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Controlled Airway Pressure Therapy, Nitric Oxide Inhalation, Prone Position, and Extracorporeal Membrane Oxygenation (ECMO) as Components of an Integrated Approach to ARDS

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Background: Recent years have seen the introduction of innovative additive therapies for acute respiratory distress syndrome. However, because there are no reliable predictors of response to a particular therapy, potential responders to a specific therapeutic intervention may be lost. Therefore, the authors evaluated the effect of a combined therapeutic approach on the survival of patients with acute respiratory distress syndrome, when treated according to a strict algorithm.

Methods: During a 2.5-yr period, 84 patients with acute respiratory distress syndrome were assigned to a standardized treatment protocol. Data analysis was performed by retrospective review of patient charts. Patients were treated using a stepwise treatment algorithm of pressure-controlled ventilation (peak airway pressure < 35 cm H₂O), positive end-expiratory pres-

sure (PEEP; 12–15 cm H₂O), permissive hypercapnia, inhaled nitric oxide (5–20 ppm), and prone positioning. These interventions were termed “conventional therapy.” Response to treatment was defined as a more than 20% increase in arterial oxygen tension (Pa_{O₂}). Nonresponders were triaged to extracorporeal membrane oxygenation.

Results: The overall survival rate was 80%. All patients received conventional therapy up to 96 h; 71 responded to conventional therapy and 59 survived (83%). Thirteen patients (15%) did not respond to conventional therapy and underwent extracorporeal membrane oxygenation; 8 of these patients (62%) survived. For the group, the mean admission lung injury score was 3.3 ± 0.5, the Pa_{O₂}/fractional inspired oxygen tension (Fi_{O₂}) ratio was 96 ± 45, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score was 18 ± 6.

Conclusions: The 80% overall survival rate achieved in this group of patients with severe acute respiratory distress syndrome may in part reflect the additive beneficial effects of combined treatment methods, such as airway pressure control, nitric oxide inhalation, prone position, and early triage of nonresponders to extracorporeal membrane oxygenation. (Key words: Acute lung injury; airway pressure therapy; direct and indirect lung injury; inhaled nitric oxide; positive end-expiratory pressure; prediction of survival; prone position; treatment algorithm.)

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PATIENTS with acute respiratory distress syndrome (ARDS) have a high mortality rate that ranges from 45–66%.^{1–3} Because the cause of ARDS is so heterogeneous, treatment usually is supportive or symptomatic, rather than specifically directed at the underlying cause of ARDS. Conventional therapy consists of various pharmacologic and nonpharmacologic interventions, including mechanical ventilation, positive end-expiratory pressure (PEEP), permissive hypercapnia, positional maneuvers, control of infection, and dehydration.

In the absence of specific treatment for ARDS, the current approach to its management is directed at maintenance of oxygenation while attempting to avoid or reduce ventilator associated lung injury, including barotrauma and oxygenation toxicity. Three interventions

that have been introduced to help achieve these goals include inhaled nitric oxide,⁴ prone positioning,⁵ and extracorporeal membrane oxygenation (ECMO).⁶⁻⁹ Trials investigating the isolated impact of these interventions on survival in patients with ARDS have either failed to show a benefit or have not been convincing. One reason may be that a single therapeutic intervention is not able to alter patient outcome in a disease as severe and complex as ARDS. Furthermore, patients with ARDS often present with severe underlying organ dysfunction or complicating disorders, making the impact of cointerventions more difficult to control.

Nitric oxide is a potent endogenous vasodilator,¹⁰ and inhaled nitric oxide selectively decreases elevated pulmonary artery pressures and improves oxygenation in patients with ARDS.⁴ Prone positioning is considered primarily to enhance matching of perfusion to ventilation, although recent reports suggest that mechanism may be more complex.¹¹ ECMO has proven to be effective in maintaining oxygenation in the failing lung sufficiently to allow airway pressure therapy provided by mechanical ventilation to be decreased to safer levels.⁶⁻⁸

To date, there have been no studies about whether combined treatment regimens, *e.g.*, inhaled nitric oxide plus ECMO, improves survival in patients with ARDS. Standardized treatment algorithms have been proposed as a guide to clinical decision making and a means of enhancing comparative studies. Recently the impact of standardized treatment algorithms on clinical performance and mortality rates in patients with ARDS has been evaluated.⁷ However, these study protocols excluded the use of inhaled nitric oxide or did not provide a structured treatment algorithm. We therefore decided to evaluate the impact of an integrated therapeutic approach on survival of patients with ARDS.

