Pediatr Surg Int (1993) 8: 283–293

Pediatric Surgery International

Main topic

Extracorporeal membrane oxygenation (ECMO) for pulmonary parenchymal disease in older children

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Abstract. Extracorporeal membrane oxygenation (ECMO) for the support of children outside the newborn period who have pulmonary failure is only recently becoming accepted. It is again being applied, after earlier failures, because well-trained teams and improved equipment and techniques are available following the success of neonatal ECMO. In addition, in Europe extracorporeal CO_2 removal ($ECCO_2R$) in adults has been more successful. The use of ECMO for pulmonary failure in children does not have fixed indications and has had considerably less success than neonatal ECMO. Patients who require inspired oxygen fractions of over 0.5 and positive end-expiratory pressures of over 6 cm H_2O for more than 12 h after being treated for more than 48 h should be considered candidates, given the high mortality of children with ARDS (70%). Survival averages 50% to 60%. Circuits and patient management techniques are very similar to those for newborn ECMO, but patients usually require longer times on ECMO. There are many more options for cannulation for both venoarterial and venovenous techniques than in neonatal and cardiac ECMO. The improving results indicate that ECMO will play a part in treating children with pulmonary failure. Further studies will be required to determine which patients can benefit from ECMO as well as the exact application in each case.

Introduction

The correct term for extracorporeal circulation when it is used to treat children with parenchymal lung disease is unsettled. The official umbrella organization for centers treating patients with lung and heart failure by means of an extracorporeal blood circuit is the Extracorporeal Life Support Organization (ELSO)[1], and many authors feel that the term "extracorporeal life support" (ELS) is appropriate, as it embraces support of both lung and heart function. The older term from experience with open-heart surgery is "cardiopulmonary bypass", or CPB, which is difficult to pronounce. The recent applications of this technology to adults have emphasized circuit blood flows less than the cardiac output and using the membrane lung mainly to remove carbon dioxide, with the acronym of "$ECCO_2R$" for "extracorporeal CO_2 removal." Those who wish to unite both oxygenation of the blood and removal of CO_2 have suggested "ECLA" for "extracorporeal lung assist." I believe that the early term, ECMO, for "extracorporeal membrane oxygenation" is the most appropriate, since it was, in fact, the membrane oxygenator that made long-term extracorporeal circulation outside the operating room possible. The early oxygenators utilizing a direct blood-gas interface (bubble, disk, screen) were neither safe nor effective for long-term application.

There are two important questions for those considering pediatric pulmonary ECMO. The first is: "Why might ECMO be expected to work?" Why should we turn our attention to this therapy when so much attention was given to its failure in the 1970s? While neonatal ECMO has been successful, its success is not immediately applicable to pediatric ECMO. ECMO is effective in newborns with diseases characterized by pulmonary artery hypertension as the lung's response to injury, including congenital diaphragmatic hernia, meconium aspiration syndrome, and occasionally hyaline membrane disease, as well as primary pulmonary artery hypertension or persistent fetal circulation. ECMO supplies the best pulmonary artery vasodilator currently available, namely oxygen, and by the simple application of Boyle's law reduces pulmonary artery pressure by removing blood from the right side of the circulation. Thus, newborns on ECMO are receiving active treatment directed specifically at the underlying problem. While many older children and adults with pulmonary parenchymal disease do have some pulmonary hyperten-

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sion and right-sided heart failure as a component of their illness, it is usually not major. In these cases ECMO is used to support end-organs until the lung can recover and to protect against the oxygen toxicity and barotrauma associated with mechanical ventilation.

Another feature distinguishing the newborn from the older pediatric patient is that newborn respiratory failure develops quickly and patients tend to require ECMO in the first few days of life, while older children may be mechanically ventilated for weeks before ECMO seems to be required. The complicating effects of ventilator barotrauma and oxygen toxicity then make the application of ECMO less likely to be successful. The success of neonatal ECMO, however, has led to the development of trained teams at major medical centers throughout the world who are able to apply the latest technology at an hour or two's notice. The existence of these teams has also generated more interest on the part of industry in developing safe and effective devices.

In addition to improvements in equipment and techniques, another reason for considering ECMO for the treatment of pediatric pulmonary disease is the work of Gattinoni et al. [18] in Milan in the treatment of adults with adult respiratory distress syndrome (ARDS). This work has been reproduced by Knoch et al. [30] in Marburg. Prior to these reports, patients with ARDS responded poorly to all therapies, including ECMO. ARDS is common in children, with perhaps 150,000 cases in the United States each year [10]. The incidence per 1,000 intensive care unit admissions is between 7 and 15, and the mortality averages 70% [6, 13, 25, 27, 33, 34, 39, 43, 46, 52, 54]. The disease is similar in adults and children, so the use of ECMO in adults with ARDS has very real applicability to pediatric pulmonary ECMO.

Studies of ECMO in children frequently report very specific etiological diagnoses such as hydrocarbon aspiration [47], respiratory syncytial virus (RSV) infection [50], varicella pneumonia [23], and near-drowning [15]. No data have yet shown that the use of ECMO differs in any of these forms of pulmonary parenchymal injury. Many ventilator strategies have been applied to the treatment of ARDS without demonstrable success. These include positive end-expiratory pressure (PEEP) up to 40 or 45 cm H_2O [16, 28], high-frequency ventilation [8, 26], and airway pressure release ventilation [44]. Anecdotal experience with ECMO for the treatment of ARDS was encouraging [19, 20, 24], but a randomized trial demonstrated no benefit [59]. In an early (1976) report from Bartlett et al.'s original ECMO group describing 28 cases, both of the older children with pulmonary failure died [5].

Gattinoni has applied to patients concepts developed first theoretically and then in the animal laboratory by Kolobow [31], who also designed the current silicone rubber membrane oxygenator that is the standard for ECMO. These investigators have demonstrated that oxygenation can be maintained by diffusion even in the diseased lung by keeping it distended with oxygen and using only occasional breaths or "sighs." This technique of ventilation is called low-frequency positive pressure ventilation (LFPPV), or sometimes "apneic oxygenation." It is usually combined with inverse-ratio ventilation (IRV). In 1984

