Medical Intelligence
Anesthesiology

Extracorporeal Membrane Oxygenation for Acute Respiratory Failure

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SUPPORT of patients who have severe acute respiratory failure (ARF) with the extracorporeal membrane oxygenator (ECMO) has been used for ten years.† Perfusion with a membrane lung corrects hypoxemia and hypercapnia while relieving the patient's lungs of their primary burden of respiratory gas exchange. During perfusion the previously elevated Fio2 and ventilator pressure, which may cause pulmonary injury, can be lowered, while access to the airway permits safe tracheal suctioning and pulmonary lavage.‡ In addition, venoarterial perfusion provides hemodynamic support.§ Clinical experience to date has shown that membrane lung bypass for one to three weeks provides time for the injured lung to heal in some cases, but in most there has been no evidence of recovered function.¶ Several technical advances have been achieved secondary to long-term ECMO support.† This article reviews relevant membrane lung technology, modes of clinical perfusion and cannulation, hemodynamic adaptation to bypass, and management of hematologic problems. Pulmonary disorders that have been alleviated during bypass are discussed.

Membrane Lung Technology

The membrane lung exchanges respiratory gases across polymer membranes.⁵ As these gases diffuse along a partial pressure gradient, the blood is oxygenated and carbon dioxide is removed. The most common commercially available oxygenators consist of thin blood films sandwiched between parallel plates of silicone rubber; examples include the Landé-Edwards, K Kolobow spiral coil,⁷–⁹ Bramson-IMS⁴⁹ and Travenol silicone membrane lung¹¹ (see Drinker's comprehensive review of the history and theory of membrane lungs¹²).

The following are some of the many well-studied physical and chemical determinants of O₂ and CO₂ transport in parallel-plate gas exchangers.¹³–¹⁶

O₂ and CO₂ Transfer Rates:

are directly related to membrane surface area, diffusivity and solubility of the two gases in the membrane.

are inversely related to the thickness of the membrane and adjacent stagnant plasma and gas boundary layers.

are limited by uneven distribution of gas and blood flow (V/Q disparity).

increase with blood flow rate when measured with constant input blood hemoglobin concentration, temperature, and gas tensions (Fig. 1).

reach a plateau reflecting the resistance of the blood boundary layer.

O₂ Transport:

is primarily impeded by the plasma boundary layer due to low solubility of O₂ in plasma.

is a function of input blood Pao₂, hemoglobin concentration, and oxygen partial pressure in the gas phase.

CO₂ Transport:

is a function of input blood Paco₂ and gas phase Pco₂.¹⁷

ABBREVIATIONS

ARF = acute respiratory failure
AV = arteriovenous
ECF1 = extracorporeal blood flow rate index
ECMO = extracorporeal membrane oxygenator
FFSR = filler-free silicone rubber
PEEP = positive end-expiratory pressure
Paco₂ = mixed venous oxygen tension
Qb = pulmonary blood flow
Qo/Qa = right-to-left shunt
VA = venous arterial
Vd/Vt = ratio of deadspace to tidal volume
V/Q = ventilation/perfusion ratio
VV = venovenous

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is modified by ventilation rate, *i.e.*, at low gas flow rates exchange is limited, can lead to hypocarbia during bypass with large-surface-area lungs or small body mass. This can be avoided by ventilating the membrane lung with 3–5 per cent CO₂, is sufficient to maintain physiologic arterial concentrations with large surface areas (3–6 m²) of thin silicone rubber membranes (125 μm) or smaller surface areas of ultrathin polymer membranes (0.5 μm) cast on microporous substrates.

The surface area needed for bypass depends on both the quantity of respiratory gas to be exchanged and the efficiency of the membrane lung. For example, a Kolobow spiral coil lung used for partial respiratory support of a normothermic patient requires a minimum area of 0.5 m²/10 kg body weight.