Material and Methods

Eighty-four patients were treated for ARDS in a general intensive care unit (ICU) in a 30-month period between 1995 and 1997. The diagnosis of ARDS was confirmed by the criteria defined by the American-European Consensus Conference on ARDS¹² (Miami, Florida, May 1992, and Barcelona, Spain, October 1992) and all patients had a lung injury score¹³ equal to or greater than 2.5. We excluded patients with malignancies diagnosed as incurable and patients younger than 12 years and older than 76 years. If hemodynamics and respiration were stable, computed tomography (CT) of the head, thorax, and

abdomen was performed before admission to the ICU to rule out any contraindication for possible ECMO treatment. Survival was defined as discharge from the ICU. All discharged patients had their tracheas extubated and required no intravenous drug therapy, were mobilized to a minimum of standing with support, and were fed enterally.

Patient data were collected at admission and entered into a database on-line (Care Vue 9000, Hewlett Packard, Böblingen, Germany). Data analysis was performed after completion of the study period. The Acute Physiology and Chronic Health Evaluation (APACHE) II and lung injury score were calculated using the worst values during the first 24 h of the ICU stay. Organ system failure was defined according to published guidelines.¹⁴

Treatment Algorithm

With the start of the ECMO program at the University of Vienna (1995) we defined a standardized treatment protocol to guide decision making, regardless of whether a patient should be treated with ECMO. All subsequent patients referred to our ICU with the diagnostic criteria of ARDS were included in this standardized treatment protocol and proceeded through a defined sequence of what we termed "conventional therapy" (fig. 1): (1) pressure-controlled mechanical ventilation; titration of positive end-expiratory pressure (PEEP) to 12–15 cm H₂O; (2) prone positioning; (3) negative fluid balance with furosemide or continuous venovenous hemofiltration (CVVH); (4) inhaled nitric oxide at a dosage of 5–20 ppm.

All patients were entered into the standardized treatment algorithm at admission. Failure of response to conventional therapy was defined as a less than 20% improvement of Pa_O₂ during an evaluation period up to 96 h. If these patients then met the criteria of ECMO (see Extracorporeal Membrane Oxygenation section), venovenous extracorporeal carbon dioxide removal with low-frequency positive-pressure ventilation (ECCO₂-R-LFPPV)⁶ was instituted.

Mechanical Ventilation

All patients required mechanical ventilation (Evita, Draeger, Luebeck, Germany, and Servo300, Siemens, Elema, Sweden) in a pressure-controlled ventilation mode and with a PEEP of 12–15 cm H₂O. We kept peak airway pressures below 35 cm H₂O and applied tidal volumes of 5–7 ml/kg. The target oxygenation parameters were Pa_O₂ greater than 50 mmHg and arterial oxygen saturation (Sa_O₂) greater than 90%. To achieve sufficient removal of carbon

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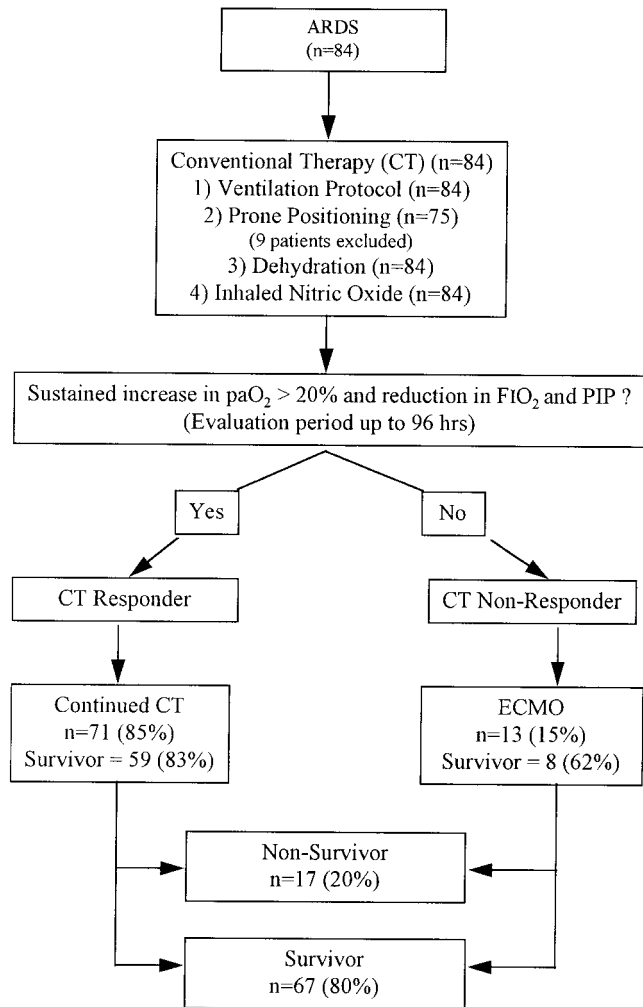


Fig. 1. Treatment algorithm.

dioxide we adjusted ventilator frequency up to 35 breaths/min. If hypercapnia developed despite a high frequency, we accepted levels of Pa_{CO_2} less than 70 mmHg. If renal compensation did not occur within 24 h when a pH less than 7.20 was reached, respiratory acidosis was corrected with a slow infusion of trishydroxymethyl-aminomethan. All patients were sedated with midazolam and sufentanil infusions, and muscle relaxation was achieved with vecuronium when necessary.

