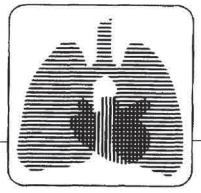

Interest of a Therapeutic Optimization Strategy in Severe ARDS*

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Study objective: **Evaluate the interest of the response to a therapeutic optimization as a predictor of prognosis in ARDS.**
Design: **Prospective study.**
Setting: **ICU of a University Hospital.**
Patients: **Thirty-six consecutive patients with severe ARDS addressed for extracorporeal carbon dioxide removal ($ECCO_2R$).**
Interventions: **We studied the response during the first 2 days after arrival to the therapeutic optimization strategy consisting in a combination of the following: (1) decrease in extravascular lung water (diuretics or hemofiltration); (2) selection of the best ventilatory mode; (3) permissive hypercarbia; and (4) correction of hypoxemia by alveolar recruitment, additional continuous oxygen insufflation, body position changes (prone position), inhaled nitric oxide, enhancement of hypoxic pulmonary vasoconstriction with almitrine, and drainage of pleural or mediastinal effusions. In patients remaining severely hypoxemic despite these modalities, $ECCO_2R$ was then proposed.**
Measurements and results: **Thirty-six patients were addressed after 8.3±5.5 days of mechanical ventilation. On arrival, mean simplified acute physiologic score was 46.8±14.2, multiple system organ failure score was 1.8±1.6, Murray score was 3.4±0.4, PaO_2 was 75.3±31.3 (fraction of inspired oxygen [FIO_2]=1) for a positive end-expiratory pressure level of 12.3±3.4 cm H_2O. Nineteen of 36 patients improved their gas exchange within 2 days and their mortality was 21%. The seventeen remaining patients did not improve PaO_2/FIO_2; $PaCO_2$ and airway pressures remained high and their mortality was 88%. This different response to therapeutic optimization appeared using stepwise logistic regression as the most predictive factor for mortality ($p<0.05$).**
Conclusions: **In patients with severe ARDS, the response to an early performed therapeutic optimization used to improve hypoxemia appeared to be a highly discriminant factor distinguishing deceased from surviving patients.** ***(CHEST 1997; 111:1000-07)***

Key words: adult respiratory distress syndrome (ARDS); extracorporeal CO_2 removal ($ECCO_2R$); hypoxia; prognosis factor; severity scores; therapy

Abbreviations: $ECCO_2R$=extracorporeal carbon dioxide removal; ECMO=extracorporeal membrane oxygenation; FIO_2=fraction of inspired oxygen; LFPPV=low-frequency positive pressure ventilation; MSOF=multiple system organ failure; NO=nitric oxide; PEEP=positive end-expiratory pressure; PIP=peak inspiratory pressure; SAPS II=simplified acute physiologic score II; TO=therapeutic optimization

More than 25 years after its initial description,[1] ARDS remains a challenging organ failure to assist, with a high mortality rate. Despite efforts to clinically define ARDS,[2] a multifactorial disease, a disparity between mortality rates is noted according

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Partially supported by Institutional Grants from University Paris VII, and the Direction de la Recherche et de l'Enseignement Doctoral (DRED).
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to the different diagnosis criteria used.[3] The last decade has consisted in development of several techniques or therapies to support lung failure, but none of them has been evaluated in terms of mortality and morbidity. The recent introduction of permissive hypercapnia,[4-7] ultrafiltration for lung water control,[8-10] low insufflation pressures to prevent barotrauma,[5,6,11,12] and nitric oxide (NO) inhalation,[13-16] associated or not with almitrine,[17,18] might modify the therapeutic management of such patients. Finally, if extracorporeal carbon dioxide removal ($ECCO_2R$) has been proposed for many years,[19] its indications remain difficult, especially if one considers that the recent therapeutic advances improve the parameters originally used to indicate such an invasive support. Recently, it has been shown that the number of extracorporeal membrane oxygenation (ECMO) procedures performed in pediatric patients has been reduced with the introduction of NO inhalation therapy.[20]

The impact on mortality or morbidity of most of these recent therapies has not been yet evaluated by multicentric studies (to our knowledge). However, they might help to stratify the patients as responders or nonresponders to supportive therapies for hypoxemia. We hypothesized that the response to a therapeutic optimization strategy, prospectively tested in patients with severe ARDS, could predict the outcome of such patients. Using stepwise logistic regression, this response was the strongest predictive factor for outcome. Finally, such an approach selected a subgroup of patients with extremely severe disease for whom future trials could be proposed.