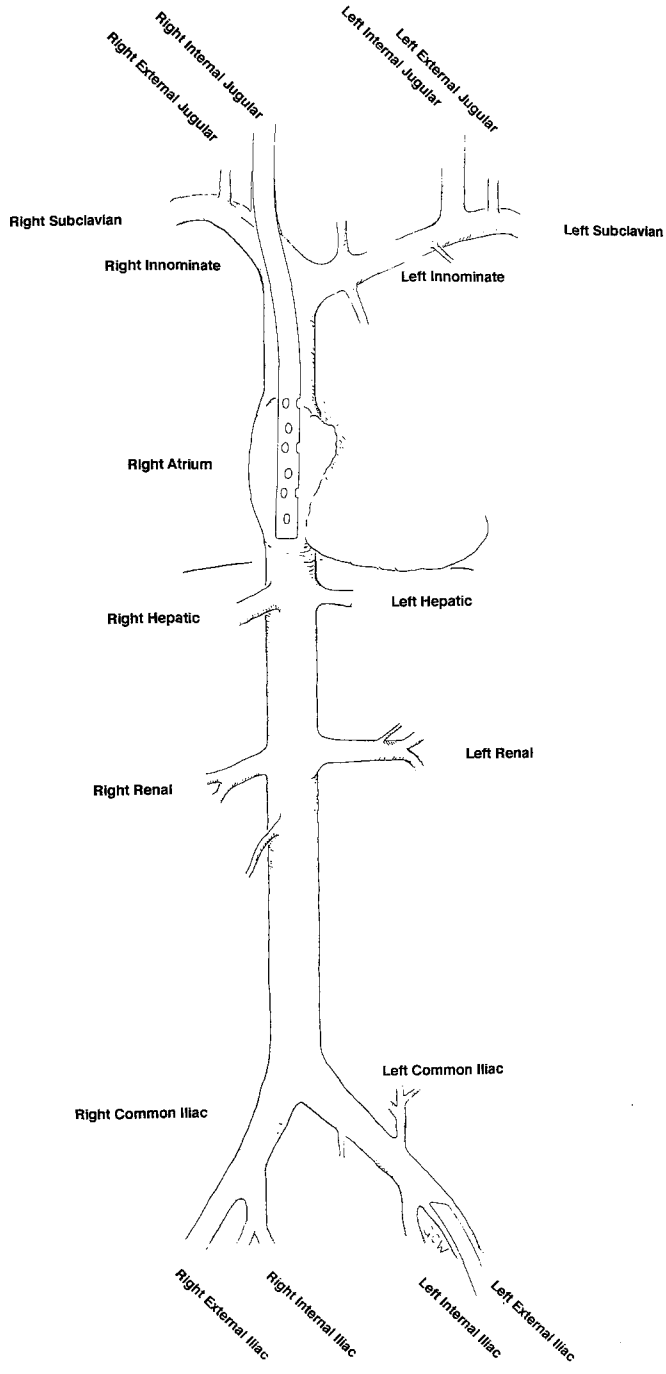

Fig. 1. Venous cannula positions showing cannula passed to right atrium from right internal jugular vein and short venous cannula from left common femoral vein to iliac vein for perfusion in venovenous (vv) ECMO

Gattinoni et al. reported on 36 patients with ARDS meeting blood gas criteria for 90% mortality [17]. They were first changed from conventional ventilation with PEEP to pressure-control IRV (PC-IRV) or continuous positive airway pressure (CPAP). Forty-eight hours later, only 19 of the 36 patients required cannulation for $ECCO_2R$ and the overall mortality was 23%.

No patient with a total static lung compliance (TSLC) lower than 25 ml/cm H_2O tolerated PC-IRV or CPAP alone, while all patients with TSLC >30 ml/cm H_2O were effectively treated with LFPPV and $ECCO_2R$. Typical ven-

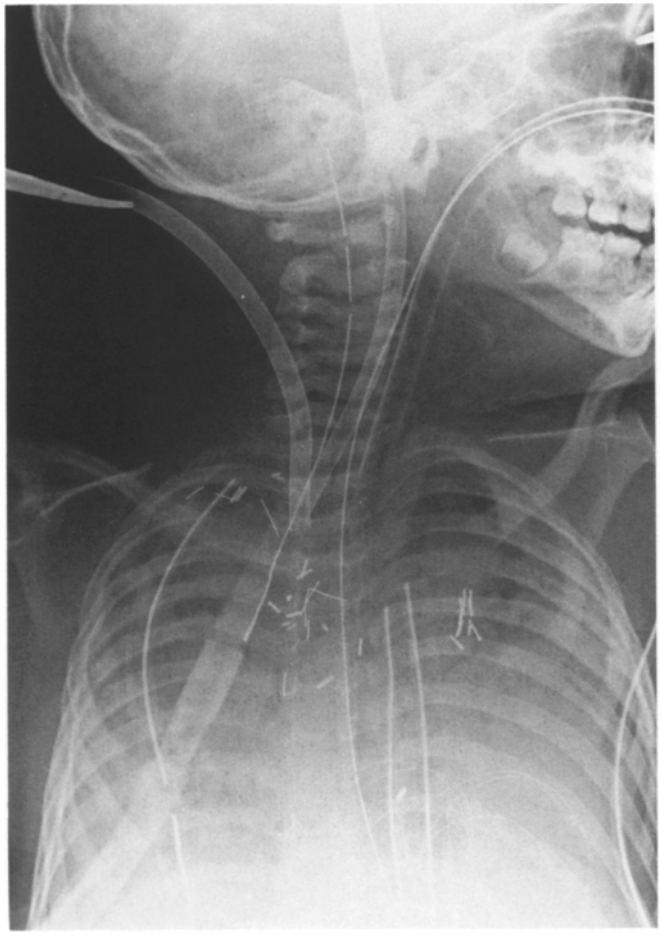

Fig. 2. Venoarterial ECMO with two venous drainage cannulas, one in right atrium from right internal jugular vein and one cephalad through same venotomy. Arterial perfusion cannula is passed to level of aortic arch from right common carotid artery

tilator settings might be a rate of 4, peak inspiratory pressure (PIP) 35 cm H_2O, inspiratory time 2 s, inspiratory pause 2 s, end-expiratory pause 16 s, and PEEP 20 cm H_2O. The extracorporeal circuit is then needed only to remove CO_2, a process that can be done at flows of only 20% to 30% of the cardiac output as the membrane lung is much more efficient at CO_2 removal than at oxygenation, which requires flows of 100% to 150% of the cardiac output. A combination of the use of IRV and ECMO (or $ECCO_2R$ as used in this manner) resulted in an overall 79% survival in patients who would have historically had only a 9% chance of survival [18]. Those patients who actually required $ECCO_2R$ had a survival of 49%, which compares favorably with the 9.5% survival reported for ECMO in patients with similar entrance criteria in 1979. At the University of Michigan, ECMO has been applied to adults with similar success using more traditional extracorporeal support of both oxygenation and CO_2 removal [2].