Prone Positioning

We turned patients every 12 h from the supine to the prone position and *vice versa*. If CT of the thorax showed pronounced basal atelectasis or if respiratory parameters deteriorated after repositioning to supine, or both, we shortened the supine position intervals to 4 h.

Prone positioning was performed on all patients, except for those with conditions prohibiting prone positioning, such as elevated intracranial pressure. Patients who underwent laparotomy, sternotomy, or tracheostomy were not excluded from prone positioning, nor did we consider hemodynamic instability or dependency on cardiotoxic drugs to be a contraindication.

Inhaled Nitric Oxide

Nitric oxide was administered using a nitric oxide delivery and monitoring system (PulmonoxMini, Messer, Gumpoldskirchen, Austria). This device delivers nitric oxide from a tank (900 ppm nitric oxide in nitrogen; Pulmomix, Messer, Gumpoldskirchen, Austria) directly into the inspiratory limb of the ventilator and 100 cm proximal to the endotracheal tube. The nitric oxide flow is electronically controlled and adjusted to the inspiratory gas flow to achieve reliable administration of the desired nitric oxide concentration. Nitric oxide and NO_2 concentration were continuously monitored by electrochemical cells.¹⁵ Gas samples were withdrawn a short distance proximal to the patient's endotracheal tube, ensuring that a length of 100 cm was maintained between the central nitric oxide instillation and the withdrawal of gas for analysis.

Inhaled nitric oxide was added in increments of 5 ppm up to a maximum of 20 ppm. Response to treatment was defined as an increase in Pa_{O_2} of greater than 20% or a decrease in mean pulmonary artery pressure of greater than 20%, or both. If there was an initial lack of response to nitric oxide, it was reevaluated after 24 h. Treatment failure was defined as two unsuccessful applications of inhaled nitric oxide. Nitric oxide inhalation was discontinued in a stepwise fashion after the first successful return of the patient to spontaneous breathing in a pressure-supported ventilation mode.

Extracorporeal Membrane Oxygenation

Patients were considered for ECMO if their Pa_{O_2} /fractional inspired oxygen tension ($\text{F}_{\text{I}_{\text{O}_2}}$) did not increase above 70 despite a PEEP greater than 10 cm H_2O within 96 h. Patients with diseases diagnosed as "incurable," "severe underlying bleeding complications," "severe immunosuppression," "irreversible brain damage," or "severe chronic pulmonary disease" were excluded.

A venovenous cardiopulmonary bypass system was set up according to a technique described by Gattinoni *et al.*⁶ Percutaneous vascular access was achieved *via* the right internal jugular vein and the right femoral vein using spring wire-reinforced cannulas sized between 19

and 25 French. The extracorporeal circuit consisted of a heparin-coated tubing system with two heparin-bonded membrane oxygenators (Medtronic, Anaheim, CA) connected in parallel to the circuit. Blood flow was driven by an occlusive roller pump (Stoekert, Munich, Germany) and adjusted to 25–30% of total cardiac output. Membranes were ventilated with a heated and humidified gas mixture through a gas blender. During extracorporeal carbon dioxide removal with low-frequency positive-pressure ventilation the lungs were silenced with a PEEP of 20 cm H₂O, peak airway pressure was 30 cm H₂O, mean airway pressure was 24 ± 4 cm H₂O, and respiratory rate was 4–6 breaths/min at tidal volumes of 100–200 ml. Low-dose heparin was additionally infused intravenously to achieve a partial thromboplastin time of 50 to 60 s.

Weaning Procedures

We reduced ventilator settings stepwise to achieve the following target values: $F_{I_{O_2}} < 0.5$; peak inspiratory pressure (PIP) < 30 cm H₂O; PEEP < 8 cm H₂O. When target ventilator settings were reached during stable conditions within the defined range, weaning from controlled mechanical ventilation (CMV) to synchronized intermittent mandatory ventilation (SIMV). Pressure support ventilation (PSV) and spontaneous breathing with continuous positive end-expiratory pressure (CPAP) was proceeded. Inhaled nitric oxide was reduced in stepwise decrements of 2 ppm after target ventilator settings were reached and nitric oxide was then discontinued. Prone positioning was discontinued after patient weaning from controlled mechanical ventilation began, except for patients with radiologic evidence of basal atelectasis, for whom prone positioning was continued overnight during light sedation.

