EXTRACORPOREAL MEMBRANE OXYGENATION FOR NEONATAL CARDIORESPIRATORY FAILURE

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Cardiorespiratory failure is one of the major cause of mortality in the newborn period. The main etiology of cardiorespiatory failure includes hyaline membrane disease, meconium aspiration, persistent fetal circulation, sepsis and congenital diaphragmatic hernia. The standard treatment of these conditions involves the use of mechanical ventilation and drugs but about 5 to 10% of newborn fail to respond to this treatment(1).

Extracorporeal membrane oxygenation (ECMO) uses extracorporeal circulation and gas exchange to provide temporary life support in patients with cardiorespiratory failure. ECMO allows "lung rest" at low ventilator settings. The technique of ECMO has now been used for 20 years in newborns and children for respiratory failure only during the past 15 years(2). This mode of treatment has been used in nearly 7000 newborns up till now with a survival rate of 81%. The predicted mortality in newborns undergoing ECMO has been 80%, thus confirming the effectiveness of membrane oxygenation(3).

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The key component of ECMO is the transport of oxygen into blood across a semipermeable membrane. This phenomenon was first observed by Kolff when he noted that blood became oxygenated as it passed through the cellophane chamber of his artificial kidney(4). The first successful membrane oxygenator was made by Clowes in 1956(5). The 1960's and 70's were noted for further advances in membrane oxygenation but it became successful when Barlett *et al.* in 1982 pioneered the treatment for term and near term infants in respiratory failure(6). At present there are many centres mainly in the USA, Europe and Australia which have facilities for ECMO. The data from all these centres is collected by a central ECMO registry at Ann Arbor, Michigan. This is a new and exciting therapy and a full understanding of the physiology of ECMO and the functioning of the bypass equipment is mandatory before the clinical application of this technology(7).

Pathophysiology of Respiratory Failure and Role of ECMO

Persistent pulmonary hypertension of the newborn (PPHN) is the common denominator in most forms of neonatal respiratory failure. Whether it occurs as a primary event or as a response to some other pathologic process such as meconium aspiration, congenital diaphragmatic hernia or sepsis, the response is similar(8). High pulmonary artery pressure caused by reactive vasospasm leads to shunting of desatu-

rated blood from the right heart away from pulmonary vasculature through a patent ductus arteriosus or foramen ovale. The result is arterial hypoxemia resulting in tissue hypoxia and acidosis which leads to further worsening of the right to left shunt.

The conventional treatment is directed at increasing ventilation pressure, respiratory rate and increasing fraction of inspired oxygen(FiO_2) to cause alkalosis and increased hemoglobin saturation which finally leads to a decrease in pulmonary pressure and a decrease in shunt(9). The increased airway pressure causes barotrauma, decreased venous return, cardiac output and worsens the already poor perfusion and oxygen delivery. ECMO has an impact on this pathophysiology at several points. Firstly, the richly oxygenated blood returns from the membrane lung and this occurs without the high airway pressure and FiO_2 thus removing two prominent sources of iatrogenic lung damage. Secondly, CO_2 is removed by the membrane lung without high ventilator rate, or pressure. Thirdly, when the high intrathoracic pressure is reduced, venous return is enhanced. The well oxygenated and mildly alkalotic blood decreases the pulmonary artery pressure leading to a pink, well perfused infant experiencing "lung rest"(10).

Technique and ECMO Circuitry

There are two methods of vascular access for ECMO:

1. *Venoarterial (VA) Bypass:* VA bypass is the conventional cardiopulmonary bypass. Blood in this technique is drained from the right atrium through a catheter placed in the right internal juglar vein with the tip of the catheter in the right atrium. The blood is oxygenated and returned to the patient through the right common carotid artery. VA bypass provides both cardiac and pulmonary support (*Fig. 1*). The right common carotid artery can be ligated without any ill effects(11). The circle of Willis is usually a complete structure and blood flow from left common carotid artery prevents any ischemic damage(12,13). However, there are other reports showing a right sided brain lesion following right common carotid artery ligation for ECMO(14,15). The right common carotid artery can be reconstructed after ECMO is over with good results and flow characteristics(16,17). VA bypass provides excellent oxygenation at low flows and non-dependence on cardiac function. The disadvantages of VA bypass include any particles, bubbles or emboli in the circuit getting infused directly into arterial system, *i.e.,* brain, and potential hyperoxia of the blood supplied to the brain can cause retinopathy of prematurity.