Recent oxygenator design has succeeded in increasing oxygen transport by facilitating mixing at the blood boundary layer. A whirling microporous disc in the Searle membrane oxygenator is used for short-term surgical bypass. The Oxford–Bellhouse design induces mixing (“secondary flows”) with repeated membrane furrows. High efficiency devices have not been employed for long term clinical bypass. New membrane materials and lung designs are being developed to increase gas exchange efficiency and diminish thrombogenicity.

**CIRCUIT TECHNOLOGY**

A pump is necessary to overcome the hydraulic resistance of the membrane lung, tubing, and systemic vasculature. Most clinical perfusions are performed with roller pumps. Extruded polyurethane tubing is exceedingly strong and withstands several weeks of occlusive pumping. Ventricle and centrifugal-type pumps are being investigated.

A representative bypass circuit is shown in figure 2. Bubbles in venous blood caused by suction are avoided by using large-bore cannulas and tubing, and a servo-controlled reservoir automatically stops the pump when gravity drainage of blood is inadequate. Use of these techniques in prolonged perfusion has eliminated hemolysis and erythrocyte sequestration.

Silicone rubber tubing is commonly used for circuitity. When coated with filler-free silicone rubber (FFSR) or pure silicone gum and irradiated, the tubing provides a smooth, additive-free, highly thromboresistant surface without leachable components.

Specially designed thin-walled cannulas of segmented polyurethane reinforced with a stainless steel spring have been constructed and used for high-flow venous drainage and arterial return.
These cannulas are flexible and non-kinking. They are valuable for umbilical cannulation in the newborn and for retrograde arterial cannulation of the adult aortic root (see venoarterial perfusion section).

The prime volume needed for a 3.5 m² FFSR Kolobow spiral coil membrane lung for partial respiratory support is 1,300 ml of heparinized (4,500 units/l) whole blood. To prime membrane oxygenation circuits without bubbles, it is necessary either to prime the circuit with CO₂ or to prime in a vacuum. Preliminary studies indicate improved platelet lifespan after perfusion with bubble-free circuits.

The following are some additional important design considerations: Direct gas-blood interfaces must be completely eliminated. The circuit should have ports for infusion and sampling and provisions for changing pump chambers and artificial lungs without interrupting bypass. Most investigators do not use in-line 40-μm filters, as the membrane lung filters large thrombi. A heat exchanger is not needed for bypass; core temperature can be easily maintained at 32 to 37°C by regulation of the ambient temperature. The gas ventilating the membrane lung is heated and humidified.

**Perfusion Routes and Extracorporeal Gas Exchange**

Several cannulation techniques have been used for extracorporeal gas exchange: they differ in their effects on \( P_{aO_2} \) in different parts of the body, hemodynamic alterations, and clinical usefulness.

**VENOUS-VENOUS (VV) Perfusion**

Venous blood is drained from the inferior vena cava via the common femoral vein, oxygenated in the membrane lung, and returned to the superior vena cava (fig. 3A). Because two incisions are necessary for cannulation, nursing care and chest physiotherapy are more difficult to perform.

Gas exchange is shared by the natural lung and the artificial lung. A major fraction of the patient's oxygen uptake can be provided without changing pre-bypass cardiac output. Mixed venous oxygen tension (\( P_{vO_2} \)) can be elevated to 40–50 mm Hg. Total oxygen consumption may increase with bypass, accompanied by an increase in cardiac output, which may be due to improved myocardial function at elevated \( P_{aO_2} \). Direct circulatory support cannot be provided by VV perfusion. In the absence of an anatomic right-to-left shunt, changes of natural pulmonary function during bypass directly modify \( P_{aO_2} \); thus, changes of pulmonary function can be easily monitored.

Kolobow has described VV perfusion carried out for 16 days in sheep, and several groups have performed extensive clinical VV perfusion. Venous recirculation of returned oxygenated blood into the drainage catheter (i.e., extracorporeal recirculation) is usually not a limiting factor, but Hill prefers right ventricular blood return to avoid this possibility. White described prolonged VV perfusion in five infants who had hyaline membrane disease, draining blood from the right atrium via the internal jugular vein and returning blood to the umbilical vein. None of the infants survived.

