

Extracorporeal Membrane Oxygenation for Nonneonatal Acute Respiratory Failure

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Hypothesis: Extracorporeal membrane oxygenation (ECMO) is effective in nonneonatal acute respiratory failure under certain circumstances.

Design: Retrospective medical record review.

Setting: The intensive care unit of a tertiary care hospital.

Patients: Thirty-four nonneonatal patients (mean age, 22 years; range, 8 days to 56 years), with ratios of the PaO₂ to the fraction of inspired oxygen persistently below 70, who were treated with ECMO after maximal ventilator therapy had failed (mean time of ventilator therapy, 6.9 days; range, 1-41 days). The mean ECMO duration was 304 hours (range, 56-934 hours). Patients were grouped into 7 categories based on their diagnosis: sepsis or sepsis syndrome (n = 3), bacterial or fungal pneumonia (n = 10), viral pneumonia (n = 5), trauma or burn (n = 2), inhalation injury without burn (n = 1), immunocompromised state (due to transplantation or chemotherapy) (n = 8), and acute respiratory failure of unknown origin (n = 5).

Main Outcome Measure: Survival to hospital dis-

charge following ECMO therapy.

Results: Overall survival was 53% (18 patients). All 6 patients (100%) with viral pneumonias or isolated inhalation injuries survived. Of 13 patients with bacterial pneumonia, sepsis, or sepsis syndrome not complicated by multiorgan failure, 10 (77%) survived. In contrast, all but 1 of the immunocompromised patients died. Survival in patients who were intubated for less than 9 days before ECMO was 64%, whereas survival fell precipitously to 22% for patients who experienced mechanical ventilation for 9 or more days before the implementation of ECMO. Finally, the proportion of patients who died while receiving ECMO therapy was greater when the ECMO duration exceeded 300 hours (62% vs 38%; $P < .05$).

Conclusions: Nonneonatal survival with ECMO therapy is strongly dependent on the diagnosis. Pre-ECMO intubation for less than 9 days had little effect on survival. Survival rates decreased when the length of time of receiving ECMO exceeded 300 hours.

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ACUTE RESPIRATORY failure (ARF) in nonneonatal patients is an infrequent occurrence with devastating consequences. Although fewer than 2% of all admissions to intensive care units are complicated by severe ARF, mortality rates reported in the pediatric and adult literature^{1,2} exceed 80%. Conventional mechanical ventilatory support is designed to improve gas exchange without worsening the underlying lung injury. The support these critically ill patients require, however, often exceeds the supplemental oxygen, positive end-expiratory pressure (PEEP), and positive pressure ventilation limits that have been shown to cause irreversible damage and fibrosis of the lung parenchyma.^{3,4}

Extracorporeal membrane oxygenation (ECMO), introduced successfully in 1972,⁵ has been most commonly used as a means of cardiopulmonary support for patients with recoverable pulmonary insufficiency

in whom maximal conventional therapies were exhausted. Generally accepted as an alternative method of ventilatory support in neonates, it has only recently begun to attract advocates of its use in nonneonatal, noncardiac patients.⁶⁻⁹ Most recently, in a retrospective review, Green et al⁹ showed an ECMO-dependent improvement in survival for 331 pediatric patients aged 13 days to 18 years from 32 hospitals. Still, many critics¹⁰ argue that ECMO remains a futile or expensive technology that extends intensive care unit admissions but offers little more for outcome than current optimal therapies do. The controversy has spurred the users of ECMO technology to review current management schemes frequently and to provide evidence for changing them based on experience. These reviews have also provided further insight into identifying when ECMO has ceased to be beneficial for the subset of patients described here.

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PATIENTS AND METHODS

Between February 1, 1990, and April 30, 1998, 34 patients aged 8 days to 56 years with refractory ARF were consecutively treated with venoarterial or venovenous extracorporeal lung support in the neonatal, pediatric, and adult intensive care units at the Massachusetts General Hospital, Boston. Patients were identified retrospectively by reviewing office records from the pediatric surgical service ECMO database. The hospital medical record for each patient was reviewed, and pertinent information was recorded. A favorable outcome was defined as patient survival and discharge from the hospital.