We started weaning from ECMO when the target ventilator settings were reached and included the following steps: (1) reduction of the extracorporeal oxygen concentration to 0.21, (2) reduction of extracorporeal blood flow to a minimum level of 1.0 l/min. At this point, extracorporeal gas flow was discontinued and, if the patients hemodynamics and gas exchange remained stable over 12 h, decannulation was performed.

Patient Treatment

Patients were monitored continuously by ECG, peripheral oxygen saturation (Sp_{O_2}) (CareVue 9000; Hewlett-Packard, Böblingen, Germany), and an indwelling peripheral arterial catheter (Ohmeda, Swindon, United Kingdom). A 7.5-French fiberoptic pulmonary artery

catheter (REF-Sat, Baxter, Irvine, CA) was placed *via* the internal jugular or the subclavian vein. Hemodynamic measurements included heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and pulmonary artery occlusion pressure (PAOP). Cardiac output was measured by the thermodilution technique and expressed as the mean of four injections of 10 ml normal saline at 5°C (Explorer, Edwards Critical Care, Baxter, Irvine, CA). The right ventricular ejection fraction (REF) and systemic (SVRI) and pulmonary (PVRI) vascular resistance indices were calculated according to standard formulas. Arterial (Pa_{O_2}) and mixed venous (Pv_{O_2}) oxygen tensions were measured with standard blood gas electrodes (AVL 995-Hb; AVL, Graz, Austria), and the total hemoglobin concentration, hemoglobin oxygen saturation, and methemoglobin levels were measured with spectrophotometry (AVL 912, AVL). The ratio of the partial pressure of arterial oxygen and the fraction of inspired oxygen ($Pa_{O_2}/F_{I_{O_2}}$) was used as a parameter for arterial oxygenation because the admixture of nitric oxide in nitrogen decreases the actual $F_{I_{O_2}}$.

Cardiotonic and vasotonic drugs were infused to maintain a mean arterial pressure more than 50 mmHg and a cardiac index (CI) more than $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. If oliguria occurred, crystalloids were infused to maintain a pulmonary artery occlusion pressure more than 10 mmHg and a urine output more than $0.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. At admission, all patients received total parenteral nutrition with a caloric intake not exceeding $105 \text{ kJ} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. Enteral feeding was started as early as possible. When copious bronchial exudates were present we performed bronchoscopy to clear the airways and gain material for cultures. Antibiotic therapy was guided by information gained from cultures of blood, wound secretions, urine, sputum, and bronchoscopically derived distal airway sections. When systemic signs of infection were present (*i.e.*, unexplained tachycardia of more than 100 beats/min, leukocytosis of more than 20,000/ml, or leukopenia of less than 5,000/ml, body temperature of more than 38°C or less than 35°C) and no positive culture could be obtained, we started an empiric regimen of broad-spectrum antibiotics (cefpirom + vancomycin).

Statistical Analysis

Data are expressed as the mean value \pm SD, except for days, which are expressed as the median \pm range. Quantitative parameters were compared with the nonparametric Mann-Whitney test, qualitative parameters were

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Table 1. APACHE II Score, Lung Injury Score, Oxygenation Parameters, and Ventilator Setting on Admission

	Number of Patients	APACHE II	LIS	Pa _{O₂} /Fi _{O₂}	Fi _{O₂}	RR	PAP	P _{mean}	PEEP	PA _{O₂} -Pa _{O₂}
All patients	84	18 ± 6	3.3 ± 0.5	96 ± 45	0.81 ± 0.2	22 ± 8	32 ± 6	19 ± 6	12 ± 4	442 ± 155
Nonsurvivors	17	20 ± 5	3.6 ± 0.4*	65 ± 24*	0.93 ± 0.11*	24 ± 8	35 ± 5*	22 ± 5*	12 ± 3	553 ± 74*
Survivors	67	17 ± 6	3.2 ± 0.5	103 ± 46	0.78 ± 0.21	21 ± 8	32 ± 6	19 ± 6	12 ± 4	416 ± 157
CT responders	71	18 ± 6	3.2 ± 0.5†	103 ± 45†	0.78 ± 0.2†	21 ± 8	32 ± 6†	19 ± 5†	11 ± 4†	415 ± 152†
CT nonresponders	13	18 ± 7	3.8 ± 0.3	58 ± 15	0.96 ± 0.13	25 ± 9	35 ± 6	24 ± 4	15 ± 3	587 ± 52
ECMO survivors	8	19 ± 8	3.9 ± 0.1	58 ± 12	0.94 ± 0.17	20 ± 7†	32 ± 7†	23 ± 4	15 ± 3	581 ± 59
ECMO nonsurvivors	5	16 ± 3	3.8 ± 0.4	59 ± 19	0.96 ± 0.05	32 ± 7	40 ± 6	26 ± 3	14 ± 2	598 ± 41

Values are mean ± SD.