**VENOARTERIAL (VA) Perfusion**

Venous blood is drained from the inferior vena cava, oxygenated, and returned to the aorta and femoral artery. Drainage and return cannulas can be inserted via the same inguinal incision (fig. 3B). The distribution of returning blood during VA bypass varies with the position of the arterial cannula outflow in the aorta, cardiac output, and the extracorporeal blood flow rate. Low-flow VA bypass (<30 per cent of pre-bypass cardiac output) with femoral-artery return rarely, if ever, succeeds in distributing well-oxygenated blood above the diaphragm. Improvement in oxygenation of the upper body is due to decreased \( Q_s/Q_h \) (via cardiac output reduction) and increased \( P_{vO_2} \). Increasing the extracorporeal blood flow rate advances the well-oxygenated stream into the thoracic aorta. Even at a high extracorporeal blood flow rate (>80 per cent of pre-bypass cardiac output), the coronary
bed may be perfused with hypoxic blood from the natural lung. Unless diagnostic arteriography is performed, one is uncertain whether the P_O₂ of blood in the radial artery reflects primarily membrane or pulmonary gas exchange.

Oxygenated blood returning to a right axillary or internal carotid artery cannula allows proximal aortic distribution of oxygenated blood at a lower extracorporeal flow rate. However, the coronary arteries may still be perfused by hypoxic pul-

**Fig. 3.** Common routes for prolonged bypass. A, right, venovenous perfusion. B, below left, venoarterial perfusion with femoral artery return. C, below center, venoarterial aortic root perfusion. D, below right, mixed venovenous and venoarterial perfusion. This figure is reprinted from Zapol et al. by permission of the author.
monary blood. Because the axillary or carotid artery accommodates only a small catheter, high pump pressures are necessary. This increases the mechanical danger of extracorporeal perfusion. In addition, proximity of the axillary artery to the brachial plexus increases the hazard resulting from local sepsis following prolonged cannulation. Bartlett has reported using the internal carotid artery for arterial return in several of nine newborns and four children who had ARF, of whom four survived. The carotid artery was ligated upon completion of perfusion.

Placement of the return cannula tip at the aortic root (fig. 3C) permits uniform oxygenation of the systemic circulation, and the coronary arteries are perfused during diastole by extracorporeal oxygenated blood. Complete aortic root mixing of ECMO and pulmonary blood streams is established with this route. Thus, left ventricular blood gas tensions and therefore natural pulmonary function can be estimated during bypass from gas tensions of arterial blood drawn at any site (fig. 4). With a spring-reinforced (8.1 mm OD, 7.1 mm ID) urethane cannula, flows of more than 5 l/min are possible with less than 75 mm Hg pressure difference across the cannula.

VA perfusion offers the hemodynamic advantages of partial bypass for circulatory support and decreased pulmonary blood flow. We prefer this route when pulmonary arterial pressures are high or right ventricular dysfunction is present. We have rarely observed a reduction in pulmonary arterial pressure following VA perfusion, possibly because our patients have had extensive pulmonary vascular injuries or because of our use of lower bypass flow rates. Unlike VV perfusion, decreases of cardiac output by VA perfusion may alter the gas exchange characteristics of the diseased lung. Hill and LeMaire have reported that VA perfusion occasionally decreases mean pulmonary arterial pressure in severe acute respiratory failure. When bypass is associated with a decrease in pulmonary blood flow, then the intra-pulmonary right-to-left shunt ($Q_s/Q_p$) may decrease (fig. 5). This blood flow-dependent increase in pulmonary efficiency must not be confused with improvement of pulmonary function due to resolution of disease. Markedly reduced pulmonary blood flow may promote thrombosis in the injured lung, as suggested by Ratliff.