There are several reasons for the failure of early trials of ECMO for pulmonary disease in addition to the lack of trained teams and the use of older technologies. The patients were much more ill than anyone had suspected. Those designing the entry criteria had felt that they had chosen criteria predicting 50% mortality and found that they predicted 90% mortality. Also, time on a ventilator prior to ECMO had not been used in the criteria, thus allowing patients with an advanced stage of pulmonary fibrosis to be included in the study. Most current experience in the United States demonstrates that adult patients with ARDS who have been ventilated for longer than 5 days and children with ARDS who have been ventilated for longer than 7 days are unlikely to survive. In addition, the time on ECMO in the 1979 study was limited to 5 days, while most centers doing ECMO for pulmonary support now find that patients frequently require ECMO not just for days, but for weeks and often as long as 1 month.

Morris et al. in Salt Lake City have tried to reproduce the European results with a prospective, randomized, controlled trial. In order to be sure that the ECMO and non-ECMO groups were comparable, they spent several years devising protocols for the management of patients with ARDS. They found that their success with the treatment of ARDS had not changed from 1977 to 1988: the mortality was still 11%. Instituting the protocols alone raised the survival to 45% [51]. Patients in the ECMO group also had a survival of 45%, essentially the same as that achieved in Europe with $ECCO_2R$. The fact that protocol treatment without and with ECMO had similar results in this adult study presents the same quandary as that associated with neonatal ECMO. In newborns, at least two groups of researchers have been able to achieve results similar to ECMO with varying schemes of ventilator management, yet many others have tried to copy these non-ECMO treatments in newborns in their own practices without the same success.

ECMO methods

Cannulation

Cannulation for ECMO for pulmonary support in the pediatric patient is a very unsettled area. Consideration of the alternatives is important for pediatric surgeons. Arteriovenous perfusion as often used in low-flow extracorporeal circulation such as hemodialysis does not provide adequate blood return for pulmonary support, probably due to spasm of the artery just proximal to any cannula tip. Thus, all the methods discussed here drain blood from the venous system.

Venoarterial perfusion

Standard venoarterial (VA) ECMO, as employed in most newborns, is frequently utilized to treat older children with pulmonary parenchymal disease. The venous drainage cannula is passed to the level of the right atrium via the right internal jugular vein (IJV) by an open cutdown technique (Fig. 1). Venous drainage of the right heart in this fashion relieves the element of right heart failure that often accompanies lung disease and lowers pulmonary artery pressure by decreasing the volume on the right side of the circulation. Some authors have feared that this could lead to pulmonary infarction or ischemia by decreasing lung

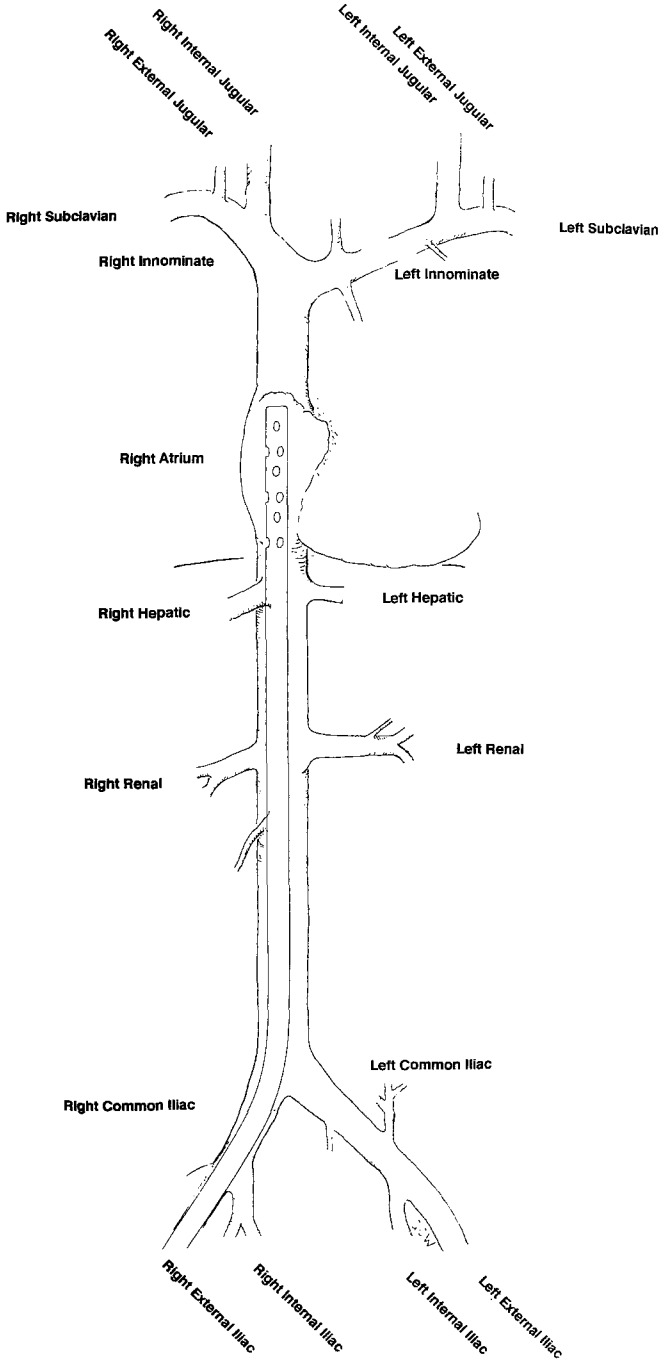

Fig. 3. Venous cannula positions showing long venous drainage cannula placed from common femoral vein to right atrium