Patients were considered for enrollment using a modification of Extracorporeal Life Support Organization criteria¹¹; all patients were treated with ECMO after severe ARF developed and maximal ventilator therapy that required prolonged oxygenation with 100% oxygen failed. The patients had mean \pm SD ratios of PaO₂ to the fraction of inspired oxygen of 85.0 \pm 22.9 for survivors and 56.9 \pm 4.8 ($P=.27$) for nonsurvivors. They were considered for ECMO therapy only after all septic foci had been drained, pulmonary air leaks were managed with thoracostomy tubes, and all identified infections were treated with appropriate antibiotic therapy.

Patients were separated into 2 groups: survivors ($n = 18$) and nonsurvivors ($n = 16$). The characteristics for these patients—age, the duration of ECMO therapy, ventilatory support variables before ECMO therapy, and laboratory values—are shown in **Table 1**.

Ventilator management while receiving ECMO was directed at limiting airway pressures by maintaining peak inspiratory pressures of less than 30 cm H₂O and PEEP between 20 and 24 cm H₂O. Large air leaks were treated with no PEEP and minimal ventilation until they resolved. Anticoagulation maintained activated clotting times at 180 \pm 20 (mean \pm SD) seconds for all patients.

Statistical analyses on the data presented in Table 1 were performed using the Student *t* test. To determine whether age was a significant predictor of outcome, analysis of variance was performed.

The purpose of this retrospective study is to report the results of the ECMO experience in nonneonatal patients with severe ARF. In addition, the data presented here provide confirmatory evidence that ECMO can be beneficial in this patient population. Finally, this report may aid in the design of more appropriate selection criteria for critically ill patients with ARF for whom conventional therapy has failed.

RESULTS

Thirty-four nonneonatal patients received ECMO support during the 8 years that were reviewed. The male-to-female ratio was 5:9 for the survivors and 13:3 for the nonsurvivors. Of the 34 patients with ARF, 21 (62%) re-

covered lung function and were weaned from extracorporeal support. Of these, 18 patients (53%) survived and were discharged from the hospital. Of patients who were weaned from ECMO and subsequently died, 1 patient died of complications from an underlying congenital heart lesion, and 2 patients who were previously treated with bleomycin sulfate had gradually progressive respiratory failure. The mean age for the group as a whole was 22 years (range, 8 days to 56 years). The age of the patients in the survivor group ranged from 8 days to 53 years (mean, 19.8 years) compared with the patients in the nonsurvivor group, whose age ranged from 2 months to 56 years (mean, 24.6 years). The mean of the 2 groups did not differ significantly; however, a bimodal distribution was observed when patient age was plotted against the frequency of survival (**Figure 1**). Furthermore, there was a significant increase in survival of patients in the later peak ($P<.05$) as the ECMO experience progressed through the 8 years (**Figure 2**).

The total number of days during which the patients were treated with assisted ventilation before ECMO therapy varied from 1 to 41 days (mean, 6.9 days). The duration of ECMO ranged from 56 to 934 hours (mean, 304 hours). The proportion of patients who died while receiving ECMO was greater when the ECMO duration exceeded 300 hours (8/13 [62%] vs 8/21 [38%]; $P<.05$). Survival by the duration of mechanical ventilation preceding ECMO is shown in **Figure 3**. Patients who received ventilatory support for fewer than 9 days had a significantly better outcome ($P<.05$).

For all categories, differences between the survivors and nonsurvivors were not significant, with the exception of the number of hours that PEEP exceeded 8 cm H₂O and the number of units of packed red blood cells transfused before and during the implementation of ECMO. Patients were grouped into 7 categories based on their primary discharge diagnosis: sepsis or sepsis syndrome ($n = 3$), bacterial or fungal pneumonia ($n = 10$), viral pneumonia ($n = 5$), trauma or burn ($n = 2$), inhalation injury without burn ($n = 1$), immunocompromised state (due to transplantation or chemotherapy) ($n = 8$), and ARF, unknown origin ($n = 5$). Survival for each group is shown in **Table 2**.