**MIXED VENOVENOUS AND VENOARTERIAL (VVA) PERFUSION**

During concomitant venovenous and venoarterial perfusion, oxygenated blood is returned to the aorta and the superior vena cava (fig. 3D). Like VV
but not VA perfusion, this technique has the disadvantage of requiring two incisions. In addition, it requires the insertion of a flowmeter to measure the blood flow directed to each route. Hill has recently favorably reviewed the hemodynamic and respiratory effects of this clinical technique, while Falke has demonstrated in sheep that this technique provided optimal $P_{aO_2}$ and $P_{aC_0}$ when $Q_s/Q_p > 50$ per cent.\textsuperscript{32,41}

**Arteriovenous (AV) Perfusion**

Arterial blood is propelled either by the heart or by a pump through a membrane lung and returned to a vein.\textsuperscript{32} Low-flow-resistance lungs can be perfused without a pump; this accounts for the appeal of this technique. Important bypass oxygen exchange rates can be obtained only during severe arterial hypoxemia, when a large increment of oxygen can be transferred across the membrane lung. If total peripheral blood flow is to remain unchanged during bypass, the heart must provide the additional flow to the oxygenator. Inability to increase cardiac output has limited the application of AV bypass in adult patients who have acute pulmonary disease. Neonates with hyaline membrane disease with a dilated ductus arteriosus and parallel ventricular pumping have been perfused with this cannulation technique via the umbilical vessels.\textsuperscript{32,33} The presence of interatrial and ductal blood shunts in newborns makes it difficult to assess pulmonary function during bypass.

**Hemodynamic Response to Partial Bypass**

The circulatory response of the ARF patient to bypass is complex, and depends upon the site of cannulation, extracorporeal blood flow rate, distribution of oxygenated blood, and metabolic status (hypoxemia, acidosis, etc.). In addition, positive airway pressure, blood volume, drugs such as $d$-tubocurarine or morphine, and isotropic and vasoactive agents will modify the circulatory response to bypass. Disease-related changes in cardiac function, as well as injury to the pulmonary and systemic vascular beds, may also alter the circulatory response.

Snider measured the normoxic circulatory response to bypass in anesthetized animals.\textsuperscript{3} Table 1 illustrates the hemodynamic changes with three bypass modes. The magnitude of change is proportional to extracorporeal blood flow rate. With a large-bore venous drainage cannula, more than 80 per cent of the pre-bypass cardiac output can be pumped from vein to artery. VA bypass partially empties and AV bypass increases the filling of the right ventricle. Ventricular filling determines cardiac output by the Frank-Starling mechanism.\textsuperscript{34} Heart rate, afterload, and contractile state are modified by changes in arterial baroreceptor stimulation.\textsuperscript{35} Decreased cardiac output at constant systemic blood flow during VA bypass in animals is accompanied by diminished end-diastolic right and left ventricular volumes, bradycardia, decreased myocardial contractility, narrowed arterial pulse pressure, increased mean arterial pressure, and decreased pulmonary arterial pressure. Increased cardiac output with AV bypass is accompanied by opposite changes.

In contrast, VV pumping does not modify hemodynamic values of normoxic anesthetized animals.\textsuperscript{36} The only measurable effects are altered venous blood gas tensions.

The effect of blood volume on man's circulatory response to extracorporeal bypass has not been studied. Canine VA perfusion indicates that increased cardiac outputs and extracorporeal blood flow rates occur in hypervolemic states, while cardiac output and extracorporeal flow rate are decreased during hypovolemia.\textsuperscript{36} Regional blood flow has not been studied during prolonged bypass.

Hypoxemia and hypercapnia are common in

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**Table 1. Hemodynamic Response to Healthy, Normoxic ECMO (3,*)**

<table>
<thead>
<tr>
<th></th>
<th>VA</th>
<th>AV</th>
<th>VV</th>
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</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total systemic flow</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean pulmonary arterial pressure</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Mean systemic arterial pressure</td>
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<td></td>
</tr>
<tr>
<td>Contractility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricular end-diastolic volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>


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1 Martinez J: Personal communication, 1976.
severe ARF. Hultgren describes the major hemodynamic responses to alveolar hypoxia as tachycardia, increased cardiac output, and pulmonary hypertension with unchanged systemic arterial blood pressure. Hypoxemic changes become marked when Pao2 is less than 40 mm Hg. During severe ARF hypercapnia can cause hypertension and elevated peripheral resistance. Hemodynamic changes accompanying bypass for ARF may be partly due to the amelioration of hypoxemia and hypercapnia.

