of scarce resources. There is therefore a huge need for the adoption of modern medical technology in the field of mechanical circulatory systems, including extracorporeal membrane oxygenation (ECMO) treatments. The development of ECMO in particular has been extremely slow, and no system is currently approved and available for clinical application in developing countries, such as Pakistan. Reasons include financial constraints which have been a barrier to the development of robust adult and pediatric cardiac intensive care units critical to the success of such programs. Secondly, because of the substantial resource limitations, existing models of such care cannot be applied in their existing forms without addressing the numerous challenges that limits the delivery of ECMO in the developing world. Other limitations include absence of skilled technologists and material resources for adapting such technologies. Additionally, there is need to adopt strategies for delivering to the patients and healthcare providers such technologies at affordable costs. Here, we present a framework for the establishment of a new ECMO program in a resource-limited environment typically encountered in the developing world and the emerging economies.

Keywords: Axial pump; Intra-aortic pump; Centrifugal pump, Veno-Arterial ECMO

Introduction
The provision of health care for children and adults with complex heart disease has progressed by leaps and bounds in the last 60 years [1]. With developments in perfusion technology and refinement of surgical techniques, most complex heart and lung malformations can be treated adequately. Parallel developments in the field of cardiology such as early diagnosis and rapid stabilization, improvements in imaging, advanced interventional techniques, and newer treatment options for pulmonary artery hypertension and heart failure have complemented the growth in this field [1-3].

Extracorporeal Membrane Oxygenation (ECMO) has been an established technique in the field of critical care medicine for more than two decades. The origin of the ECMO treatments, its concept is based on the principles of provision of both cardiac and respiratory support to patients whose heart and lungs are unable to provide an adequate gas exchange to sustain life [1-4]. Its principle of working depends on removing blood from the body and artificially oxygenating red blood cells [4]. There are two main forms of ECMO, the veno-arterial and the veno-venous configuration [3-5]. In both types, blood from venous system is oxygenated outside the body.

Extracorporeal Life Support Organization (ELSO) registry data reported that the use of ECMO has been shown to improve survival rates in patients with acute respiratory failure, from 50 to 70 % [1-5]. In a population of nearly 51,000 respiratory failure patients, ECMO is associated with 75% survival for neonatal respiratory failure, 56% survival for pediatric respiratory failure and 55% for adult respiratory failure [6-8]. In contrast, conventional medical therapies have not been successful in these patients. Indeed, a randomized trial compared conventional ventilation versus ECMO for Severe Adult Respiratory Failure (CESAR Trial) patients showed improved survival for patients supported with ECMO [9-11].

The aim of this review is twofold, namely;
A. To review the challenges of setting up ECMO centers in the developing world
B. To review the outcomes of the ECMO centers in the developing world

Successful ECMO programs in the developed world
There are a number of successful ECMO programs in the developed world that have been recognized with ELSO. Such centres of excellence include UPMC Presbyterian Hospital,
Pittsburgh, Pennsylvania, USA, Comer Children’s Hospital, University of Chicago Medicine, Illinois, Rhode Island Hospital and Hasbro Children Hospital, Providence, Rhode Island, USA, and many others. There are also successful centers in UK such as the Glenfield Hospital, Leicester. The published data demonstrate that in developed countries ECMO programs are running with huge success. Openings are also being created for developing countries to practice ECMO. This can only be possible if experts from developed countries transfer their experience to developing countries, with the consequence of this adoption of such modern technology would be to significantly reduce mortality rate for patients with acute respiratory failure [1].

Many developing countries lack ECMO program due to a number of reasons, but the most important of all is the lack of resources. In addition, there is an absence of significant evidence to suggest that the risk-to-benefit ratio of ECMO in this setting is favourable.

We propose that a successful ECMO programme should be organized at the regional and national levels to provide the best care possible in high-volume, dedicated centers. This is because inappropriate use of ECMO may markedly increase hospital costs and expose individual patients to serious risks [10,12]. The establishment of an ECMO referral center is important to ensure that there is adequate volume, to allow teams to build sufficient competence through sharing knowledge and training. This is also consistent with the literature on the number of mechanically ventilated ICU patients, where it has been shown that the more cases a center performs, the better the outcomes [13]. Such a center should be able to maintain the skills and institutional support to justify the costs of such a comprehensive program. Neonatal and pediatric literature has shown that data from ECMO centers caring for >20 cases per year produced significantly better outcomes than centers that have <20 cases per year [14,15]. Moreover, the learning curve to establish competence requires at least 20 cases for optimal results [14,16].