Materials and Methods

Patients

Thirty-six consecutive patients suffering from primary or secondary ARDS, without any history of respiratory failure and addressed for $ECCO_2R$ with low-frequency positive pressure ventilation (LFPPV) from April 1991 to November 1995 were studied if the following criteria were present: (1) a Lung Injury Score (Murray Score)[21] higher than 2.5; and (2) entry criteria used in the ECMO study,[22] *ie*, either rapid entry criteria (PaO_2 <50 mm Hg for >2 h when measured at an inspired oxygen fraction [FIO_2] of 1.0 and a positive end-expiratory pressure [PEEP] ≥5 cm H_2O) or slow entry criteria (PaO_2 <50 mm Hg for >12 h when measured at FIO_2 ≥0.6 and a PEEP ≥5 cm H_2O after 48 h of maximal medical therapy). On arrival, simplified acute physiologic score II (SAPS II)[23] and multiple system organ failure (MSOF) scoring were calculated according to criteria of Gattinoni et al.[19] Patients were sedated, paralyzed, and mechanically ventilated (with a Servo 900 C Ventilator; Siemens Elema; Lund, Sweden). Quasistatic lung compliance, mean peak inspiratory, and end-expiratory airway pressures were measured using a ventilatory module (Sirecust 1280; Siemens). Presence of barotraumatic lesions[24] with evidence of extra-alveolar gas (pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, subpleural air cysts) was analyzed on chest radiograph and thoracic CT scan.

Decision-Making Strategy

Thoracic, abdominal, and cerebral CT scans were obtained in all patients. The initial thoracic CT scan allowed the evaluation of the extent of pulmonary edema, pleural effusion, localization of condensation, existence of barotrauma lesions, and bronchial alterations. These CT scan observations and the recently acquired advances in ARDS pathophysiology allowed us to define the following therapeutic optimization (TO) strategy, in addition to classical therapeutic support: (1) decrease in extravascular lung water (with diuretics or continuous hemofiltration) when water balance was positive; significant interstitial edema was present on thoracic CT scan and/or chest radiograph; (2) drainage of bilateral pleural effusion, especially when diffuse lung edema was present;[8-10] (3) tentative action to limit pulmonary blood flow when a hyperkinetic syndrome was present, since in addition to the relationship between intrapulmonary shunt and pulmonary blood flow, passive pulmonary hypertension may potentially worsen lung edema;[25,26] (4) selection of the best ventilatory mode to obtain the lowest possible tidal volume, peak inspiratory pressure (PIP), and mean airway pressure ensuring an adequate alveolar recruitment;[12] a goal of a maximum of 35 cm H_2O for PIP was considered acceptable, and permissive hypercarbia[4-7] was allowed; and (5) correction of arterial hypoxia by ventilation/perfusion ratio manipulation: best alveolar recruitment ("best PEEP" level, insiration to expiration (I/E) ratio modification); additional continuous tracheal oxygen insufflation;[27,28] reduction of blood flow to shunting areas with body position changes based on CT scan imaging, vasodilation of nonshunting zones (NO inhalation <15 ppm monitored with chemiluminescence technique), and/or reinforcement of hypoxic pulmonary vasoconstriction with almitrine bismesylate (Servier; Suresnes, France).[13-18,29-31]