PULMONARY VASCULAR RESISTANCE

Severe ARF is generally accompanied by a twoto fivefold increase in pulmonary vascular resistance. Bachofen and Weibel used morphometric techniques and demonstrated reduced alveolar vascular volume in specimens of lung after severe clinical ARF. Zapol et al. performed silicone rubber polymer casting of human lungs following VA bypass and demonstrated widespread occlusion of the pulmonary vascular bed (figs. 6 and 7). The causes of diffuse vascular obstruction are poorly understood, yet its clinical consequences are clear: pulmonary hypertension, increased right ventricular dysfunction, and an inability to lower pulmonary arterial pressures significantly despite a 50 per cent reduction of pulmonary blood flow rate.

MEASUREMENT OF PULMONARY BLOOD FLOW

Accurate measurements of cardiac output during VA and VV bypass may be difficult to obtain. Right atrial injection of indicator can cause diversion of part of the bolus into the extracorporeal drainage cannula (figs. 8A). Advancing the injection site into the right ventricle minimizes this problem (fig. 8B). Indicator dilution techniques are usually accurate when right ventricular or pulmonary-artery injection is performed during VV bypass or VA bypass with aortic root return; they are often erroneous when performed during VA femoral perfusion because the aorta is no longer a homogeneous compartment. Using a thermal indicator with pulmonary-artery temperature monitoring allows estimation of right ventricular end-diastolic volume and ejection fraction.
COAGULATION CONTROL

Although hemolysis and protein denaturation are minimal during membrane lung bypass, thrombocytopenia and hemorrhage are problems caused by both pulmonary disease and bypass. 62-66 Many patients who have severe acute respiratory failure develop thrombocytopenia (platelet count <100,000/μl). Diffuse intravascular coagulation (low platelet count, elevated partial thromboplastin time and fibrin and fibrinogen degradation products) is present in 70 per cent of ARF patients. 67 All severe ARF patients studied have had shortened platelet lifespans and increased platelet turnovers. 67

Plasma coagulation factors are maintained during prolonged bypass in sheep with minimal fibrin and fibrinogen breakdown, but both sheep and human platelet counts decrease by 50-75 per cent after 24 hours, and 51Cr-labelled platelet lifespan is markedly shortened. 63,66 Platelet aggregation in the bypass circuit and removal by the liver and spleen have been suggested as causes. 64

For safe clinical perfusion, the following factors appear necessary to maintain adequate circulating platelet levels and minimize hemorrhage:

1) Filler-free silicone, polyurethane or other highly thromboresistant materials must be used for pump chambers, tubing, connectors and membrane lungs. 28,57

2) CO2 or vacuum prepriming of the circuit and lung is necessary to remove all air bubbles. 57

3) Extensive electrocautery of cannulation sites should be done to minimize surgical bleeding.

4) Initial anticoagulation with 100 units heparin/ kg body weight at the time of cannulation must be followed by precise control of heparin infusion to maintain the activated coagulation time (ACT) at 120–150 seconds (normal 90–110 seconds). 4,6,8,9 The ACT measures kaolin-activated whole-blood clotting time and is a rapid method of monitoring the status of anticoagulation.

These techniques minimize major bleeding during bypass. Usually one unit of blood is
transfused daily to replace sampling loss. Minor gastric bleeding usually ceases with iced saline lavage. All patients are given antacid therapy. Platelet transfusions should be reserved for the treatment of persistent oozing. Transfusion of 6–10 platelet units usually stops such bleeding. Small laparotomy and thoracotomy incisions have been performed during bypass without blood loss when extensive electrocautery was used.