Starting an ECMO program in developing countries

Some centers in the developing world have also started ECMO programs, which are available only for selected patients. The ECMO programs are feasible but require a greater more effort and willingness to share experiences between different centers. The exact prevalence of heart failure among children of developing countries is not known as the data is limited. Children of developing countries face a doubleburden of etiologies. Congenital heart diseases, myocarditis, and cardiomyopathies lead to fetal heart failure. In addition rheumatic heart disease, nutritional deficiencies, and other tropical diseases also result in heart failure among children of developing countries. This indicates that there is a dire need in the developing world for programs like ECMO in order to save lives. Besides other problems, late repair of tetralogy of fallot (TOF) has also been one that could benefit from post-cardiomyotomy ECMO in some circumstances [17,18].

Pakistan is a developing country that lacks basic infrastructure for health. Like other developing countries, the implementation of ECMO is still at an initial stage. A case of a 35 days old neonate was presented in Pakistan with transposition of great arteries. Due to limited resources and unavailability of specialized extracorporeal membrane oxygenation machine, cardiac bypass was converted into an extracorporeal membrane oxygenator machine. The neonate was successfully decannulated after 72 hours and discharged home after 3 weeks of the operation without any sequel. The experience of this ECMO-like technique in a low-income country with limited resources and no advanced equipment where the only option is the reversible cardiopulmonary which is a compromise refractory to standard ICU therapy [19,20].

Research on the role of ECMO in neonate patients with persistent pulmonary hypertension and severe hypoxic heart failure in centers across developing countries and ECMO showing positive responses in these cases [21,22]. When developing a new program, dose coordination with the receiving ECMO center is essential. A centralized programme ensures that quality control is maintained across many indications and cannulation techniques. The likely diminished cost-effectiveness of a low-volume ECMO program, must be taken into account [23-28]. Hospitals in these networks should adhere to a written standardized protocol for both the initiation of ECMO (indications and exclusions) as well as optimization of conventional treatments (such as low-volume, low-pressure, lung-protective ventilation or the use of prone positioning [29] in patients with severe acute respiratory distress syndrome (ARDS).

What are the most indications for ECMO in developing countries?

A. Adults

In the past five years, the world has seen a huge increase in the use of ECMO in adults with respiratory and cardiac failure in developing countries. ECMO is also now being used in adults with septic shock. It is also used to support cardiopulmonary function for early graft failure after heart or lung transplantation with good results. It has also been used in patients with acute respiratory failure associated with Influenza A H1 N1 infection.

B. Pediatrics

Indications for ECMO in pediatrics in developing countries include acute respiratory and cardiac failure. ECMO has also been used in reversible cardio-respiratory compromise refractory to standard ICU therapy. It has also been used in patients with acute respiratory failure associated with Influenza A H1 N1 infection.

The indications for ECMO (both for adult and paediatric patients) according to ELSO guidelines are summarized as follows [24]:

a) Severe neonatal respiratory failure refractory to medical management.

b) Support for severe respiratory failure in older children and adults with a potentially reversible cause, not responsive to optimal conventional management along the guidelines recommended (however, we have found peri-resuscitation iatrogenic drowning/ fluid overload of such patients to be a depressingly frequent event). A useful severity guide for
smaller children is an oxygenation index $>40$, and for larger patients a Murray score $>3.0$.

c) Support for cardiorespiratory failure after surgery for congenital heart disease.

d) Bridge to heart, lung, and heart-lung transplantation.

e) Support for reversible right heart failure in acute pulmonary embolism, and postoperative pulmonary hypertension in acquired heart disease.

Developing a Heart Lung ECMO Program in Pakistan

ECMO technology is now playing an important role in the Pakistani critical care setting. Despite the reality that this is not a health care priority in Pakistan, we at the Cardiac Eye International Foundation (CEIF: www.cardiaceye.com, a non-profit charitable heart surgery service) introduced a complete state of the art ECMO program.

Introduction of ECMO through the CEIF Heart Lung & Research Institute significantly raised enthusiasm for the technology in the whole country within the specialty of Critical Care medicine. At CEIF, despite our limited resources and with only the occasion donations from well wishers introduced the first successful ECMO unit in March 2016. On 19th March, the first ARDS due to H1N1 influenza case was connected to veno-venous ECMO and successfully weaned off after 96 hours. The results from our center were benchmarked against the ELSO registry and hence we were able to secure the ELSO Centre membership for Pakistan.