All these modalities were used together or separately according to the repetitive evaluation of lung function and status based on gas exchange, radiologic patterns, and lung mechanics. The results of the TO allowed us to stratify the population of patients as shown in Figure 1. A patient was considered as a responder, when PaO_2 on FIO_2 of 1 was improved and stabilized over 100 mm Hg during at least 6 h. A patient was considered as a nonresponder when (1) PaO_2 on FIO_2 of 1 was lower than 100 mm Hg, or did not improve during at least 6 h; (2) control of $PaCO_2$ was difficult (even considering permissive hypercapnia); or (3) lung mechanics deteriorated. In these patients, even after several days of evaluation, $ECCO_2R$-LFPPV was discussed as a "last chance therapy." This invasive technique was performed as described by Gattinoni et al[19] only after careful consideration of its contraindications:[19,32] potential hemorrhagic lesions of the CNS with contraindications to anticoagulation; hemorrhagic disease; refractory shock; persistent organ failures exceeding four; major burns (total body surface >40%); chronic systemic disease that limits survival (*eg*, cancer, hematologic malignancy, severe inflammatory disease). When a contraindication to $ECCO_2R$-LFPPV was present, the patient was maintained under a regimen of conventional ventilation.

When $ECCO_2R$-LFPPV was performed, the extracorporeal circuit used was a venovenous bypass through two cannulas inserted percutaneously into the two femoral veins (the drainage cannula being located in the lower part of the inferior vena cava, and the return cannula just below the right atrium). The continuously rewarmed and heparinized blood was driven by an occlusive pump (COBE; Lakewood, Calif) through two silicone artificial membrane lungs [7 m^2 total membrane surface area