CT = conventional therapy; ECMO = extracorporeal membrane oxygenation; APACHE II = APACHE II score; LIS = lung injury score; Pa_{O₂}/Fi_{O₂} = oxygenation index; Fi_{O₂} = fraction of inspired oxygen concentration; RR = respiratory rate; PAP = peak airway pressure (cm H₂O); P_{mean} = mean airway pressure (cm H₂O); PEEP = positive end-expiratory pressure (cm H₂O); PA_{O₂}-Pa_{O₂} = alveolar-arterial oxygen difference (mmHg).

* $P < 0.05$ versus survivors.

† $P < 0.05$ versus ECMO nonsurvivors.

‡ $P < 0.05$ versus CT nonresponders.

compared using the chi-square test. For comparison of survival rates a log-rank test was performed. We applied a multivariate analysis to identify possible relations between ventilatory and oxygenation parameters at admission and survival, and duration of supportive measures and survival. For multivariate analysis we used a Cox proportional hazards regression model. Parameters significant in univariate analysis were entered into the model. A P value < 0.05 was considered to represent statistical significance.

Results

We studied a total of 84 patients, of whom 27 were female and 57 male, with a median age of 37 yr and an age range of 12-73 yr. Fifty-eight patients (69% of total) were referrals from other hospitals for evaluation for ECMO. At admission, the mean lung injury score was 3.3 ± 0.5 and the mean APACHE II Score was 18 ± 6 . Before admission, patients required mechanical ventilatory support for a median of 2 days (1-26 days), had a PEEP level of 12 ± 4 cm H₂O, a peak airway pressure of 32 ± 6 cm H₂O, and an Fi_{O₂} of 0.81 ± 0.2 . The Pa_{O₂}/Fi_{O₂} ratio was 96 ± 45 and the alveolar-arterial oxygen difference (PA_{O₂}-Pa_{O₂}) was 442 ± 155 mmHg (table 1).

All patients were provided conventional therapy according to the stepwise treatment algorithm. Seventy-one patients responded with improvement in oxygenation parameters; of these 59 (83%) ultimately survived. Thirteen patients (15%) did not respond and underwent ECMO; of these, 8 (62% of ECMO patients) survived. The overall survival rate, including patients triaged to ECMO,

was 80% *i.e.*, 67 of 84 patients. Of 67 patients discharged from the ICU, 2 patients died in the hospital (patient 1: massive pulmonary embolus 11 days after discharge; patient 2: acute pancreatitis with sepsis and multiple organ failure 17 days after discharge).

Comparison of Responders to Conventional Therapy with Nonresponders

The severity of lung injury appeared to be substantially greater in patients who did not respond ($n = 13$) to conventional therapy than in those who did respond ($n = 71$). Nonresponders had significantly lower Pa_{O₂}/Fi_{O₂} ratios, higher lung injury scores, and greater PA_{O₂}-Pa_{O₂}. In addition, nonresponders required significantly higher Fi_{O₂}, PEEP, and peak airway pressure to achieve these values (table 1). These differences in oxygenation values at admission, although significant at univariate analysis (table 1), were not sufficient to predict the individual response of a patient to the treatment protocol when analyzed by multivariate analysis (Cox proportional hazards regression, not significant). Nonresponders had a median of 10 ventilator days before admission compared to 2 days for responders, although this difference was not statistically significant. Inhaled nitric oxide therapy was necessary for significantly more days in nonresponders: a median of 17 *versus* 5 days (table 2). Finally, the median duration of mechanical ventilation was significantly greater in nonresponders (40 *vs.* 15 days), as was the median duration of ICU stay (31 *vs.* 16 days). There were no differences with respect to age, cause of ARDS, or APACHE II scores.

Table 2. Duration of Therapeutic Measures

	Number of Patients	ICU (days)	Total Mechanical Ventilation	Mechanical Ventilation before Admission	Inhaled Nitric Oxide (days)	ECMO (days)	Ventilation before ECMO
All patients	84	18 (1–98)	19 (1–94)	2 (1–26)	6 (1–69)	—	—
Nonsurvivors	17	17 (1–69)	20 (1–80)	2 (1–20)	13 (1–69)*	—	—
Survivors	67	18 (2–98)	19 (1–94)	2 (1–26)	6 (1–50)	—	—
CT responders	71	16 (1–98)‡	15 (1–94)‡	2 (1–26)	5 (1–50)‡	—	—
CT nonresponders	13	31 (19–80)	40 (19–80)	10 (1–14)	17 (6–69)	10 (2–68)	9 (1–31)
ECMO survivors	8	31 (24–80)	34 (19–72)	6 (1–12)	14 (6–46)†	8 (2–24)†	7 (1–13)
ECMO nonsurvivors	5	46 (19–69)	48 (20–80)	10 (1–13)	45 (19–69)	43 (11–68)	12 (2–31)

Values are median days (range).