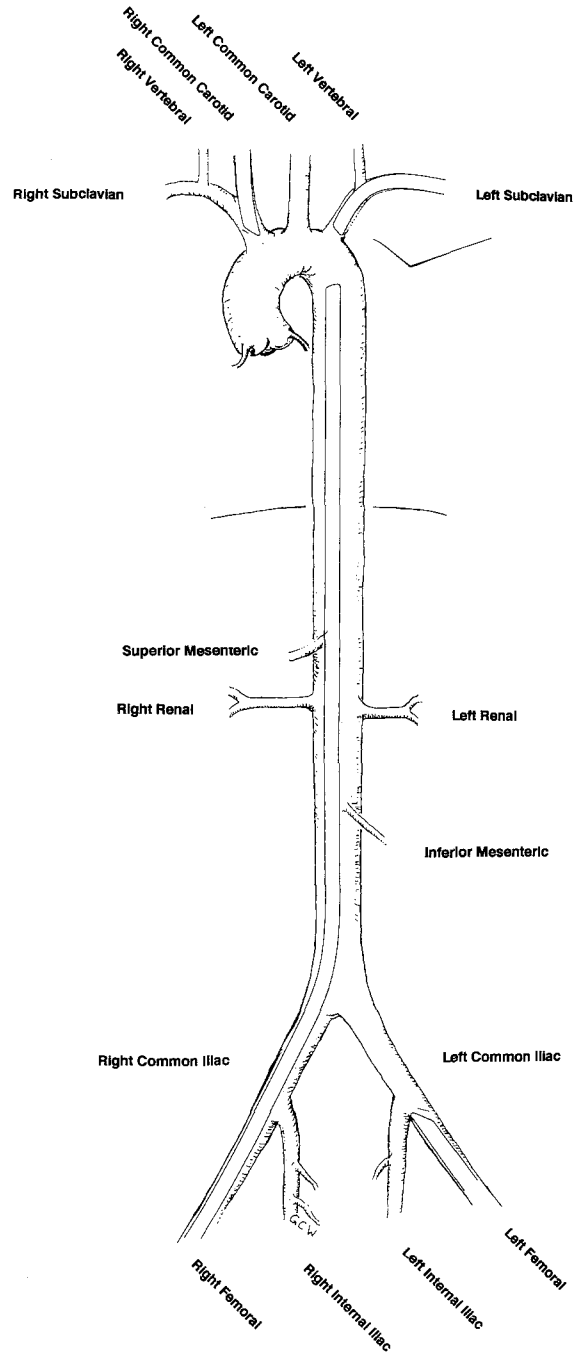

Fig. 4. Arterial perfusion cannula positions showing standard cannula passed to level of aortic arch from right common carotid artery as well as short femoral arterial cannula that can be used when left ventricular output is poor, longer femoral artery cannula reaching to aortic arch, which is necessary when left ventricular output is effective, and axillary artery cannulation

blood flow, but most of the lung's nutrient supply of blood comes from the bronchial arteries. The IJV also allows placement of the largest possible cannula to provide adequate venous return for blood flows equal to or greater than the cardiac output.

There have been theoretical concerns that ligation of the IJV can increase intracranial pressure and lead to intracranial hemorrhage. This has led some authors to spearately drain the distal IJV and "Y" the two drainage lines together to the pump. We have found that as much as 20% of the venous return can be obtained by using this distal drainage, making it much easier to increase pump flows, and have continued to use it in older children in whom venous return from the atrium can be inadequate to provide normal blood gases no matter how large the venous cannula (Fig. 2). We also attempt to repair the vein when it has been drained distally at the time of decannulation, since there would appear to be few if any complications associated with this procedure.

The venous drainage cannula can also be placed from the groin, either by open cutdown or percutaneously

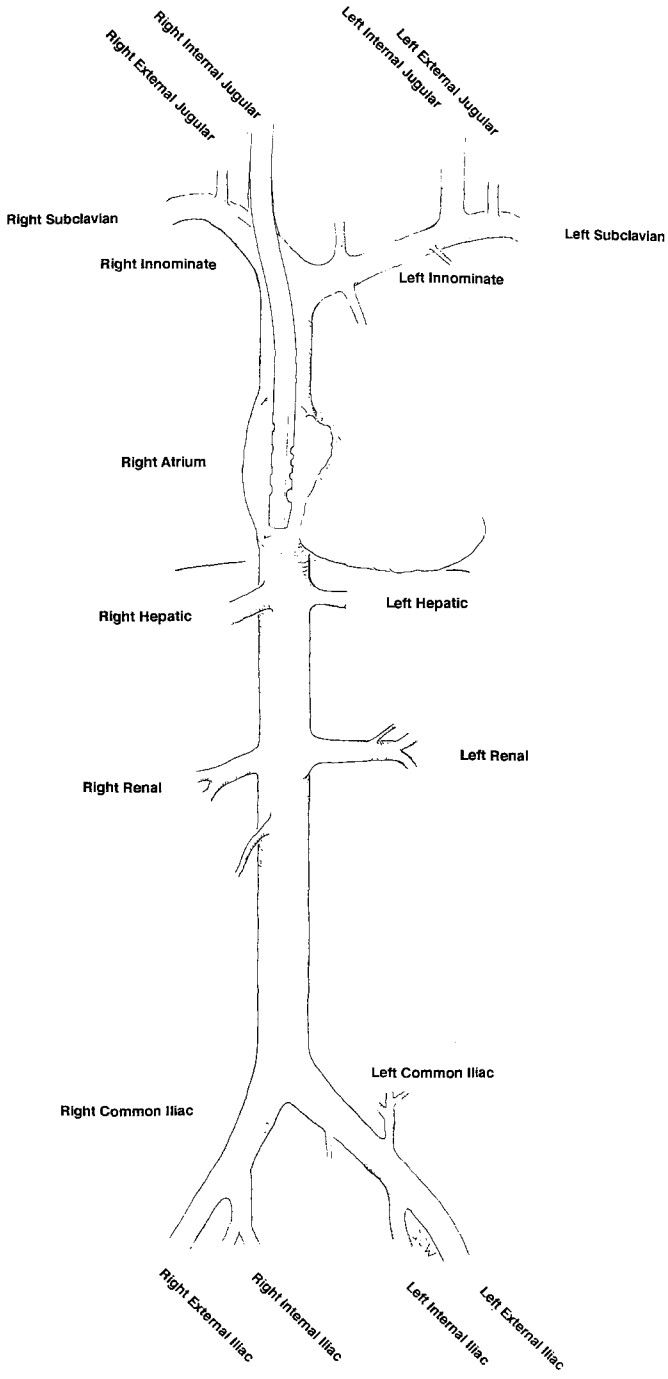

Fig. 5. Dual-lumen cannula passed to right atrium from right internal jugular vein that is used for single-catheter VV ECMO in newborns