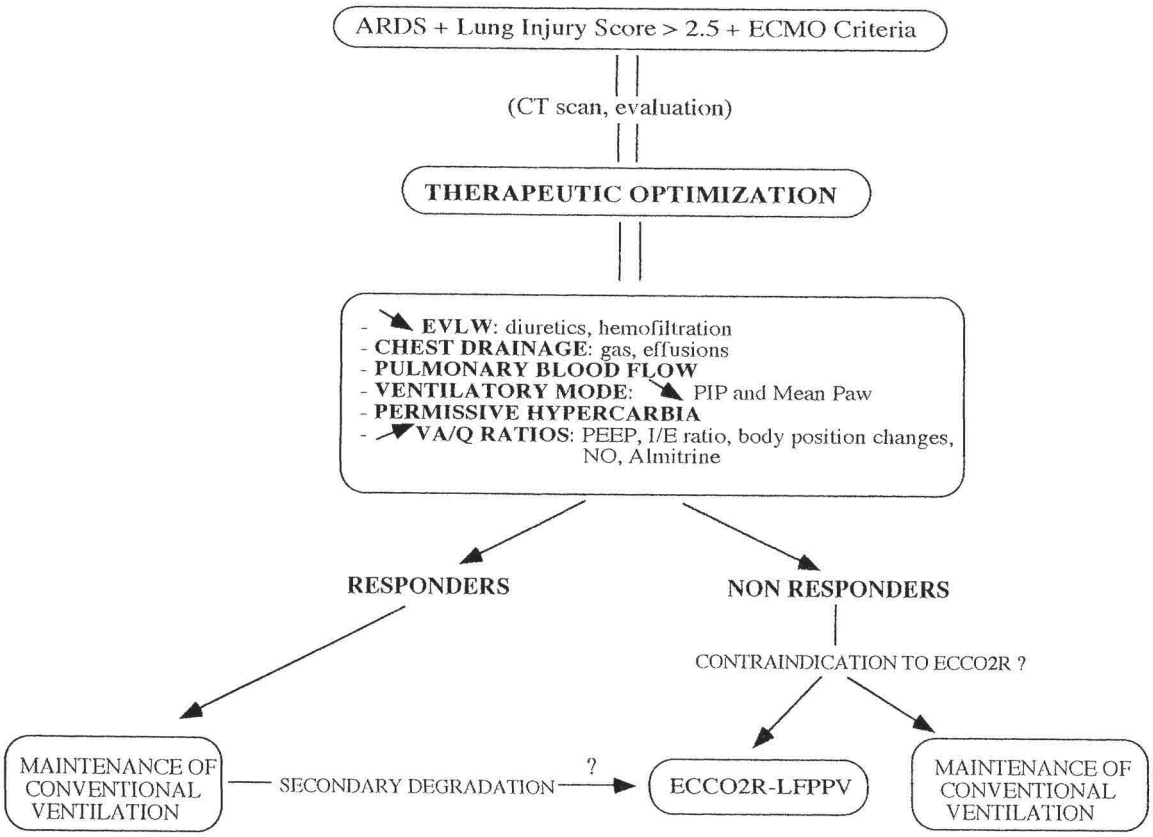

FIGURE 1. Clinical decision-making strategy proposed.

(Ultrox I; Sci Med; Minneapolis)] used in series. A bypass flow of 20 to 30% of cardiac output allowed us to remove CO_2 since membranes were ventilated with a heated humidified mixture of air and oxygen. Lungs were continuously maintained inflated by a permanent positive pressure associated with three to four mechanical cycles per minute with peak airway pressure limited to 40 to 45 cm H_2O by pressure control. Mean airway pressure was kept similar to pre-$ECCO_2R$ value (*ie,* close to the PEEP level). A continuous 1 to 2 L/min oxygen flow was added through a small catheter positioned in the tracheal tube, just above the carina, to cover the needs of whole body oxygen consumption. This average flow rate was increased in case of pleural leak by bronchopleural fistula.

Statistical Analysis

Comparisons between responders and nonresponders (including those treated or not with $ECCO_2R$) were performed with the nonparametric Mann-Whitney test, and evolution of a given parameter within a group with the nonparametric Wilcoxon test. Results are expressed as mean±SD. A p value <0.05 was considered significant.

Potential univariate correlates of mortality were identified by χ^2 analysis for qualitative parameters and Student's *t* test for quantitative parameters. Multivariate analysis was performed using stepwise logistic regression (Biomedical Data Processing Package; UCLA; Los Angeles). Many authors have stressed the difficulty in knowing precisely the exact value of alpha in multiple regression procedures,[33,34] which may lead to an overestimation of the number of predictive variables. In the present study, we used conservative criteria to select predictive variables: (1) limits to enter or remove variables in the regression equation must have had a 5% probability value; (2) for each candidate as a predictive factor, the ratio between the corresponding regression coefficient and its SE must have been greater than 2;[35] and (3) results were verified using two different numerical procedures, an asymptomatic covariance estimate and the maximum-likelihood method; p values corresponding to the improved χ^2 are given in the tables.

RESULTS

Patients' Characteristics on Arrival

Table 1 summarizes the clinical characteristics of the 36 patients on arrival. Mean SAPS II was 46.8±14.2, MSOF was 1.8±1.6, and Murray score was 3.4±0.4 (range, 2.6 to 4). Only nine patients suffered from isolated respiratory failure, without other system organ failure. The etiologies of the ARDS were both primitive (25 patients) and secondary (11 patients). Duration of mechanical ventilation before arrival was 8.2±5.5 days (range, 1 to 20 days). All patients had the rapid or slow ECMO criteria.