COMMENT

Respiratory insufficiency in nonneonatal patients is usually self-limiting. In the few patients in whom fulminant respiratory failure develops, however, reported mortality exceeds 50%. If pulmonary failure progresses in this group, and conventional management schemes are exhausted, mortality rates approach 90%.¹² Experimental models³ suggest that the irreversible progression to death in nonneonatal patients is caused in part by the iatrogenic damage of the lung occurring with prolonged positive-pressure mechanical ventilation needed to overcome the ventilation-perfusion mismatches resulting from parenchymal shunting. Management strategies have been designed¹³ to improve oxygenation and minimize the mechanical damage associated with high alveolar pressure. These include low-volume and high-frequency ventilation, reversed inhalation to exhalation ratios, pressure-

Table 1. Patient Characteristics, Arterial Blood Gas Values, and Laboratory Values*

Variable	Survivors (n = 18)	Nonsurvivors (n = 16)	P
Age, y	19.8 ± 3.9	24.6 ± 4.3	.46
Time on ECMO therapy, h	250.0 ± 42.1	366.0 ± 72.7	.16
Pre-ECMO ventilation			
Ventilatory support, d	4.8 ± 2.5	9.3 ± 0.8	.08
Peak inspiratory pressure (PIP), cm H ₂ O	46.4 ± 3.0	53.8 ± 4.7	.18
Positive end-expiratory pressure (PEEP), cm H ₂ O	13.6 ± 1.1	15.8 ± 1.2	.19
FiO ₂ > 0.9, h	32.3 ± 9.7	74.3 ± 43.8	.33
PIP > 40 cm H ₂ O, h	37.7 ± 9.7	134.5 ± 55.9	.08
PEEP > 8 cm H ₂ O, h	42.7 ± 6.6	177.8 ± 58.4	.02
Pre-ECMO arterial blood gas values			
pH	7.30 ± 0.02	7.32 ± 0.03	.57
Pao ₂ , mm Hg	78.8 ± 20.4	53.9 ± 3.5	.26
Paco ₂ , mm Hg	61.4 ± 5.5	60.8 ± 5.7	.94
Alveolar-arterial gradient	531 ± 30	559 ± 21	.46
Pao ₂ /FiO ₂ ratio	85 ± 23	57 ± 5	.27
Laboratory values			
Pre-ECMO PRBC transfusion, U	2.3 ± 0.9	9.6 ± 3.2	.03
PRBC transfusions on ECMO therapy, U	15.5 ± 4.6	41.7 ± 9.6	.02
Pre-ECMO WBC count, × 10 ⁹ /L	18.0 ± 1.9	15.7 ± 3.7	.57
Pre-ECMO hematocrit, %	34.0 ± 1.3	33.7 ± 1.6	.87
Pre-ECMO platelet count, × 10 ⁹ /L	215 ± 40	170 ± 37	.42
Pre-ECMO serum creatinine, μmol/L (mg/dL)	66.0 ± 8.8 (0.8 ± 0.1)	97.2 ± 17.7 (1.1 ± 0.2)	.09

*Data are given as mean ± SEM. ECMO indicates extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; PRBC, packed red blood cell; and WBC, white blood cell.

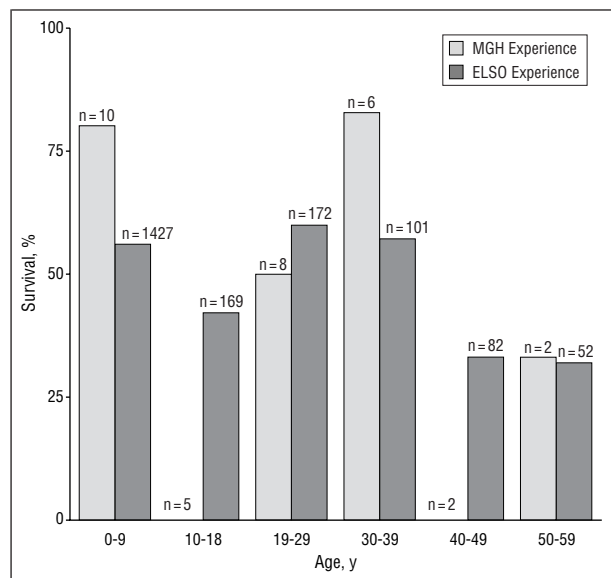


Figure 1. Patient survival (percentage) by age. The Massachusetts General Hospital (MGH), Boston, experience was compared with the Extracorporeal Life Support Organization (ELSO) database.