**Patient Selection and Results**

Patients with severe ARF selected for perfusion generally have compliances <35 ml/cm H₂O and bilateral diffuse opacification of the chest radio-

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**Fig. 8.** A, above, schema showing pathway of indicator steal during venovenous or venoarterial perfusion with right atrial injection of indicator. Standard Swan-Ganz thermistor catheter. Reprinted from Snider et al. with permission of the author and publisher.

B, below, schema showing right ventricular indicator injection. Modified Swan-Ganz catheter. The tricuspid valve shields the injectate from the drainage cannula. A valid cardiac output measurement can be obtained with this technique. Reprinted from Snider et al. with permission of the author and publisher.
### Table 2. Long-term Survivors of Partial Perfusion for Respiratory Failure

<table>
<thead>
<tr>
<th>Patient’s Age (Years)</th>
<th>Route</th>
<th>Blood Flow (l/min)</th>
<th>Duration (Days)</th>
<th>Pulmonary Disease</th>
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<tbody>
<tr>
<td>Hill et al.(^{88})</td>
<td>24</td>
<td>VA</td>
<td>3 - 3.6</td>
<td>5</td>
</tr>
<tr>
<td>Hill et al.(^{49})</td>
<td>19</td>
<td>VA</td>
<td>3.8</td>
<td>5</td>
</tr>
<tr>
<td>Geelhoed et al.(^{77})</td>
<td>36</td>
<td>VV</td>
<td>2.3</td>
<td>5</td>
</tr>
<tr>
<td>Hanson et al.(^{79})</td>
<td>25</td>
<td>VA</td>
<td>2.3</td>
<td>3</td>
</tr>
<tr>
<td>Newhall et al.(^{86})</td>
<td>12</td>
<td>VV</td>
<td>2</td>
<td>9.5</td>
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<tr>
<td>Gannon(^{*})</td>
<td>46</td>
<td>VA</td>
<td>1.2 - 2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Zapol et al.(^{78})</td>
<td>37</td>
<td>VA</td>
<td>2.4</td>
<td>5</td>
</tr>
<tr>
<td>Hill et al.(^{49})</td>
<td>27</td>
<td>VVA</td>
<td>4 - 5</td>
<td>3.5</td>
</tr>
<tr>
<td>Hill et al.(^{49})</td>
<td>32</td>
<td>VVA</td>
<td>4 - 5</td>
<td>3.5</td>
</tr>
<tr>
<td>Nicoloff (^{f})</td>
<td>21</td>
<td>VA</td>
<td>4 - 5</td>
<td>3</td>
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<tr>
<td>Goulon et al.(^{102})</td>
<td>35</td>
<td>VA</td>
<td>2 - 3</td>
<td>2</td>
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<tr>
<td>Goulon et al.(^{102})</td>
<td>55</td>
<td>VA</td>
<td>2 - 3</td>
<td>2</td>
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<tr>
<td>Edmunds (^{f})</td>
<td>4</td>
<td>VA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Zapol</td>
<td>37</td>
<td>VA</td>
<td>2 - 3</td>
<td>3</td>
</tr>
<tr>
<td>Cooper et al.(^{103})</td>
<td>20</td>
<td>VA</td>
<td>2 - 3</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^{*}\) Gannon PG: Personal communication, 1976.
\(^{f}\) Nicoloff D: Personal communication, 1976.
\(^{f}\) Edmunds LH: Personal communication, 1976.

Specific diagnosis early in the course of ARF. For this reason open lung biopsy should be considered in all cases.\(^{73,74}\) Patients who have posttraumatic pulmonary insufficiency,\(^{76}\) fulminant gram-negative sepsis and pneumonia,\(^{78,79}\) Pneumocystis carinii pneumonia,\(^{77,78}\) and Goodpasture’s syndrome with intrapulmonary bleeding\(^{80}\) have recovered during bypass and survived (see table 2). Influenza pneumonia and the pathologic abnormalities caused by aspiration do not appear to heal on bypass, and most patients progress to total pulmonary failure.\(^{80}\)

Contraindications to bypass include active hemorrhage, disseminated malignancy, advanced age, chronic or irreversible pulmonary insufficiency, and major neurologic or other organ failure. A marked increase in pulmonary vascular resistance (>3 mm Hg min/l) signals extensive obliteration of the pulmonary vasculature and may contraindicate perfusion.\(^{78}\) Patients who have had pulmonary disease for more than two weeks are unlikely to heal during one to two weeks of bypass. Renal failure is not a contraindication; concomitant hemodialysis and membrane lung perfusion have been performed successfully.\(^{79}\) Patients who have recently undergone major operations or trauma can be perfused successfully if 6–12 hours are allowed after the insult to achieve hemostasis.