Table 1—*Clinical Characteristics of Patients on Arrival*

Patient No./Age, yr/Sex	Diagnosis or Risk Factor for ARDS	SAPS II	MSOF*	Murray Score	Duration of Mechanical Ventilation,† d
1/17/M	Fat embolism	42	3	3.7	1
2/22/F	Pneumonia	41	1	3.5	11
3/25/M	Pneumonia	37	2	3.7	1
4/22/M	Multiple trauma	46	0	3	11
5/36/M	Pneumonia	24	1	2.7	13
6/22/M	Multiple trauma	29	0	3.3	19
7/36/F	Gastric aspiration	26	1	3.5	7
8/44/M	Pneumonia	43	4	3	3
9/41/F	Gastric aspiration	41	0	2.6	2
10/51/M	Pneumonia	50	2	4	5
11/52/F	Vasculitis	52	4	3.66	7
12/48/M	Sepsis	47	1	3.75	7
13/25/F	Lung contusion	23	0	2.7	6
14/42/F	Pneumonia	31	1	3	2
15/26/F	Eclampsia	40	0	3.5	9
16/20/F	Sepsis	85	3	3.75	10
17/20/F	Multiple trauma	50	0	3.7	18
18/47/M	Pneumonia	58	4	3.5	9
19/55/F	Sepsis	70	3	3.75	11
20/28/F	Gastric aspiration	56	2	3.25	21
21/39/F	Gastric aspiration	38	0	3	11
22/31/F	Pneumonia	51	2	3.5	9
23/33/M	Pneumonia	60	3	3.25	10
24/33/F	Pneumonia	62	4	3	20
25/60/M	Sepsis	49	2	3	10
26/47/M	Pneumonia	56	5	3.75	6
27/16/F	Pneumonia	35	1	4	1
28/21/M	Multiple trauma	36	1	4	4
29/43/F	Pneumonia	48	4	3.33	5
30/29/F	Gastric aspiration	81	4	3.66	10
31/45/M	Pneumonia	38	0	3.33	7
32/39/M	Gastric aspiration	55	1	3.33	13
33/58/M	Pneumonia	41	0	3.33	10
34/38/F	Sepsis	54	4	4	3
35/21/F	Pneumonia	35	1	3.75	2
36/39/F	Eclampsia+aspiration	54	1	3.25	1
Mean 35.3, F=20	Primary=23	46.8	1.8	3.4	8.2
SD 12.4, M=16	Secondary=11	14.2	1.6	0.4	5.5

*Calculated with the same definitions as Gattinoni et al.[19]
†Duration of mechanical ventilation reflects total duration before admission.

Mean PaO_2 was 75.3±31.3 mm Hg at an FIO_2 of 1 for a mean PEEP level of 12.3±3.4 cm H_2O. Mean $PaCO_2$ was 50.7±13.7 mm Hg. PIP and mean airway pressures were elevated (39.7±8 and 22.1±4.9 cm H_2O, respectively). Quasistatic pulmonary compliance was 26.9±10.4 mL/cm H_2O. Fifty-five percent of the patients had barotraumatic lesions.

Response to TO

According to their response to TO, the population was separated in two groups named "responders" and "nonresponders" (see "Materials and Methods" section). Considering the severity criteria on arrival in the two groups, the only differences concerned MSOF score and $PaCO_2$ values, which were initially higher in nonresponders (Table 2). It should be noted that Murray score, lung mechanic parameters, PaO_2, PEEP level, and duration of mechanical ventilation on arrival did not differ.

Responders Group (n=19): Nineteen of 36 patients were considered as responders according to the defined criteria and were maintained under conventional ventilation. All these patients improved their gas exchange within 2 days. In addition to PaO_2/FIO_2 increase, $PaCO_2$, PEEP, and mean airway pressures did not change and PIP decreased (Fig 2). This improvement seen in the first 2 days did not correspond to the best values observed, since the conditions of some patients continued to improve in the following days. Conversely, despite an initial

Table 2—*Initial Severity Criteria on Arrival in Responders and Nonresponders to TO

	Responders (n=19)	Nonresponders (n=17)
Age, yr	35.5±12.4	35.1±12.7
SAPS II	43±14	51±14
MSOF	1.3±1.3	2.4±1.7†
Murray score	3.4±0.5	3.5±0.3
Duration of mechanical ventilation, d	6.7±4.3	9.9±6.2
PaO_2 (FIO_2=1)	76.8±34.9	73.6±27.7
$PaCO_2$	47.1±13.6	54.8±13.1†
PIP	38.4±6.1	41.1±9.8
Mean Paw	22.3±5	22±5
PEEP	13.1±3.6	11.4±3.1
Cqs	29.6±12.3	23.7±6.9
Barotrauma, %	53	59

*Paw=airway pressure; Cqs=quasi-static lung compliance.
†$p<0.05$ (mean±SD).

improvement, the conditions of two patients of this group deteriorated so severely at day 5 and day 6 that an $ECCO_2R$-LFPPV was decided, with good success. In this group, four patients died (21%) after the third week because of MOSF (n=2), septic shock (n=1), and hemoptysis (n=1).