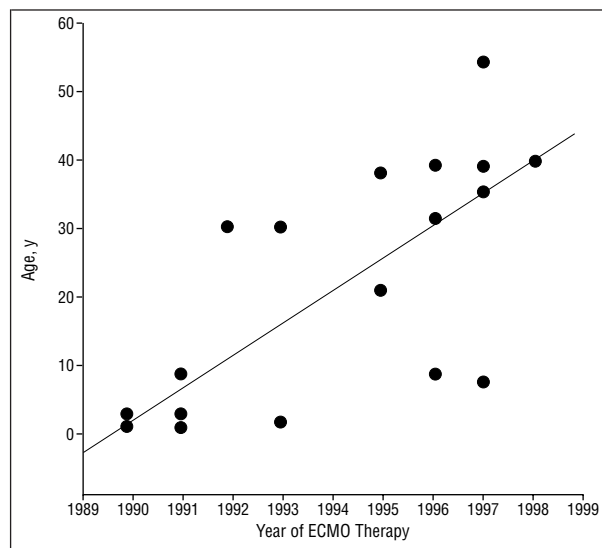


Figure 2. Survival by year of extracorporeal membrane oxygenation (ECMO) therapy and age of patient. Each circle represents a patient who survived therapy with ECMO and was discharged from the hospital.

controlled ventilation to maintain peak inspiratory pressures under 40 cm H₂O, permissive hypercapnia, and inhaled nitric oxide. All strategies are designed to promote optimal ventilation and perfusion, to minimize positive pressure–related parenchymal damage, and to afford the greatest capacity for recovery of the already-insulted lung.^{14,15} Still, the mortality of the patients not responding to these therapies exceeds 50%, and alternative methods of support have been studied.

Poor survival in adults was initially reported by Zapol et al¹⁶ after an ambitious multicenter, randomized ECMO

trial. Subsequently, the application of ECMO in this population was forestalled. At the same time, however, Bartlett et al¹⁷ showed dramatic successes in the treatment of refractory neonatal ARF by ECMO. There is little debate regarding its efficacy in these patients, as it has been shown¹⁸ to improve survival rates to 80% in patients with a predicted mortality of 90%. Soon thereafter, Gattinoni et al¹⁹ reported improved survival for adults with ARF using extracorporeal removal of carbon dioxide. The Extracorporeal Life Support Organization and its registry, as well as others,^{8,13,20} have since reported a combined survival for the nonneonatal, noncardiac group of pa-

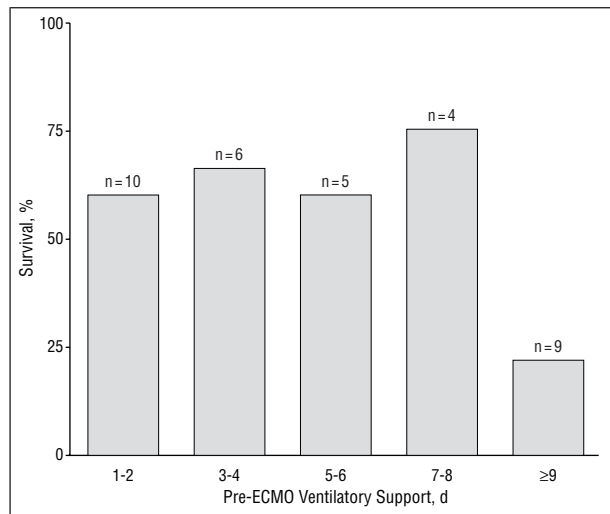


Figure 3. Patient survival (percentage) by duration of mechanical ventilation. A significant difference ($P < .05$) in survival after extracorporeal membrane oxygenation (ECMO) therapy was observed when mechanical ventilation before ECMO exceeded 8 days.

tients of greater than 50%. The growing neonatal experience, together with reports of successes in adults, has led to an expanded use in patients other than neonates. In addition to longer treatment periods, the improvement in survival is thought to have been most influenced by the development of newer technologies, management strategies, and a better understanding of which patients may benefit from these technologies. Guidelines have been established to aid in the selection of patients who would be the most appropriate candidates for ECMO. These were defined as those who had “severe but reversible” ARF.²¹ Despite changes in protocols and improvement in outcomes, several controversies remain as to how ECMO should be implemented so that risks are outweighed by benefits and outcomes are better than they would be if conventional therapies were applied.