2. *Venovenous (VV) Bypass:* VV bypass is achieved by a single double lumen right atrial catheter or by a two catheter technique(18). It provides gas exchange but no cardiac support and requires about 20 to 50% greater flow of blood through the cannulae. There is a decreased risk of embolisation. VV bypass was initially thought to be useful in primary pulmonary hypertension of newborn (PPHN) but there is no evidence to support this view(19). VV bypass should not be attempted until adequate experience with VA bypass has been achieved.

Physics of the ECMO Circuit and its Setup

The ECMO circuit consists of a pump which may either be a roller occlusion pump (Stockert roller pump) or a Constrained vortex pump. The pump provides a non-pulsatile flow and with the use of Constrained vortex pump, the incidence of tubing rupture is less(20). The tubing from the pump is connected to a membrane lung or a maxima hollow fibre membrane lung. The blood

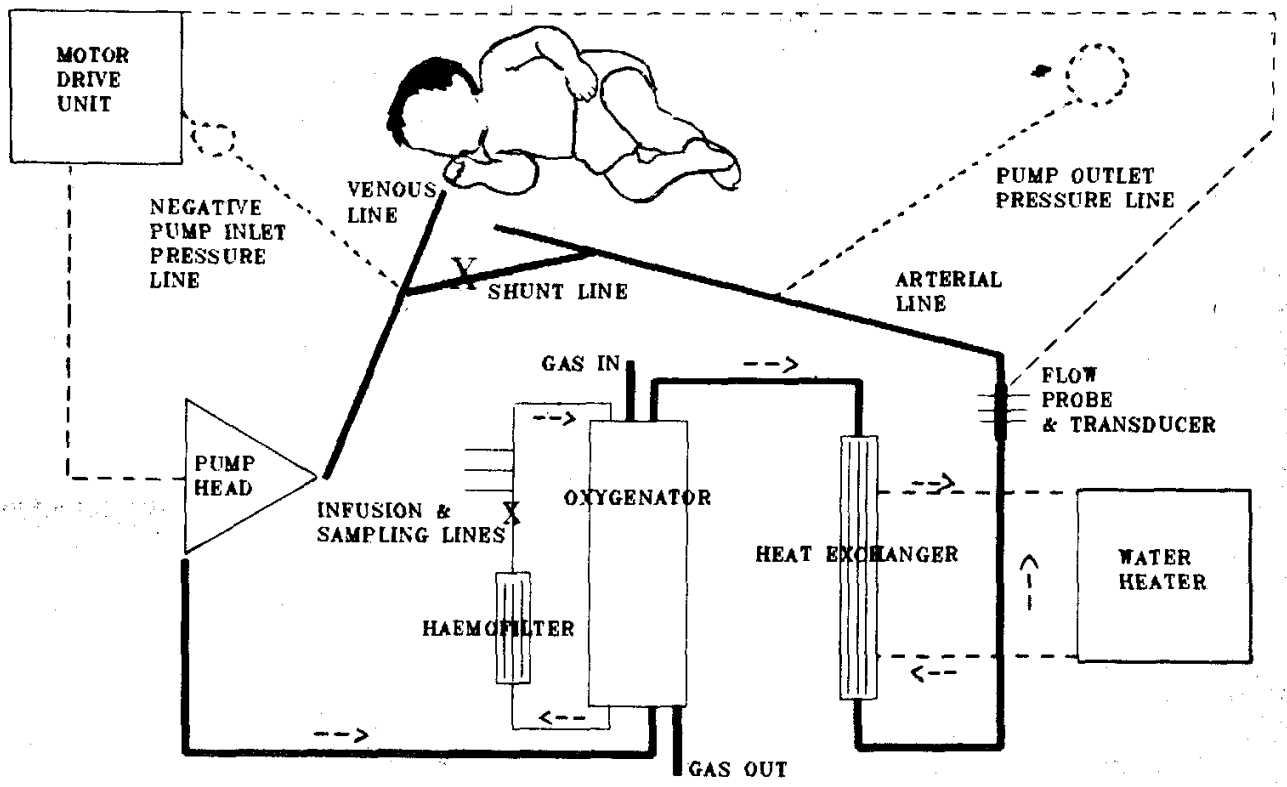

Fig. 1. VA ECMO Circuit.

flowing out of the membrane lung is connected to a heat exchanger system comprising of an Avecor heat exchanger and a Cincinnati warming pump. It works on the counter current principle and results in an uniformly warmed blood supply. This whole system is connected to the baby by arterial and venous catheters. The arterial cannula usually has a single outlet port and is of smaller diameter. Its tip should sit in the carotid artery close to the aortic arch. The venous cannula has an outlet port along with numerous side holes which allow for blood to drain from the right atrium and superior vena cava.