Nonresponders Group (n=17): Seventeen patients of the initial population (47%) did not improve their PaO_2/FIO_2 during TO during the first 2 days, as shown in Figure 2 (nonresponders). In addition, $PaCO_2$, PIP, airway pressure, and PEEP levels remained high despite maximum TO, leading us to discuss an indication of $ECCO_2R$-LFPPV. Applying the contraindication criteria described in the "Materials and Methods" section, $ECCO_2R$-LFPPV was not possible for nine patients (53% of nonresponders), all who died from different causes (78% with MSOF). For the remaining eight patients, $ECCO_2R$-LFPPV was performed, and a high morality rate (six of eight patients) was observed during the procedure. One patient died of persistent hypoxemia and barotraumatic lesions; other causes of deaths were three hemorrhagic complications (one intracerebral hemorrhage and two pulmonary/pleural bleedings), and evolution of an initially severe MSOF in two patients presenting on arrival with a score of 4 and 5, respectively. For the two surviving patients, $ECCO_2R$-LFPPV technique was maintained during 3 days. Therefore, overall mortality in nonresponders was 88%, compared with a 21% mortality rate in responders ($p<0.0001$).

Univariate and Multivariate Analysis

Table 3 summarizes the variables analyzed in relation to outcome. Considering the initial severity criteria on arrival in responders and nonresponders to TO listed in Table 2, univariate analysis revealed that, in addition to a favorable response to TO, SAPS II, MSOF, previous duration of mechanical ventilation on arrival, and $PaCO_2$ were associated with an adverse outcome. Age, Murray score, PaO_2, airway pressures, lung compliance, and existence of barotrauma lesions were not univariate correlates of adverse outcome.

Stepwise logistic regression analysis was then performed, and the response to TO appeared as the most predictive factor for survival. Then SAPS II was selected as the second independent predictor. None of the other parameters tested fulfilled the selection criteria of the multivariate procedure.

Discussion

ARDS remains one of the most challenging organ failures to assist, even using sophisticated modes of mechanical ventilation.[5,12,36] Since the initial definition by Ashbaugh et al[1] in 1967, the improvement in outcome remains debated, even if mortality is probably lower than previously reported.[3] The absence of a clear amelioration in the outcome may result from different causes. First, the definition is large (although a new definition has been recently attempted[2]) and concerns different abnormalities and mechanisms; second, the underlying conditions of the patients play a crucial role; third there is no widely accepted consensus on the therapeutic strategy. During the past decade, the concept of MOSF has become increasingly crucial in the prognosis of severely ill patients, including those with ARDS. In addition, the better understanding of the pathophysiologic condition had led us to take into account different aspects of the lung lesion mechanisms, especially those induced by mechanical ventilation itself.[37,38] Moreover, to our knowledge, no data have clearly demonstrated that a symptomatic correction of hypoxemia results in improved outcome of such patients.

Using the approach of the response to different therapeutic strategies aimed at correcting hypoxemia while limitating iatrogenic lung lesions, one could expect to obtain a useful classification of the patients in terms of (1) outcome, (2) pathophysiology, and (3) selection of subgroups of severely ill patients for whom future controlled trials or sophisticated assistance techniques could be tested. In the present study, despite a relatively small number of patients, a combination of techniques was used to improve hypoxemia, and the response to such a strategy discriminated responders from nonresponders. The absence of any response to TO was frequently