Recently, several investigators¹³ have studied the outcomes for nonneonatal patients with ARF based on the cause of their respiratory failure. Similarly, we reviewed our patient base and placed each into 1 of 7 categories based on their discharge diagnosis (see “Results” section). As other groups have suggested, we observe that several disease states portend better outcomes, whereas the course of others is unchanged by ECMO therapy. Overall survival in our institution was 53% (18 patients). More interestingly, survival in patients presenting with isolated viral pneumonias, isolated inhalation injuries, or with sepsis or sepsis syndrome with ARF but not complicated by multiorgan failure was 100% (9 patients). In contrast, 1 (12%) of the 8 patients who were immunocompromised either as a result of chemotherapy for the treatment of cancer or by immunosuppression for organ transplantation survived to hospital discharge. Although 2 of the 7 nonsurvivors were weaned from extracorporeal support and the cannula removed, they subsequently died of a progressive respiratory failure thought to be related to their past bleomycin therapy. Therefore, as many have thought, these patients may not be suitable candidates for ECMO therapy. Similarly poor

Table 2. Cause of Acute Respiratory Failure and Outcome

Diagnosis	No. of Patients (n = 34)	Survival, No. (%)
Sepsis or sepsis syndrome	3	3 (100)
Bacterial or fungal pneumonia	10	4 (40)
Viral pneumonia	5	5 (100)
Trauma or burn	2	0 (0)
Inhalation injury without burn	1	1 (100)
Immunocompromised state*	8	1 (12)
Unknown etiology	5	4 (80)

*Transplantation or chemotherapy.

outcomes were seen for patients with ARF complicated by multiorgan failure or precipitated by trauma or burns. In this series, the disease process appeared to be significantly effective in identifying those patients with “reversible” lung injury in whom ECMO may be of benefit.

Most authors agree that limiting lung injury before and during ECMO is of paramount importance when considering whether a patient is capable of survival. Identifying patients earlier in their “reversible” disease progression, and thereby limiting the well-characterized pre-ECMO ventilatory insult, should improve survival. Prankoff et al²⁰ showed that pre-ECMO mechanical ventilation exceeding 5 days was a poor prognostic indicator in adults. Our data suggest that there is no significant difference in survival in those patients who had had up to 9 days of pre-ECMO ventilatory support and that a lesser but substantial percentage of patients who receive mechanical ventilation for longer than 9 days will survive to discharge after ECMO therapy.

Early in the ECMO experience, Zapol et al¹⁶ considered the appropriate duration of ECMO therapy in adults to be equivalent to that seen by investigators treating neonates. Most authors at that time failed to take into account any possible differences in the resilience of the damaged lung parenchyma that may be expected in the nonneonates compared with neonates. The results reported by Zapol et al, therefore, as many have come to realize, came early in the ECMO learning curve and underestimated the time necessary for the return of lung function in the nonneonatal group. The centers that participated in the National Institutes of Health–sponsored adult trial allowed only 5 days of ECMO, and if no improvement was seen, it was considered futile and discontinued. Since then, the average time of extracorporeal support in nonneonatal patients has been better defined, the mean \pm SD duration of ECMO for these patients now being reported as 10.3 ± 6.8 days.²² The cannulation time for our patients ranged from 2.3 to 38.9 days (mean, 12.6 days). More important, the difference in the mean cannulation time of the survivors (10.4 days) from that of the nonsurvivors (15.3 days) is apparently not significant. The proportion of patients who died while receiving ECMO, however, was greater when the ECMO duration exceeded 12.5 days (8/13 [62%] vs 8/21 [38%]; $P < .05$). Still, 5 of the 18 patients in the survivor group had ECMO durations exceeding 300 hours.

When considering a patient with ARF of unknown origin, age may prove to be a useful prognostic indicator. When the age of the patients in this series was plot-

ted as a function of survival, a bimodal distribution resulted. The survivors tended to cluster between 8 days and 9 years of age and then again between 29 and 38 years of age (Figure 1). Patients who were older than 38 years had poorer outcomes. Meyer and Jepson⁶ made a similar observation for their group of patients. We first thought that this phenomenon was a reflection of the small number of patients in our series. When all available data from the Extracorporeal Life Support Organization database for the nonneonatal, noncardiac patients was accumulated and plotted in the same way, however, this distribution was confirmed (Figure 1). Although we cannot conclusively identify the reason for this observation, a likely explanation may be, as Meyer and Jepson suggest, that diseases (viral or bacterial pneumonias) that cluster in certain age groups may result in more easily reversible pulmonary dysfunction. The Extracorporeal Life Support Organization database should be reviewed to compare the underlying diseases in the various age groups.