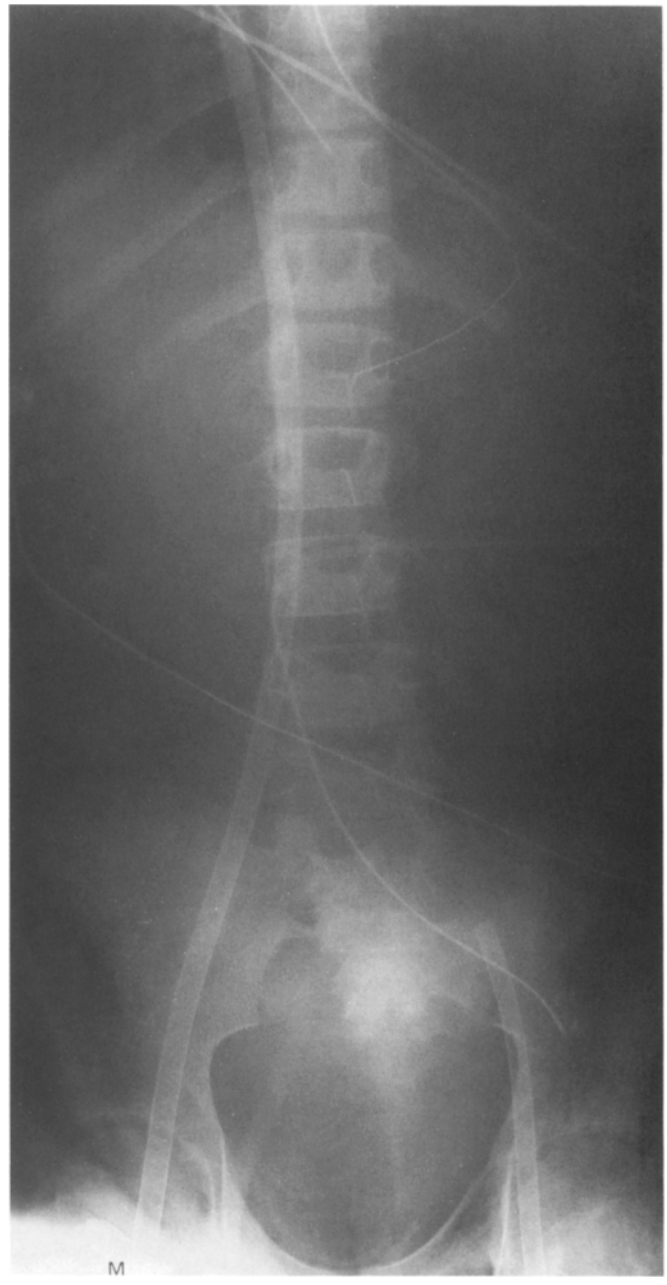

Fig. 6. VV ECMO. Long, 21 Fr venous drainage cannula passed percutaneously from right femoral vein. Return or perfusion cannula is 17 Fr, short cannula in left iliac vein

(Fig. 3). Cannulas for this purpose are generally available for the more widespread practice of supported angioplasty in adults [22, 56], a technique in which cardiac output is supported by an ECMO circuit while coronary arteries are occluded by the angioplasty balloon. It has also been used to support adults in cardiac arrest until a diagnosis can be made and the underlying cardiac lesion corrected [45]. These drainage cannulas can reach as high as the right atrium and are quite effective.

The arterial perfusion cannula is most often passed via the right common carotid artery to the level of the aortic arch (Fig. 4). This provides excellent end-organ support. Animal studies have raised some concern that the blood returned via this cannula is jetted distally and does not supply the coronary and cerebral circulations well [38, 48], but in humans it may provide just the turbulent flow necessary to perfuse these organs. Much concern has been raised about permanent ligation of the carotid artery. To date there is little experimental or clinical evidence that this has any deleterious effects, but some centers repair the carotid artery at decannulation [1]. Our concern has been that if ligation of the carotid artery does cause ischemia, the worst time to revascularize it would be after 5 to 7 days when a reperfusion injury or hemorrhage might be expected. If, on the other hand, no damage has been done, why risk the

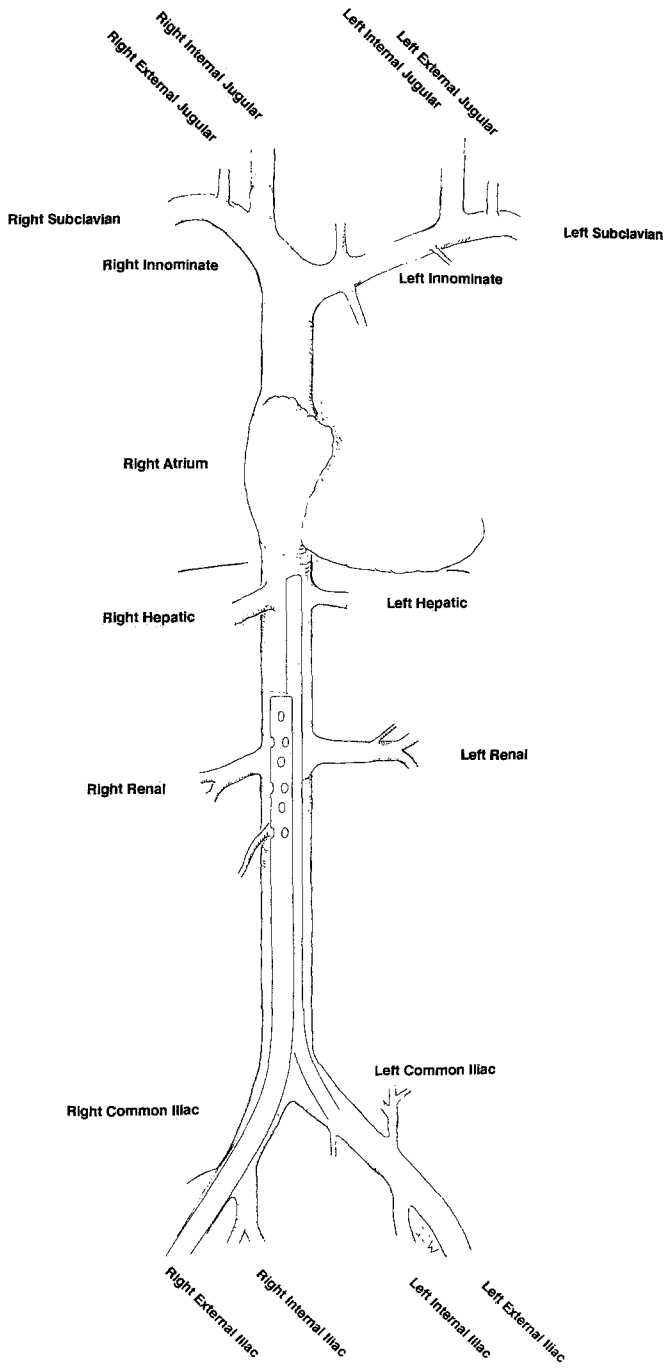

Fig. 7. Cannulation for VV ECMO as described by Gattinoni [1]. Venous drainage cannula is placed at about level of renal veins while venous return or perfusion cannula reaches just to the diaphragm

suture line that can serve as a nidus for future stenosis and platelet emboli?

The arterial perfusion cannula can also be placed from the groin, as it is in the supported angioplasty systems. This is usually a short end-hole cannula that reaches the internal iliac artery at the farthest (Fig. 4). While effective in perfusing end-organs in patients with little or no cardiac output, the aortic arch is not perfused well in patients with an effective left ventricular output [36, 58], so it is of no value in pediatric pulmonary patients in whom one can expect excellent perfusion to the lower body and continuing desaturation in the upper body. To employ groin VA ECMO, it is necessary to perfuse the aortic arch via a long arterial cannula that is not easily available (Fig. 4).

The axillary artery can also be used for perfusion (Fig. 4). The dissection is somewhat longer and the artery tends to be too small in children, although this has been an effective route in adults and should be considered in older children.