In ECMO, flow determines everything and the first determinants of ECMO flow are the cannulae. In planning an ECMO run one should plan a maximal flow rate of 125 to 150 ml/kg/min. The flow in an ECMO circuit is defined by Poiseuille's law which states that

$$F = \frac{P.r^4}{8\,L\,N}$$

(where F = flow, P = pressure, r = tube radius, N = fluid viscosity, L = length of tube).

Thus it is desirable to have a "short large lumen" cannula. For neonates, a 10 or 12 Fr Biomedicus ECMO cannula for the artery and a 12-14 Fr Biomedicus cannula for the vein are ideal. The pressures in the ECMO circuit are monitored. The pre-membrane

pressure is the highest pressure in an ECMO circuit (200-300 mm Hg). The membrane dampens this pressure by 100-200 mm Hg and post membrane pressures are monitored continuously. High pressures may cause hemolysis or even membrane rupture (21).

The aim in an ECMO circuit is to have a laminar or streamlined flow to avoid hemolysis, thrombosis and fibrin degradation. This is achieved by avoiding changes in tubing diameter, kinks or acute angles(22,23). ECMO requires exposing a majority of the blood volume to a large artificial surface which causes activation of the clotting and complement cascade(24-26). Platelets show the effect of prolonged surface interaction because of continuous platelet aggregation formation(27) and for these reasons a platelet transfusion is never given through an ECMO circuit. Even with the unusual flow patterns which the circuit produces, the effects of a roller pump, damage to blood cell components is small(28,29) unlike the findings seen in adults undergoing cardiopulmonary bypass.

Before an ECMO circuit is setup, the surface area of the patient is calculated using height and weight. The required flow rate is calculated which for neonates is usually weight × 150 ml/min. The flow rate determines the choice of the Avecor membrane oxygenator, pump head, circuit and size of arterial and venous cannulae. Once the ECMO circuit is assembled, its priming is done by first using CO_2 followed by crystalloid, albumin and finally blood to avoid bubbles and clots in the circuits. Calcium chloride is added to the prime as the citrate contained in whole blood chelates calcium and causes ionized calcium levels to be low. Sodium bicarbonate is also added as stored bank blood tends to be acidotic. Heparin is added to prevent coagulation. The circuit is made free of air by tapping and shaking all parts of the circuit.

Oxygenation and CO_2, Management During ECMO

The primary goal in oxygenation is to ensure adequate oxygen delivery which is dependent on oxygen content of the blood and blood flow. Thus,

Oxygen content
= O_2 bound to hemoglobin + dissolved oxygen.
= Hb(g/dl) × % saturation × 1.36 ml O_2/g/Hb + pO_2 × .0031 O_2/dl/mm Hg.

Oxygen delivery
= Oxygen content × flow (where flow is cardiac output)
= (Hb × % saturation × 1.36) + (pO_2 ×.0031) × cardiac output.

The normal newborn has a blood oxygen content of 20 vol %. With a cardiac output of 200 ml/kg/min, the infant can achieve an oxygen delivery of 40 ml/kg/min. The primary function of ECMO is to supply oxygenation by taking over a percentage of cardiac output and improving oxygen content via the membrane lung(30). Thus, oxygenation can be increased in the ECMO patient by increasing ECMO flow rates, hemoglobin levels and decreasing the right to left shunts. Usually once 60 to 70% of cardiac output is taken over by ECMO circuit, adequate oxygenation occurs and leads to "lung rest". This also leads to lowering of pulmonary vascular resistance and reversal of shunts(31), decrease in plasma thromboxane B_2 levels(32).

Membrane lungs are efficient in CO_2 elimination and in fact CO_2 needs to be added to the ventilating gas of the membrane lung to maintain a normal $PaCO_2$ level (Carbogen - 95% oxygen with 5% carbon dioxide). A $PaCO_2$ of less than 40 mm Hg results in decreased respiratory drive and may slow weaning from the ECMO circuit. In summary, oxygenation on ECMO

is blood flow related and CO_2 is membrane gas flow dependent.