CT = conventional therapy; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

* $P < 0.05$ versus survivors.

† $P < 0.05$ versus ECMO nonsurvivors.

‡ $P < 0.05$ versus CT nonresponders.

ECMO Patients

Two (15%) of 13 patients (conventional therapy nonresponders, $n = 13$) had to be connected to the ECMO circuit immediately at admission. In the remaining 11 patients, ECMO was instituted after a median evaluation period of 48 h. The median duration of ECMO treatment was 10 days (range, 2–68 days).

Overall survival in the ECMO group was 62% (8 of 13). Survivors of ECMO did not differ significantly from nonsurvivors regarding $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$, lung injury score, APACHE II score, Fi_{O_2} , mean airway pressure, PEEP, and $\text{PA}_{\text{O}_2} - \text{Pa}_{\text{O}_2}$ (table 1). At admission, ECMO nonsurvivors had significantly higher peak airway pressure and ventilator frequency, indicating more pronounced lung injury. In this group of patients, the strongest predictor of death was the duration of ECMO. We found no correlation between duration of mechanical ventilation before ECMO treatment and risk of death. The duration of the evaluation period also had no influence on outcome.

All Patients

Overall survival was 80% (67 of 84 patients; survivors: $n = 67$; nonsurvivors: $n = 17$; fig. 1). Actual survival differed significantly from survival as predicted by APACHE II scores. After the initial application of inhaled nitric oxide, 71 of 84 of the patients (85%) responded and continued to be treated with this method. The median duration of nitric oxide treatment was 6 days (range, 1–69 days). Seventy-five of 84 patients (89%) were placed in the prone position at least once. Patients continued to receive mechanical ventilatory support for a median of 19 days (range, 1–94 days; table 2). At admission, nonsurvivors had higher lung injury scores, peak airway pressures, and $\text{PA}_{\text{O}_2} - \text{Pa}_{\text{O}_2}$, and lower $\text{Pa}_{\text{O}_2}/$

Fi_{O_2} (table 1). The duration of ECMO, inhaled nitric oxide therapy, and hemofiltration was significantly longer in nonsurvivors, but there was no difference between the two groups of patients regarding ventilation days before admission, duration of mechanical ventilatory support, or duration of ICU stay (table 2). Analysis of survival for the influence of response to conventional therapy showed no significant difference in survival between responders to conventional therapy and nonresponders. The overall survival rate of 80% differed significantly from the 50% survival rate observed at the University of Vienna in a historical control cohort (treated for severe ARDS in the 4 yr before the implementation of the standardized treatment protocol; $P < 0.05$, log-rank test).

Cox proportional hazards regression analysis that incorporated oxygenation and ventilator parameters commonly associated with increased mortality in ARDS showed that days of mechanical ventilatory support before admission and total days requiring mechanical ventilatory support were strong predictors of mortality (table 3).

When grouped by ARDS cause, patients were divided fairly evenly between direct and indirect injury (table 4). The main direct injuries were lung contusion (31%) and diffuse pulmonary infection (17%). Among the indirect injuries, sepsis syndrome appeared most frequently (36%) and contributed most to overall mortality, accounting for 53% (9 of 17) of all deaths. Two patients died of unresponsive hypoxemia and 15 of multiple-organ system failure. Organ system failure was classified according to the number of failed organ systems in addition to the lung. Thus, grade 0 = only lung failure (19 patients), I = lung + one additional organ failure (25

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Table 3. Relation between Oxygenation and Ventilation Parameters on Admission and Duration of Supportive Measures on Survival

Parameter	P Value
Oxygenation and ventilation parameters at admission	
Peak airway pressure	0.98
FiO ₂	0.28
Respiratory rate	0.57
PaO ₂ /FiO ₂	0.21
LIS	0.09
P _{mean}	0.59
PA _{O₂} -Pa _{O₂}	0.37
Duration of supportive measures	
Total days requiring mechanical ventilation	<0.001
Days requiring mechanical ventilation before admission	0.004
Days of inhaled nitric oxide	0.7
Days of pharmacological inotropic support	0.02
Hemofiltration days	0.04
ECMO days	0.87

Results of proportional hazard (Cox) regression. Parameters, which differed at univariate analysis and duration of supportive measures, were entered into the model. Except for the LIS, which showed a trend toward predicting survival, no single oxygenation or ventilation parameter on admission was able to predict survival. A strong dependence of total days on mechanical ventilation and days on mechanical ventilation prior to admission was evident. Values were taken at time of admission, except for duration of therapeutic measures.