Prognostic criteria are necessary in order to select ARF patients who have poor prognoses early in their course, thereby minimizing the effects of barotrauma and oxygen toxicity. Prognostic indices for adult ARF have not been accepted by respiratory physicians because of variations in center experience and the small numbers of patients who have various diseases.\(^{81}\) Multivariate selection indices\(^{82}\) that include compliance and pulmonary vascular resistance, as well as gas exchange values in specific pulmonary diseases, are needed.

A collaborative randomized study is now in progress to investigate the efficacy of extracorporeal membrane oxygenation (ECMO) for support of severe ARF.\(^{83}\) The selection criteria specified to enter patients into this study are based solely on arterial hypoxemia (see table 3). Two criteria are used, a rapid-selection criterion for choosing the quickly deteriorating ARF patient who has a poor prognosis, and a slow-selection criterion indicating poor pulmonary function despite 48 hours of intensive ventilator therapy.

Early results from this collaborative study indicate that there is a 90 per cent mortality rate for ARF patients treated with either mechanical ventilator or bypass. Thus, there is no difference

### Table 3. NHLBI Randomized ECMO Study (Patients’ Ages 12–65 Years, during Optimum Mechanical Ventilation)\(^{83}\)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Notes</th>
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<tr>
<td><strong>Fast-selection criteria</strong></td>
<td>As soon as patients are studied, when</td>
</tr>
<tr>
<td>P&lt;sub&gt;1&lt;/sub&gt; &lt; 50 mm Hg (three measurements over a two-hour period)</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;C&lt;/sub&gt; = 30–45 mm Hg</td>
<td></td>
</tr>
<tr>
<td>F&lt;sub&gt;1&lt;/sub&gt; = 1.0</td>
<td></td>
</tr>
<tr>
<td>PEEP ≥ 5 cm H&lt;sub&gt;2&lt;/sub&gt;O for 5 minutes</td>
<td></td>
</tr>
<tr>
<td><strong>Slow-selection criteria</strong></td>
<td>After 48 hours of intensive medical care with conventional ventilator therapy, when</td>
</tr>
<tr>
<td>P&lt;sub&gt;1&lt;/sub&gt; &lt; 50 mm Hg (three measurements over a 12-hour period)</td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;C&lt;/sub&gt; = 30–45 mm Hg</td>
<td></td>
</tr>
<tr>
<td>F&lt;sub&gt;1&lt;/sub&gt; = 0.6</td>
<td></td>
</tr>
<tr>
<td>PEEP ≥ 5 cm H&lt;sub&gt;2&lt;/sub&gt;O for 15 minutes</td>
<td></td>
</tr>
<tr>
<td>Q&lt;sub&gt;1&lt;/sub&gt;/Q&lt;sub&gt;S&lt;/sub&gt; &gt; 30 per cent at F&lt;sub&gt;1&lt;/sub&gt; = 1.0 and PEEP = 5 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
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</table>
in survival rates for bypass or medically treated ARF patients despite selection early in their courses. At present only 80 patients have been treated, and a large fraction of these had viral pneumonia. According to a recent comprehensive review, 250 patients have undergone partial perfusion for ARF, with 13 per cent survival.\(^1\)

The ability of bypass to support life during severe ARF is shown by figure 9. Death in the ECMO-treated group follows cessation of bypass because the pulmonary injury has progressed to total pulmonary failure. ECMO maintains body perfusion and gas exchange but cannot heal the injured lung. Only a few pulmonary diseases appear capable of rapid reversal during bypass, with healing and functional recovery (table 2).