Physiologic Changes After ECMO Initiation

When ECMO is initiated, the clamp from the venous line is removed first, the roller pump RPM (revolutions per minute) is increased, then the arterial line clamp is removed and RPM increased until maximum flow is achieved with minimum RPM. The gas flow to blood flow ratio for oxygenator is initially set at 1:1 but may be increased to 2:1 or 3:1 *i.e.,* 2 litres of gas for 1 litre of blood flow. Once this is achieved, ventilator settings are reduced to minimum maintenance levels. The effect of bypass is checked by regular blood gas and other biochemical parameters are also checked.

Once 70% cardiac output is taken over by ECMO, this result in a pulseless blood flow and pulse pressure is reduced(33). The ECG remains normal despite the fact that the ventricles are not ejecting. Preload and the heart rate usually decrease during ECMO and other cardiac parameters remain constant(34,35). Studies have shown that cardiac failure is not the primary cause of clinical deterioration but there are some reports of cardiac dysfunction pre-and post-ECMO(36,37). Usually the cardiotonic and vasodilator drugs can be weaned quickly but some centres prefer to maintain a Dopamine infusion at 2.5-5.0 μg/kg/min to optimize splanchnic blood flow and renal perfusion.

The ventilation management is aimed at keeping a high PEEP and low peak pressurem, FiO_2 and rate(38,39). The improvement in lung function is seen by reduced pulmonary artery pressure. Clinical improvement can be expected when the dynamic compliance, oxygenation index and concentration of surfactant protein A in tracheal aspirates increase(40,42). The chest radiograph initially shows a 'white out' and then gradually improves over a few days with clearing of lung fields. At this stage, a slow weaning from ECMO can be attempted.

Patient Selection, Indications and Contraindications

The indication for ECMO support is acute reversible respiratory or cardiac failure that is unresponsive to conventional ventilator and pharmacologic treatment, in which recovery can be expected within a week or two of ECMO support. Conditions that may benefit from ECMO are meconium aspiration, PPHN sepsis, respiratory distress syndrome, congenital diaphragmatic hernia, adult respiratory distress syndrome and perioperative support for congenital heart disease(43).

Currently in the USA, patients with these conditions are selected for ECMO if the expectation of death with conventional medical therapy exceeds 80%(44). Every institution has to develop its own predicted mortality rate using the oxygenation index, alveolar-arterial oxygen gradient, ventilation index *etc.* These are defined as follows:

$$1.\ \text{Oxygenation index (OI)} = \frac{\text{MAP} \times \text{FiO}_2 \times 100}{\text{PaO}_2} \qquad (45)$$

(where MAP = mean airway pressure, FiO_2 = Fraction of inspired oxygen, PaO_2 = oxygen content of arterial blood).

$$2.\ \text{Alvelor-arterial oxygen gradient} = 760 \times \text{FiO}_2 - (\text{PCO}_2 + \text{PO}_2 + 47)$$
$$\{(A - a)\ \text{DO}_2 \text{ in mm Hg}\} \qquad (46)$$

$$3.\quad \text{Ventilation index (VI)} = \frac{RR \times PIP \times PaCO_2}{1000} \qquad (47)$$

(where RR = Respiratory rate, PIP = Peak inspiratory pressure, $PaCO_2$ = Carbon dioxide content of arterial blood).

Usually a ventilation index of >90 for 4 hours and an oxygenation index of >40 qualify a patient for ECMO in our institution but every institution should develop its own figures for predicted mortality. Payne *et al.*(48) compared different ECMO selection criteria used in different institutions and found that the sensitivity of the criteria in identifying fatal cases varies from 0.44 to 0.94 and the specifity of prediction of survival ranged from 0.42 to 0.69. The criteria having the highest sensitivity had the lowest specificity. The overall accuracy of the criteria differed little but three factors influenced the predictive accuracy: (*i*) A primary diagnosis of congenital diaphragmatic hernia was associated with greater mortality ($p<0.001$) and significantly higher predictive value; (*ii*) The alveolar-arterial oxygen gradient using an assumed rather than actual barometric pressure and calculation of oxygenation index (OI) by using a calculated rather than measured MAP increases false positive mortality prediction in non-CDH patients; and (*iii*) A PIP of 50 cm of water in the definition of maximal medical management rather than a PIP of 20-49 cm of water significantly increases the positive predictive value.