Venovenous perfusion

Venovenous (VV) perfusion can be performed in many ways. Its advantages are sparing of a major artery and avoiding the complication of possible arterial emboli. Even though we are treating lung disease, we would still prefer pulmonary to cerebral emboli. VV ECMO has been performed by cannulating the femoral vein proximally for drainage with the cannula reaching various levels in the IVC, sometimes with cannulation of the vein distally as well [42, 60]. The blood was then returned to the right atrium via a cannula in the right IJV. While this certainly allows the possibility of recirculation of oxygenated blood from the perfusion to the drainage cannula, as does all VV ECMO, return to the atrium may allow more blood to cross the tricuspid valve to the pulmonary circulation so that it will not be available to the drainage cannula.

The first clinical newborn VV ECMO that led to patient survival was done by draining the right atrium via the IJV and perfusing the iliac vein from a cannula in the femoral vein (Fig. 1) [4]. This had the disadvantage of essentially aiming the oxygenated blood from the perfusion cannula in the iliac vein at the drainage cannula in the atrium and causing increased recirculation. This technique provided excellent survival [29], but there were many local wound and leg edema problems from ligation of the femoral vein and a lack of demonstrable benefit from sparing of the carotid artery, which was responsible for this technique not being widely accepted. Similar circuits have been used in older children [53].

The excellent pulmonary results with IJV to femoral vein VV ECMO led to the development of a double-lumen VV cannula placed via the right IJV to the right atrium (Fig. 5) [3, 41]. Blood is drained via one lumen and then returned through the second, with the return oriented at right angles to the cannula so that blood will jet across the tricuspid valve to the right ventricle and thus minimize recirculation. Recirculation not only reduces the amount of oxygenated blood available to the circulation, but also decreases the efficiency of the oxygenator by decreasing the difference in oxygen content of blood entering and leaving it. This cannula is currently only available in 14 Fr size (Kendall Healthcare Products Company, Mansfield, MA, USA) and has not been applied to ECMO in older children.

VV ECMO can also be performed with groin cannulation alone. Most of the easily available cannulas are designed to provide right atrial drainage from a long cannula with side-holes placed from the groin. This can be done by open cutdown using the saphenous vein at the saphenofemoral junction so that at decannulation the

Table 1. Venous drainage that can be expected with various BioMedicus cannulas and Argyle chest tubes

Flow (l/min) 40 cm H_2O pressure gradient (gravity)	BioMedicus[a] cannulas, French sizes (50 cm with side-holes)	Argyle[b] chest tubes, French sizes
0.7	15	16
1.1	17	20
1.6	19	–
2.1	21	24
3.0	23	28
3.8	25	–
4.1	27	32
5.0	29	–
6.0	–	36

[a] BioMedicus, Eden Prairie, MN, USA
[b] Sherwood Medical, St. Louis, MO, USA

saphenous vein and not the femoral vein is ligated. We believe there are many advantages to percutaneous cannulation. It seems to us that much larger cannulas can be placed percutaneously, perhaps because the vessel is well supported by its surrounding tissues and perhaps by avoiding vessel spasm, which occurs to some extent whenever the vessel is exposed, no matter how gently it is handled. For decannulation, these cannulas can be withdrawn and hemostasis achieved by applying pressure at the site, making operative repair or ligation unnecessary.

The perfusion cannulas available are relatively short and provide for the type of VV ECMO originally done in the newborn with return of oxygenated blood to the iliac vein. This is frequently successful (Fig. 6), but in order to diminish recirculation most physicians doing adult ECMO have used the cannula arrangement of Gattinoni (Fig. 7). The venous drainage cannula in this technique is placed at about the level of the renal veins, and the longer perfusion cannula is specially designed with an end-hole placed at the junction of the IVC and the right atrium. The blood returning to the patient is thus more likely to be directed to the right ventricle and the pulmonary artery and less likely to be drained back to the circuit from which it came. It is unlikely that this would be applicable in a patient whose primary problem is poor oxygenation, since little or none of the SVC venous blood is captured by the circuit and therefore blood flows approaching the cardiac output cannot be achieved. Many patients beyound the neonatal age, however, primarily need CO_2 removal and will achieve satisfactory oxygenation with this circuit.

The choice of the venous drainage cannula is crucial to the success of ECMO. The rate of flow is most dependent on the amount of venous return available to the pump, as in the human heart. It is the surgeon's responsibility to place the largest possible cannula and, if necessary, to place additional venous cannulas from other veins to augment venous return. Table 1 reviews the pump flows that can be expected with some of the usual venous drainage cannulas for the pediatric age group. A smaller diameter is acceptable for the perfusion cannula for two reasons: there is no tendency for the wall of the vessel to occlude the cannula holes, and there is less hemolysis for a given pressure gradient when blood is passing from the lower to the higher pressure environment than when it is going from the higher to the lower pressure system.

Circuit management

The equipment used for pediatric pulmonary ECMO circuits is similar to that used in the newborn. The roller pump continues to be the gentlest to the blood. Centrifugal or vortex pumps such as the Biomedicus have theoretical advantages. A venous return monitor such as a bladder box is not required. Blood can be aspirated by the pump so that it does not need to drain by gravity. Most perfusionists and operating room personnel are familiar with its use. This type of pump, however, has many more disadvantages. Its use requires a functioning flowmeter. Care must be exercised in blood sampling as there is no low-pressure portion of the system, only high pressure after the pump and negative pressure with its threat of air embolus before the pump. The major problem, however, is the generation of heat and thrombus formation in the pump head, which can lead to significant hemolysis.

When a totally occlusive roller pump is used, some sort of venous return monitor (VRM) is required. Most centers use a collapsible silicone rubber bladder as the lowest part of the tubing circuit returning blood from the patient. This bladder is monitored in a device that activates an electronic control when the bladder begins to empty, which occurs when venous return becomes insufficient, and turns off the pump to avoid aspirating air into the circuit by pulling it out of solution in the blood or sucking it in through tubing connections. Other VRMs are becoming available that make use of pressure monitors to control the speed of the roller pump rather than just turning it on and off.

The silicone rubber, spiral wound, membrane oxygenator developed by Kolobow and manufactured by Avecor (Avecor Cardiovascular, Plymouth, MN, USA) is the only membrane lung approved by the Food and Drug Administration of the United States for long-term use. It is effective but relatively inefficient in that it requires more surface area for gas exchange than the newer hollow-fiber lungs in current short-term use in the operating room for CPB. Since the Kolobow lung does not take up very much room, it is difficult to see how this is much of a disadvantage. The silicone rubber lung also has a relatively high priming volume and resistance. The resistance can be overcome by mounting two of these lungs in parallel in the circuit. The hollow-fiber lungs are microporous and allow leakage of plasma and foaming, which has limited their use. One design is currently marketed with a heparin coating, but has not yet overcome the problem of requiring frequent oxygenator changes during a long run due to plasma leakage and failure of gas exchange.