FiO₂ = fraction of inspired oxygen concentration; PaO₂/FiO₂ = ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen concentration; LIS = lung injury score; PEEP = positive end-expiratory pressure (cm H₂O); PA_{O₂}-Pa_{O₂} = alveolar-arterial difference in oxygen capacity (mmHg); ECMO = extracorporeal membrane oxygenation.

patients), II = lung + two organ failures (19 patients), III = lung + three organ failures (12 patients), and IV = lung + four organ failures (9 patients). Nonsurvivors had significantly more organs failing ($P < 0.001$, table 5).

Discussion

We report a series of 84 patients with a diagnosis of ARDS that was managed with a strict treatment algorithm. All patients received conventional therapy, which included, in stepwise fashion, controlled airway pressure therapy, dehydration, inhaled nitric oxide, and prone positioning. Patients who did not respond to conventional therapy were triaged to ECMO. The overall survival rate in our patient series was 80%. This is much higher than reported in previous studies,^{2,3} although clear differences in study conditions may play a role. This survival rate was also higher than predicted by APACHE II scores at admission (36%, log-rank test $P < 0.05$).

Table 4. Etiology of ARDS, Grouped According to the Report of the American-European Consensus Conference

ARDS Categories	All Patients	Survivors
I. Direct injury		
A. Aspiration	4 (4.8)	3 (75)
B. Diffuse pulmonary infection	14 (16.7)	12 (86)
C. Near-drowning	1 (1.2)	1 (100)
D. Toxic inhalation	—	—
E. Lung contusion	26 (30.9)	23 (88)
	45 (53.6)	39 (87)
II. Indirect injury		
A. Sepsis syndrome	30 (35.7)	21 (70)
B. Severe nonthoracic trauma	4 (4.8)	3 (75)
C. Hypertransfusion	3 (3.6)	2 (67)
D. Cardiopulmonary bypass	2 (2.4)	2 (100)
	39 (46.4)	28 (72)
Total	84 (100)	67 (80)

Values are number (%).

All patients = number of patients in the different ARDS categories (percentage of all patients); Survivors = number of survivors in each category (percentage of survival of each category).

ARDS = acute respiratory distress syndrome.

Although, at admission, responders had significantly lower ventilator settings and better oxygenation parameters than nonresponders (table 1), these parameters were not sufficient to explain mortality or the response to the treatment protocol when entered into a Cox proportional hazards regression model (table 3). Multivariate analysis revealed that number of days receiving mechanical ventilation before admission and total days receiving mechanical ventilation were significant predictors of mortality (table 3). The need of prolonged sup-

Table 5. Organ Dysfunction on Admission

	Number	%
Organ dysfunction related to acute illness		
Shock	50	60
Septic	37	44
Other	13	15
Organ failure (other than lung failure)	65	77
Renal	40	48
Cardiac/hemodynamic	53	63
Hepatic	23	27
Positive inotropic support	76	90
Hemofiltration/dialysis	56	67
Organ dysfunction related to chronic underlying disease		
Pulmonary	2	2
Renal	3	4
Cardiac	12	14
Hepatic	7	8
Other	9	11

Percentages are proportions of all patients (n = 84).

portive measures might indicate a more advanced disease process or a harmful effect of the supportive therapy on the course of the underlying organ insufficiency itself. This interpretation suggests that the difference in oxygenation parameters at admission observed between groups was most likely attributable to the different duration of mechanical ventilation before admission (median of 2 vs. 10 days between responders and nonresponders), representing a different stage of disease process. In accordance with this interpretation, recent studies did not find any relation between pretreatment values of oxygenation parameters and response to inhaled nitric oxide or prone positioning¹⁶⁻¹⁸ in patients with acute onset of ARDS.

Nonresponders received supportive therapy for a longer time period and represent a subgroup of patients with severe end-stage ARDS. However, 60% of these patients effectively could be treated with ECMO, and ultimately they survived.

Because the majority of the patients (69%) were referrals from other hospitals we cannot rule out the possibility of a selection bias toward patients with better prognoses, although, as a rule, only very severe cases are referred to us. When grouped by causes of ARDS according to a recent consensus,¹² 31% of the patients presented with lung contusion and 36% with sepsis syndrome, both of which are associated with decreased survival of ARDS. Furthermore, 60% of patients were in shock at admission, 77% had additional organ failure, and 90% needed inotropic support (table 5). They had high lung injury scores (3.3 ± 0.5), low $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratios (96 ± 45), and high APACHE II scores (18 ± 6), which would have predicted a mortality rate of 36% at admission.