Having established the patient selection and indications for ECMO, some contraindications must be established to exclude patients who would not benefit by ECMO. The most frequent complications on ECMO are due to bleeding from heparinization and because infants less than 35 weeks gestation have a 90% incidence of intracranial hemorrhage(49), these infants should be excluded. The other contraindications include genetic abnormalities incompatible with life expectancy, severe neurologic impairment, proven severe lung hypoplasia or irreversible lung pathology, a high airway pressure and a FiO_2 for longer than 10 days. Patients of cyanotic heart disease are considered for ECMO if the lesion can be corrected by surgery. Patients having early Group B streptococcal sepsis should also be considered if they develop acidosis or hypotension even if they require minimal ventilation(50).

Complications of ECMO

The complications of ECMO are usually due to mechanical failure or patient related. *Tables I & II* list the international summary of complications encountered and per cent survival of patients with these complications(3). Technical complications were reported in 30% of patients and patient related complications were seen in 25 to 29% of cases in earlier reports (51-55). Now with improvement in technology and patient care, the incidence of technical and patient related complications have been reduced to 3.8% and 4.5% with a survival rate of 75.3% and 64.0%, respectively. Refinement in technique and equipment can further improve these figures.

Results of ECMO and its Current Worldwide Status

ECMO can safely support respiration and circulation in newborns with severe respiratory failure and results thus far suggest that term newborns with respiratory failure are the best candidates for ECMO with a overall survival rate of 81%(56,57).

TABLE I—*Mechanical Complications of ECMO*

Complications observed	Number reported (Percentage)	Survival rate (Percentage)
Oxygenation failure	300 (4)	197 (66)
Raceway rupture	18 (0)	11 (61)
Tubing rupture	89 (1)	69 (78)
Pump malfunction	119 (2)	100 (84)
Heat exchanger malfunction	87 (1)	64 (74)
Clots in circuit	1112 (16)	858 (77)
Air in circuit	337 (5)	250 (74)
Cracks in connectors	165 (2)	118 (72)
Cannula problems	632 (9)	484 (77)
Restrictive suture	29 (0)	21 (72)
Hemofilter malfunction	48 (1)	25 (52)
Kinking of cannula	57 (1)	47 (82)
Other mechanical	570 (8)	441 (77)
Total	3570 (3.84)	2685 (75.3)

TABLE II—*Patient Related Complications of Neonatal ECMO*

Complications observed	Number reported (Percentage)	Survival rate (Percentage)
GI Hemmorrhage	193 (3)	105 (54)
Cannula site bleed	498 (7)	363 (73)
Surgical site bleed	436 (6)	234 (54)
Hemolysis	599 (9)	432 (72)
Brain death	94 (1)	4 (4)
Seizures	936 (14)	626 (67)
Infarct or bleed by cranial ultrasound	900 (13)	450 (50)
Creatinine >1.5 mg/dl	690 (10)	413 (60)
Dialysis/hemofiltration	851 (12)	508 (60)
Pulmonary hemorrhage	163 (2)	78 (48)
Myocardial dysfunction	378 (5)	251 (66)
Cardiac arrhythmias	262 (4)	163 (62)
Pneumothorax	374 (5)	249 (67)
Infection	592 (8)	379 (65)
Dyselectrolytemia	814 (12)	512 (63)

TABLE III–*Neonatal Cases Treated with ECMO and Their Survival*

Year on ECMO	Total No. of cases	Cumulative total	Number survived	Percentage survival
Upto 1986	813	813	661	81
1987	647	1460	556	86
1988	1004	2464	828	82
1989	1106	3570	905	82
1990	1331	4901	1075	81
1991	1375	6276	1107	81
July 1992	649	6925	526	81

TABLE IV–*Neonatal Cases Put on ECMO, Their Primary Diagnosis and Survival*

Primary diagnosis	Total	Number of survivors (%)
Congenital diaphragmatic hernia(CDH)	1318	785 (60)
Meconium aspiration Syndrome (MAS)	2611	2440 (93)
Persistant pulmonary hypertension (PPHN)	859	728 (85)
Hyaline membrane disease	900	754 (84)
Pneumonia/sepsis	984	756 (77)
Air leak syndrome	28	18 (64)
Others	220	172 (78)

Table III shows the worldwide survival rate and *Table IV* illustrates the survival rate according to primary diagnosis. The figures are from the International summary of ECMO registry, Ann Arbor, Michigan, published in October 1992. Recently, high frequency oscillatory ventilation (HFOV) has been compared with ECMO, but HFOV has been found to be effective only in diffuse lung disease with normal cardiac function(58).