It is likely that the approach to future extracorporeal perfusion will widen the scope of therapy by providing bypass for patients who have less severe acute pulmonary injuries (e.g., 50 per cent lethal) to decrease the harmful effects of mechanical ventilation, maintain circulatory stability, and allow therapeutic maneuvers not otherwise possible, e.g., pulmonary lavage.\(^2\) We must learn whether early ECMO therapy can prevent progression of ARF to intractable hypoxemia.

**Current Areas of Research**

For extracorporeal membrane oxygenation to improve survival, a number of problems in the therapy of acute respiratory failure must be solved. The membrane lung can support gas exchange for as long as three weeks, but the lung is frequently destroyed. Infection, particularly from gram-negative bacteremia, rapidly destroys pulmonary vasculature and architecture, often making repair impossible.\(^2\) Prevention and more effective therapy of pulmonary infection are major problems to be resolved if survival figures are to be improved. Attempts have been made to nebulize prophylactic antibiotics into the airway.\(^8\) Pulmonary lavage for alveolar disease (*Pneumocystis carinii* pneumonia, pulmonary alveolar proteinosis, etc.) improves pulmonary function.\(^3\) We do not know whether lavage can effectively deliver antibiotics or other agents to, or safely remove debris from, the injured pulmonary interstitium.\(^6\)

Right ventricular function, estimated clinically by measuring ejection fraction using thermal washout,\(^6\) is often depressed in severe ARF.\(^4\) Pulmonary hypertension is common, and inotropic support is often necessary to ensure adequate cardiac output without excessive right ventricular filling pressures.\(^5\)

Irreversible diffuse pulmonary vascular obliteration is widespread and progressive in severe ARF.\(^6\) Its etiology is not clear, but microembolism,\(^7\) thrombosis, interstitial compression by edema,\(^8\) hemorrhage,\(^9\) and fibrosis and endothelial swelling\(^10\) are all possible sources. Several major questions concerning the interaction of bypass with the damaged pulmonary microcirculation remain to be answered. For example, it is important to know whether VV perfusion with maintenance of pulmonary blood flow is beneficial when compared with VA perfusion.

The optimum ventilatory management of bypassed patients has not been established. During bypass, patients are ventilated with higher PEEP (10–20 cm H\(_2\)O) and lowered tidal volume, peak inspiratory pressure and inspired oxygen concentration. Whether such maneuvers are conducive to repair of the damaged lung is uncertain. Alternate methods of airway management during bypass (infrequent low-pressure ventilation, static inflation, or constant ambient pressure) need to be studied.

The repair processes of the damaged lung need further study. Early clinical studies to ameliorate pulmonary fibrosis and sepsis during bypass have been initiated. $\beta$-Aminopropanitrile, an inhibitor of collagen cross-linking, has been administered in order to modify the course of pulmonary fibrosis\(^11,12\); agents that prevent collagen synthesis, cis-4-hydroxyproline and L-3,4-dehydroproline, need to be studied.\(^13,14\)

Unilateral pulmonary homotransplantation followed by eventual removal of the transplant has been proposed for patients unable to regain pulmonary gas exchange after one to three weeks of ECMO, but there is little clinical experience with this technique.\(^15,16\) One recent case demonstrated that unilateral transplantation will allow weaning from bypass.\(^1\) Difficulty in procuring and harvesting a donor lung combined with nearly universal pulmonary infection in ECMO patients limits the potential of homotransplantation.

In summary, for carefully selected acute pulmonary diseases, partial perfusion with a membrane lung allows safe patient management, lung repair, and successful weaning from bypass. Although

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\(^1\) Snider MT: Personal communication, 1976.

\(^2\) Thomas A: Personal communication, 1976.
temporary use of the artificial lung does not cure respiratory failure, it now provides a powerful clinical tool to increase the spectrum of pulmonary therapeutics, and to expand our understanding of acute respiratory failure. In the future it may provide a pathway towards lung replacement with a prosthesis.  

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