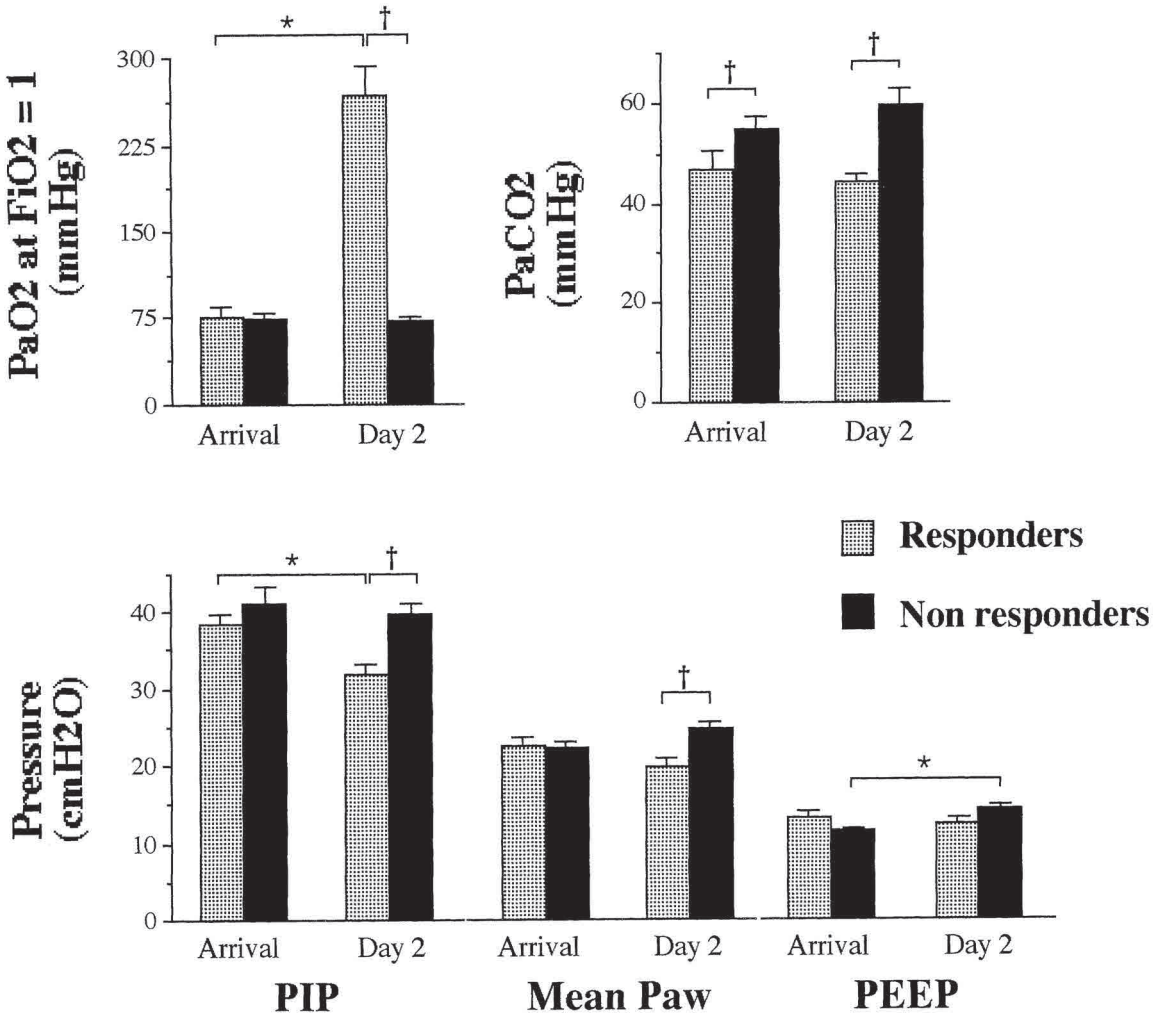

FIGURE 2. Evolution of gasometric and ventilatory parameters (mean±SE) in "responders" and "nonresponders" on arrival and during the first 48 h of TO. Mean Paw=mean airway pressure. Asterisk indicates $p<0.05$ compared with value on arrival in the same group; dagger, $p<0.05$ between responders and nonresponders.

associated with a more severe MOSF, reflecting the severity of the pulmonary and systemic inflammation.