Various types of treated circuits are under investigation to allow for less or no systemic anticoagulation with heparin. Those closest to the market involve heparin coating. There has been initial encouraging laboratory evidence and some limited clinical data indicating that they may be of use [7, 32, 35]. The newer heparin coatings use covalent bonds in contrast to the older, ionically-bonded heparin, which easily leached into the blood causing systemic heparinization. It is too early to tell whether these circuits will

Table 2. Data from ELSO registry on 285 nonneonatal children with pulmonary disease treated with ECMO

Variable	All Patients	Survivors	Nonsurvivors
Ventilator support prior to ECMO (days)	7±11	6±10	8±12
Gas exchange status prior to ECMO			
pH	7.35±0.17	7.38±0.15	7.32±0.18
$PaCO_2$ (torr)	51±22	49±22	53±22
PaO_2 (torr)	50±39	63±34	56±43
PIP (cm H_2O)	48±13	52±14	46±12
PEEP (cm H_2O)	11±5	10±6	11±5
MAP (cm H_2O)	24±8	22±7	25±8
Rate (/min)	62±75	62±75	63±75
Duration of ECMO support (h)	245±165	222±151	266±176
Medical complications (per patient)	2.4±2.1	1.6±1.6	3.2±2.2
Mechanical complications (per patient)	0.68±0.81	0.5±0.65	0.84±0.91

PIP = peak inspiratory pressure; MAP = mean airway pressure

Table 3. Complications of nonnewborn ECMO for pulmonary support in the University of Chicago/Ochsner Clinic series

	Total	Survivors	Nonsurvivors
Mechanical complications	12 (43%)	5 (33%)	7 (54%)
Hemorrhagic complications	11 (39%)	2 (13%)	9 (69%)
Other complications	14 (50%)	2 (13%)	12 (92%)

solve the bleeding problems, but it would seem likely that they must at least ameliorate it.

The patient and circuit are anticoagulated by a continuous infusion of heparin. To maintain an activated clotting time of 200±20 s, an infusion of 50 IU/kg per hour is usually required. Heparin requirements increase during the administration of fresh frozen plasma (FFP) and platelets. Most ECMO centers do not use continuous filtration for fear of causing more thrombi than are removed. We filter all administered blood and blood products and use air-elimination filters on intravenous infusions. We also use an ultrasonic air detector to alert the ECMO operator to the possibility of air entering the system. A specially trained respiratory therapist with no other duties manages the circuit continuously. A nurse manages the patient and, in contrast to neonatal ECMO, must devote all of his/her time to the ECMO patient.

Patient management

Management of the older child with pulmonary parenchymal disease on ECMO differs little from the management of the sicker neonate on ECMO. The PaO_2 can be regulated by pump blood flow and the $PaCO_2$ can be regulated by the gas flow ventilating the membrane lung. The important unsettled issues involve how to manage the native lung and how to control bleeding. Opinions as to how the patient's lung should be managed while on ECMO can be divided into two opposing camps. One advocates high PEEP and high mean airway pressure (MAP) while trying to limit PIP. This, they believe, prevents atelectasis and recruits collapsed or fluid-filled alveoli. The other group stresses lung rest to avoid the barotrauma and oxygen toxicity that appear to make ARDS irreversible by creating pulmonary fibrosis.

Most ECMO centers agree that pediatric patients with pulmonary disease require longer courses of ECMO than newborns and that bleeding will become a problem. Many options are available. We find that bleeding becomes troublesome on about the 3rd day of ECMO. It usually arises from a previously placed chest tube or operative site, although it can be from the lung, bladder, or gastrointestinal tract. We try not to operate, as our experience has been that this only creates more bleeding. We use as many nonoperative means as possible such as vasoconstrictive agents (epinephrine and phenylephrine), hemostatic agents (topical thrombin and fibrin glue), and direct pressure. We also correct, as much as possible, the coagulopathy induced by both heparin and the circuit by giving platelet transfusions to keep the platelet count over 100,000, FFP 10 ml/kg every 6 h, and vitamin K. Other components of the coagulation cascade are administered if their deficit is measureable and they are available. When bleeding persists we operate with the patient on ECMO. If bleeding persists at >10 ml/kg per hour despite all efforts, we try to take the patient off ECMO. If we feel this cannot be tolerated, we try to eliminate heparin while keeping the pump blood flow high to avoid circuit clotting [57]. It is helpful to have a second circuit primed at the bedside should clotting in the original circuit occur. Often bleeding will stop after 6 to 12 h without heparin, which may then be resumed slowly.

The use of blood and blood products can be deleterious. It is easy to massively transfuse a patient on ECMO and have this contrubute to the multiple organ failure syndrome. It is important to set limits as to how much bleeding will be accepted. It is very useful to use a hemofilter early to manage the colloid and fluid load. Also, ECMO patients frequently have renal failure in addition to pulmonary failure, which may require connecting the dialysis machine to the ECMO circuit. We have found, however, that with large-volume ultrafiltration (100 to 200 ml removed each hour) accompanied by replacement with an appropriate fluid (usually D5/0.45 normal saline) the potassium, urea nitrogen, creatinine, ammonia, and fluid balance can be controlled.

Some centers have suggested the use of open lung biopsy in the management of children on ECMO [14]. This has been done prior to ECMO in order to determine whether the process is reversible, during ECMO to determine progress and whether or not to continue, and near the end of the course to determine whether the disease is irreversible and therefore ECMO should be stopped. We would strongly argue against this practice. No pathologist has been able to make a specific and accurate diagnosis from a lung biopsy that could help determine whether or not the patient should go on ECMO. Even diagnoses such as "diffuse fibrosis" are not incompatible with recovery

and, in any event, they only report on a small part of a very large organ that is remarkable for the lack of uniformity of any process within it. Right middle lobe "hepatization" does not mean the left lower lobe is not well ventilated with "minimal thickening of alveolar septae." We find that lung biopsies only increase bleeding problems and do not really aid in decision-making. This is not to say that lung biopsy should be avoided in all patients who might become ECMO candidates: it is frequently helpful in establishing etiology and directing therapy in patients with respiratory failure, but lung biopsy has not been helpful for patients who are about to go on or are already on ECMO.