CONCLUSIONS

Improvements in ECMO technology and the reevaluation of criteria for patient selection for extracorporeal support have greatly improved survival. We provide additional data that may be helpful when deciding whether a patient with ARF might benefit from the lung rest that is afforded by ECMO. Still, many questions remain unanswered. A multicenter, randomized trial would be appropriate to better define the population of patients who would most benefit by this therapeutic option.

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DISCUSSION

Hardy Hendren, MD, Boston, Mass: The work in each of these ECMO patients, for those of you who have not witnessed it, is absolutely enormous. Yesterday I asked the authors to estimate how many hours they would spend each day at the bedside of 1 of these patients. It is conservatively about 6 hours. A little calculation—6 hours a day for 1 of the 300-hour ECMO-support patients, which is 13 days—indicates that this is roughly the equivalent of doing 20 open heart operations or 10 to 15 Whipple operations, depending on the speed of the operator.

The authors have shown us that a survival of 53% can be achieved in this group of desperately ill patients, for whom the predicted mortality would be 80% otherwise, so this is a significant salvage. They have shown us that multiorgan failure and an immunocompromised state are bad predictors for these patients and that short-term support, that is, less than 13 days, is more apt to result in success than long-term support, that is, more than 300 hours.

I would like to ask the authors 3 questions: First, you've shown that patients younger than 10 years and those in their

30s had a higher likelihood of survival. What's the problem with being in the 10- to 30-year age group?

The second question is, you've shown us that single-organ failure, that is, the lung, and short-term patients do best. Do you have absolute contraindications to the use of ECMO? And how about age? Are about two thirds of the people in this audience beyond the age limit and would you write us off or would you give us a chance with ECMO in the final analysis if it were a single-organ lung failure?

The third question is, when you cross that threshold of 300 hours or 13 days, when and how do you decide to turn off the ECMO?

Pardon Kenney, MD, Boston: Your survival data are obviously impressive. I have a quality-of-life question. How many of your survivors required permanent ventilators, and how many of them actually ended up in a chronic care hospital? How many of these patients have been referred? Are they all based at the Massachusetts General Hospital originally? Can these patients be transported for ECMO, and when would you do that?

Dr Masiakos: To answer Dr Hendren's questions, we find that these diseases cluster by ages, and we suspect that they cluster because of disease predispositions. The group that you speak of, the 10- to 30-year-olds, contains the sickest patients. They are the ones who have fungal sepsis, are immunocompromised after their lung transplants, and are most likely to present with multiorgan failure after trauma. They typically do the worst.

To your second question about the absolute contraindications: The first contraindication is head injury. Children or adults who present with head trauma or intracranial hemorrhage are refused. Irreversible lung damage, as seen by biopsy

with indications of pulmonary fibrosis, is also a contraindication. Finally, a patient with an underlying fatal disease like metastatic cancer or end-stage acquired immunodeficiency syndrome would be refused as well.

Age is not an absolute contraindication, and I know you all hate me for saying that, however, it's a patient by patient evaluation and we assume enrollment criteria based on what we find on their lung pathology report.

To your last question, the 300-hour threshold: There's no good way to tell a patient's parents or family members that their life support is going to be withheld or withdrawn. We observe the patients day to day, and if there's no evidence of lung recovery after the second or third week, the patients are offered a lung biopsy. If fibrosis is seen on lung biopsy, we consider that to mean irreversible lung damage, and at that point, we suggest that ECMO be discontinued.

The quality-of-life issues: None of the patients who were survivors after receiving ECMO therapy had poor quality of life, none of them were institutionalized, and none continued to need ventilation therapy for their disease. After they recovered, they would be terminated from ECMO and then subsequently be terminated from ventilator support.

To your question about ECMO referrals, it's imperative to understand that lung damage predisposes these patients to poor outcomes. We suggest that the patients be transferred to an institution where ECMO can be provided if in a short amount of time the patient is deemed not recoverable by the current conventional therapies. To get a patient there promptly results in fewer problems in the transfer than when the patient decompensates later.

Announcement

The *Archives of Surgery* will give priority review and early publication to seminal works. This policy will include basic science advancements in surgery and critically performed clinical research.