Therapeutic protocols have been evaluated with regard to their impact on improvement of survival and as predictors of prognosis of ARDS.¹⁹⁻²¹ Guinard *et al.*¹⁹ described 36 patients with an improved survival rate in response to a protocol that consisted of a combination of a decrease in extravascular lung water, selection of best ventilatory mode, permissive hypercapnia, correction of hypoxemia by alveolar recruitment, additional oxygen insufflation, prone positioning, inhaled nitric oxide, and almitrine. Nonresponders were defined in their study as patients whose gas exchange did not improve within 2 days, and ECMO ultimately was initiated in 29% of their patients. Improvement in gas exchange during the course of therapy was a strong predictor of survival. Survival among responders was 79% and among nonresponders was 12%. Of patients triaged to ECMO, 40% survived and the overall survival rate was 51%. The remarkably higher overall survival rate of

80% in our series could be attributed to our shorter study period (2.5 vs. 4 yr) and differences in the treatment algorithm. Because we lack precise predictors of response to any given single therapeutic step in ARDS, we made a decision to apply our therapeutic measures strictly in a stepwise fashion to every patient, as described. In our opinion, this approach distinctly decreases the risk of missing potential responders.

Lewandowski *et al.*²⁰ reported improved survival in ARDS in 122 patients treated according to a clinical algorithm that included ECMO. They demonstrated an overall survival rate of 75% over a 5-yr period with a survival rate of 55% in the ECMO group. However, inhaled nitric oxide and prone positioning were introduced as treatment methods about halfway through their series and only approximately 40% of their patients received them, compared with 84 and 89%, respectively, in ours. This may have accounted for the finding that 55% of their patients proceeded to ECMO, compared with only 15% in our series, although the overall outcome was comparable. Treatment protocols that include inhaled nitric oxide have been shown to reduce the incidence of ECMO in a population of pediatric patients, although overall survival was not improved.²² We recently demonstrated an additive effect of prone positioning and inhaled nitric oxide on oxygenation parameters in patients with ARDS,¹⁷ supporting the concept of combining different therapeutic strategies.

Our study differs from the cited studies in two important points: (1) We applied a combined, uniform stepwise treatment protocol, including multiple different steps (pressure-controlled ventilation, high PEEP, prone positioning, inhaled nitric oxide, and ECMO). (2) All patients were treated with all steps, except for ECMO. Therefore, all patients could benefit from each single step and possible additive effects of different treatments. This approach resulted in improved survival and reduced incidence of ECMO when compared to the survival rate reported by Guinard *et al.*¹⁹ and the frequency of ECMO treatment reported by Lewandowski *et al.*²⁰

Experimental data from an animal model revealed strong evidence for the hypothesis that acute lung injury can be induced and promoted by high inspiratory oxygen concentrations and high peak-inspiratory airway pressures.²³⁻²⁶ The application of large tidal volumes, generating high peak airway pressure, also has been implicated as detrimental in acute respiratory insufficiency.^{27,28} One hypothesis for ventilator-induced lung injury is that, not only alveolar overdistension, but also repeated airway space closing and reopening may dam-

age the lung by generating shear stress to the alveoli.²⁹ Therefore, a number of studies have proposed ventilatory strategies to minimize lung stretch and volutrauma.^{6,30,31} Hickling *et al.*³⁰ were the first to report decreased mortality rates for patients with ARDS treated with a ventilatory strategy of limited peak airway pressure and permissive hypercapnia, and demonstrated a mortality rate as low as 17% in an uncontrolled retrospective study. A recently performed prospective randomized trial of this protective ventilatory strategy showed that survival improved at 28 days, but there was no significant difference in overall in-hospital survival.³²

Predictions of mortality in patients who do not respond to conventional treatment are as high as 90%.^{6,8} The 38% mortality rate in our ECMO group suggests that ECMO saved patients who would have died otherwise.

Patients who responded to conventional therapy had a trend toward a better survival than nonresponders, presumably because their lung injury was less severe. However, in our study, this difference did not reach statistical significance.

Our patient population has a selection bias toward patients with an acute critical illness that is complicated by ARDS rather than toward patients with terminal diseases in which ARDS ultimately develops. Mortality was significantly related to the development of multisystem organ failure, suggesting that patients are more likely to die of a septic inflammatory response syndrome of which ARDS is merely one component.

We conclude that treatment of patients with ARDS using a standardized treatment algorithm that includes pressure-limited mechanical ventilation, low tidal volumes, PEEP, inhaled nitric oxide, and prone positioning can achieve survival rates of more than 80%. In our study, the use of ECMO in a subgroup of severely impaired patients who did not respond to conventional therapy was associated with a survival rate of more than 60%. The impact of isolated interventions in patients treated with multiple cointerventions is difficult to assess, and it has been suggested that these difficulties might be resolved by application of standardized treatment protocols.³³ To establish the role of this approach, further prospective studies are needed to evaluate standardized protocols for the treatment of ARDS.

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