Results

The discussion of results of treating children with pulmonary parenchymal disease with ECMO is limited by the lack of concurrent control groups. In nearly all centers patients were considered ECMO candidates when they were judged clinically certain to die with continued conventional therapy rather than based on specific criteria, as is done in most neonatal ECMO centers. There is so far, however, only one published study that tries to develop perdictive criteria for the need for ECMO after the newborn period; this is from the Royal Children's Hospital in Parkville, Victoria, Australia [46]. Forty-two children aged 1 month to 18 years admitted to the intensive care unit who were mechanically ventilated for more than 12 h and received greater than 90% oxygen and had PIPs greater than 25 cm H_2O were studied. A combination of an index of ventilation and of oxygenation reliably predicted death. When the ventilation index was greater than 40 and the oxygenation index was greater than 0.4, the mortality was 77% (sensitivity 65% and specificity 74%). When the PIP was greater than 40 cm H_2O and the A-aDO_2 was greater than 580, the mortality was 81% (sensitivity 74% and specificity 79%).

The Pediatric Critical Care Study Group has implemented a multi-institutional retrospective review of ARDS mortality predictors in children. While no results are available, a consensus appears to be developing that ECMO might be offered in two situations. First (or "fast criteria") are a PaO_2 <50 mm Hg for more than 2 h when the FiO_2 is 1.0 and PEEP $\geq$5 cm H_2O. Second (or "slow criteria") are FiO_2 $\geq$0.5 and PEEP $\geq$6 cm H_2O for more than 12 h after the patient has been treated for 48 h.

Fifty-two (60%) of the 90 ECMO centers participating in ELSO treated 285 nonneonatal children with pulmonary disease with ECMO from January 1982 to September 1991 (Table 2) [40]. Most patients were placed on standard VA ECMO with neck cannulation. Diagnoses and survival included viral pneumonia (92 patients, 48% survival), ARDS (79 patients, 42% survival), aspiration (31 patients, 61% survival), and bacterial pneumonia (23 patients, 48% survival). The overall survival was 47%. Entry data for this ELSO study would certainly have predicted a very high mortality using the Royal Children's Hospital criteria noted above. The best FiO_2 was in the survivors (0.96 ± 0.09) and the lowest PIP was in the nonsurvivors (46 ± 12 cm H_2O). The Ann Arbor group, with very similar patients, had a survival (or weaning from the ventilator after decannulation) of 60%. The patients most likely to survive were younger (2.1 vs 7.1 years) and required less ventilatory support pre-ECMO (PIP 43 vs 58 cm H_2O; MAP 18 vs 27 cm H_2O, and PEEP 8 vs 12 cm H_2O) [37].

Chevalier et al. in Paris have treated 32 children with a method very similar to that of Gattinoni, using LFPPV with a rate of 4 to 6, PEEP 10 to 18 cm H_2O, and PIP 50 cm H_2O. CO_2 is removed by an extracorporeal circuit using a single atrial cannula and a nonocclusive roller pump that allows to-and-fro flow. The mean age of their patients was 36.7 months and the mean time on $ECCO_2R$ was 8.5 days. Diagnoses included postoperative RDS 4, lung transplantation 3, burn-RDS 5, AIDS 4, and ARDS 14. The overall survival was 62% [9]. The Ochsner Clinic ECMO team has treated 35 nonnewborn pulmonary patients (excluding patients with bronchopulmonary dysplasia, BPD) through November 1991 with 18 survivors. Only 1 survivor had been mechanically ventilated for more than 10 days prior to ECMO. There were no survivors among those who required an FiO_2 of 1.0 for more than 24 h prior to ECMO [11]. Doody and Ryan reported 100% survival in five patients with bronchiolitis, viral pneumonia, pulmonary hemorrhage, toxic epidermal necrolysis, and cat scratch disease using VA support in three patients and VV in two [12]. Spray et al. at Washington University Medical Center in St. Louis have used ECMO in four lung transplantation patients with two survivors. In one patient ECMO was used as a bridge to transplantion; the other required 4 days of ECMO support due to respiratory failure starting 5 h after transplantation [49]. ECMO has also been useful in the support of children following liver transplantation, with Uitvlugt et al. reporting three survivors out of four patients treated for respiratory infections [55].

Complications are common in all pediatric pulmonary ECMO series and are more common in the nonsurvivors. Glynn et al. presented a combined series of patients from the Ochsner Clinic and the University of Chicago [21]; their representative data are presented in Table 3.

Discussion

The success of ECMO in the treatment of ARDS has been variable. With recent improvements in technique, apparatus, and expertise, a feeling currently exists that certain children with pulmonary parenchymal disease will benefit from ECMO. The question as to which children these are remains unanswered. To that end, it is necessary to first determine predictors of mortality in children with respiratory failure who receive conventional therapy. With the establishment of accurate predictors of mortality, those patients who are expected to do poorly on conventional therapy may be assigned to receive rescue treatment such as ECMO in the early course of the syndrome when barotrauma and oxygen toxicity have not yet resulted in additional parenchymal damage.

Neonatal ECMO is labor-intensive; pediatric ECMO is nearly abusive. The successes that each center has had are gained at the cost of personal sacrifice on the part of every member of the team and emotional stress on nursing staff

family, and physicians. Early in the experience, patients would be taken off ECMO because there seemed to be no hope or because the parents and nurses could no longer tolerate the anxiety or the disagreeable appearance of an edematous, jaundiced, bleeding organism bearing no resemblance at all to a pretty, 5-year-old girl. The first successes in any unit are due to the dogged persistence of a physician, nurse, or parent who refuses to let the team quit. They can then look back at the first success and move on to others.

In children with pulmonary parenchymal disease, there are few short cases. One cannot use oxygen to reverse pulmonary artery hypertension or use cardiac decompression to rest the heart for 3 days: one must support the end-organs and treat the lung and wait for it to recover when in most situations the natural history of the disease is not known. For these reasons, the center with an established neonatal program is best prepared to begin pediatric ECMO. It has committed and organized teams who rotate each 8 h, unlike units that only occasionally employ ECMO and must frequently rotate 12-h shifts.

There appears to be enough evidence to state that it is reasonable for experienced ECMO teams to attempt the rescue of children dying with pulmonary parenchymal disease. Many important advances are on the horizon. The development of criteria for choosing which patients might benefit from ECMO [46] will make it easier to make the commitment to the lengthy ECMO courses frequently required. Standardization of a percutaneous cannulation technique will allow rapid application of ECMO without the sacrifice of important vascular structures. The development of techniques for limiting the amount of anticoagulation required, whether platelet-active agents, heparin-coated circuits, or regional anticoagulation of the device, should decrease the amount of bleeding and the deleterious pulmonary effects of the attendant massive transfusion. More sophisticated ECMO devices should allow some decrease in the number of personnel required to treat an ECMO patient. Given the current increase in laboratory research and clinical experience along with the growing success, it seems appropriate to predict that ECMO will become a part of the critical care of children with pulmonary parenchymal disease.

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