Neurodevelopmental Outcome and Long Term Follow Up

The first successful neonatal ECMO was reported by Bartlett *et al.* in 1974(2) and since then nearly 7000 newborns had undergone the procedure for acute cardiorespiratory failure. The long term neurodevelopmental outcome of the infants may be affected by the hypoxia of respiratory failure (pre ECMO) and by post ECMO complications (*Tables I & II*). Various studies of long term follow up have appeared in the literature and normal mental function is reported in 70 to 80% of survivors(59). A study of similar patients treated with conventional ventilation therapy also showed 77% normal mental function (60). The various

TABLE V–*Long Term Neurodevelopmental Outcome of ECMO Survivors*

Investigator (Reference)	No. of pts.	Age of exam	Metod of exam	Normal (%)	Neuro deficit/ complications
Krummel (64)	6	1-2	CT, EEG, By.	5 (83)	1(17) CP
Towne (60)	18	4-11	US, EEG, Mc, Pb, PsL.	16 (89)	5(28)gr.rtd.
Glass (65)	42	1	By.	36 (86)	9(21)dv.rtd.
Lott (66)	10	4-9	US, EEG.	7 (70)	1(10)Seiz.
Andrews (59)	14	1-3	CT, EEG, By, DDST, St.B.	12 (86)	4(28)CLD 3(21)CP
Schumacher (67)	92	1-7	By, St.B., Spch., Lang.	68 (74)	14(16)Neuro. deft.
Campbell (15)	12	2	Neuro. Ex	9 (75)	2(25)Seiz & CP.
Adolph (68)	57	0.5-4	Neuro. Ex, By, Mc,Gs,DDST	45 (79)	1(2)rtd. 11(19)delay
Griffin (62)	22	0.5-2	By, US, MRI.	119 (86)	2(9)CP, 3(12)dv.
Hofkosh (69)	67	10	Neuro. Ex, CT, St.B, Aud.	43 (64)	10(14) Abn.CT 16(21) Abn. hear.

Abbreviations: abn-abnormal, Aud-Audiological exam., By-Bayley*, CP-cerebral palsy, CLD-chronic lung disease, CT-computerised tomography, deft.-deficit, dv-development, DDST-Denever development screening test, EEG-Electroencephalogram, gr-growth, Gs-Gessel*, hear-hearing, Lang-Language*, Mc.-McCarthy*, MRI-magnetic resonance imaging, Neuro. ex.-Neurological examination, Pb-Peabody*, Ps.L-Psycholinguistic assessment*, Pts.-Patients, rtd.-retarded, seiz-seizures, spch.-speech, St.B-Stanford Binet*, US-cranial ultrasound.

Note: Figures in parentheses{ } indicates author's reference and ( ) percentages. * Neurodevelopmental studies.

studies of neurodevelopmental outcome of ECMO are summarized in *Table V*. The studies concluded that ECMO does not increase the neurodevelopmental morbidity associated with neonatal cardiorespiratory failure. Most of the newborns found later to develop a neurological deficit or developmental delay had evidence of abnormal cranial ultrasound, computerized tomography of brain or magnetic resonance image scans (61-63).

Costs and Requirements for an ECMO Centre

The establishment of an ECMO centre is possible in a tertiary level III centre for neonatal intensive care, where facilities for open cardiac surgery are available with a good laboratory backup(70). An ECMO programme is a team work of neonatologist, cardiologist, cardiac surgeon, emergency transport system and trained nurses. An

ECMO centre should have a follow up and active research programme to succeed in long term.

The cost of ECMO has been quoted to be Rs. 20,000 per day in the West(43), but the cost in India will be different, as besides the one time cost of buying eqipment (*viz.*, vortex pump, Cincinnati heat exchanger pump, *etc.*) the cost of disposable equipment is only Rs. 30,000 for a 7-day run of ECMO. Most of the equipment needed is already available in many Neonatal intensive Care Units (NICUs) and cardiac surgery units, but the need is to bring these together and organize a team.

ECMO in the Indian Scene

There is always resistance to the introduction of newer technologies and many will argue that a developing country like India with a high neonatal mortality first need Level II and III care of neonates. However, ECMO in established or developing Level III centres can help reduce the neonatal mortality rate(71). At present there are many established and upcoming centres in the private sector which provide excellent facilities for cardiac surgery and have a well equipped NICU, these can provide ECMO services at a reasonable cost.

There has been a great resistance even in the West to the introduction of this efficacious mode of treatment for neonatal respiratory failure(72-76), but ECMO has come to stay despite all the criticisms. In a large country like India we need a few centres where state-of-the-art treatment modalities are available and we do not lag behind the world in this field.

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