For a new centre in Pakistan, the first challenge was the mode of bypass (VV-ECMO) in respiratory failure sparing a lot of potentially life threatening complications. The second challenge was the associated coagulopathy as coagulation system activation occurs immediately after contact with the non-biological surface of ECMO unit through tissue factor activation [11,30,31]. Platelet adhesion and activation occurs upon exposure to the circuit resulting in thrombocytopenia and thrombosthenia [32,33]. To overcome these issues, for the first time in Pakistan, we introduced the technology of polymethylpentene (PMP) hollow-fibre oxygenators. These are long-lasting and have much lower adhesion and activation upon exposure to the circuit including the coronary arteries, will have similar oxygenation. VA-ECMO, which has the advantage that the whole arterial system, is ejecting against an increased after load. We have always favored pressure in the aorta may cause ‘cardiac stun’, because the heart is ejecting against an increased after load. VA-ECMO has the advantage that the whole arterial system, including the coronary arteries, will have similar oxygenation. Although 100% oxygen saturation may not be achieved, >85% is adequate and achievable even with no lung function. VA-ECMO is reserved for situations when there is additional right heart failure in cases of pneumonia, and conditions such as pulmonary embolism or postoperative pulmonary hypertension.

Future approach to ECMO program in Pakistan

Cardiac-Eye International Foundation introduced an ECMO network manned by a mobile ECMO team to retrieve patients and to attend to patients with critical cardiopulmonary failure refractory to conventional therapy. Its coordination is through a tertiary ECMO referral center. This mobile team is available 24 hours a day, 7 days a week and is comprised of experienced personnel trained in the transport of critically ill patients, insertion of ECMO cannula as well as circuit and patient management. The team variably includes a mix of physicians, transport specialists, nurses, perfusionists or other ECMO specialists. Imaging requirements at the referring hospital must be considered before transfers are made.

The Cardiac-Eye International Foundation ECMO center is developing specific guidelines and training for staff to provide a 24-hours intra-hospital transportation of patients conforming to the relevant international guidelines for multi-organ failure.

Conclusion

ECMO is an advanced modality of life support for neonatal, paediatric and adult patients with cardiopulmonary compromise resistant to conventional critical care management. ECMO is not a novel therapy, the first adult patient having been treated in 1972. Beyond these general considerations, one should not be too prescriptive. Key to the assessment is potential reversibility. Each case should be judged on its merits, as case selection depends not on patient factors but also on the experience and expertise of the centre offering treatment in a developing country.

Clearly, patients with specific contraindications should be excluded. The mode of ECMO is an important consideration. Indeed, opinion is that the assertion that veno-arterial ECMO (VA-ECMO) produces better gas exchange than VV-ECMO for respiratory failure is not strictly correct. ECMO is not synonymous with cardiopulmonary bypass, wherein the latter the heart is normally filled and ejecting. With VA-ECMO the high returning arterial pressure in the aorta may cause ‘cardiac stun’, because the heart is ejecting against an increased after load. We have always favored VV-ECMO, which has the advantage that the whole arterial system, including the coronary arteries, will have similar oxygenation. Although 100% oxygen saturation may not be achieved, >85% is adequate and achievable even with no lung function. VA-ECMO is reserved for situations when there is additional right heart failure in cases of pneumonia, and conditions such as pulmonary embolism or postoperative pulmonary hypertension.

Removal of carbon dioxide can be done in two ways, either with VV-ECMO or with the arteriovenous umb-less extracorporeal lung assist (PECLA) system [34]. The predominant feature here is low blood flow allowing CO$_2$ removal. The high cost of ECMO for developing nations such as Pakistan is always argued as a reason why it is not a viable treatment option. Although the cost of the circuit is expensive, the largest cost of ECMO lies in staff costs and the disposable circuits. With the new generation ECMO circuit technology, costs of the disposable circuits are decreasing, plus...
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blood priming of the circuit can be avoided. In future, it is likely that use of the conventional methods of respiratory support such as positive-pressure ventilation may decrease, while the use of non-invasive methods of oxygenation such as ECMO may increase for instance, in our case scenario of the young patient with H1N1 viral pneumonia with poor gas exchange and oxygenation.

Summarising, ECMO should be available for selected cases in healthcare systems in Pakistan and other developing countries, and it should be performed in centres that have done the necessary planning, preparation and training. The exact method of achieving this goal depends on the particular healthcare system and the balance between public and private providers. In general, we believe that neonatal and paediatric ECMO should be available in centres doing large numbers of congenital heart operations (>300 cases per year). The organisation for adult ECMO is more problematic, owing to the low turnover of cardiac surgical cases requiring ECMO support. Rather than a free-for-all, there should be a formal discussion between the public sector, private sector providers and donors as to whether ECMO should be supported as a treatment modality, and if so where and how it would best be provided.

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