The population selected in the present study was similar, considering Murray score,[21] to recently published series,[32,39] with a comparable global mortality rate.[3,32,40] Mortality was mainly due to MOSF, sepsis, and $ECCO_2R$ adverse effects, but rarely to respiratory failure *per se,* and, except for SAPS II, it was impossible to predict outcome based on initial data upon arrival in the ICU. In the present study, the TO used included various individual elements such as inhaled NO, prone position, or permissive hypercarbia. Considering the difficulty in conducting prospective controlled studies on the benefit of each of these individual therapies on outcome, we observed that the response to TO was the strongest discriminant criterion for outcome.

Using this TO strategy, we observed that half of the patients improved in terms of PaO_2/FIO_2. The follow-up of this group showed a significantly better prognosis than in nonresponders. The discussion of these results can only be speculative. First, comparison of the two groups suggests that nonresponders were more severe in terms of inflammatory reaction, since the incidence of organ failure was higher. In addition, their lung disease might also have been worse since $PaCO_2$ was higher for a similar ventilation. Although gas exchange function is not the main parameter to assess severity in ARDS, its improvement can be viewed as a dynamic means to evaluate the severity of the underlying inflammatory disease. Finally, although it has not been clearly demonstrated that hypoxia might precipitate organ failure, these consequences might be limited by hypoxemia correction. In the present population, severe hypoxia

Table 3—*Univariate and Multivariate Analysis of Outcome*

	Deceased Patients (n=19)	Surviving Patients (n=17)	p Value Univariate Analysis	p Value Multivariate Analysis
Responders to TO, %	21.1	88.2	<0.05	<0.05
Age, yr	37.4±13	32.9±11.6	NS	NS
SAPS II	54.1±13.6	38.6±9.8	<0.05	<0.05
MSOF	2.5±1.6	1±1.1	<0.05	NS
Murray score	3.5±0.3	3.3±0.5	NS	NS
Duration of mechanical ventilation, d	10.5±5.3	5.6±4.5	<0.05	NS
PaO_2 (FIo_2=1)	74.5±24.8	76.2±38	NS	NS
$PaCO_2$	57.4±15.6	43.2±5.1	<0.05	NS
PIP	41.4±8.9	37.8±6.7	NS	NS
Mean Paw	23.6±4.8	20.5±4.6	NS	NS
PEEP	12.7±3.3	11.8±3.6	NS	NS
Cqs	26.1±10.2	27.7±11	NS	NS
Barotrauma, %	52.6	58.8	NS	NS

*See Table 2 for explanation of abbreviations. NS=not significant.

was the cause of death for only two patients. Such a proportion is low, but not negligible, and promotes the idea of a low threshold of hypoxia tolerable by the organism. Above this level (around 60 mm Hg), the benefit for tissues of a PaO_2 increase is still debated. Experimental data suggest, nevertheless, that in addition to the metabolic aspects, hypoxia worsens the immunologic response and stimulates cytokines release.[41,42] Conversely, the reoxygenation might also induce some tissue damage.[43,44] It is then difficult to conclude about the role of the correction of a hypoxia as a prognosis factor rather than a marker of severity. Accordingly MSOF, rather than acute respiratory failure, remains the main cause of mortality in ARDS despite efficiency of supportive therapy.[45-47]

Following the above discussion, the use of $ECCO_2R$ as a technique to improve PaO_2 and to limit induced-lung lesions is questionable. The present data suggest again that the benefit of such technique is influenced by the origin group, *ie*, responders or nonresponders. Two patients in the responders group were treated by $ECCO_2R$ because of a secondary deterioration and survived. Conversely, in nonresponders, survival rate when $ECCO_2R$ was performed was only 25%. Despite these very small numbers of patients, it is important to note that all patients with a contraindication to $ECCO_2R$ died. This might suggest that $ECCO_2R$ could be helpful as a last therapeutic support in selected patients failing to respond to TO, although the efficiency of this technique is still limited by its intrinsic complications.

The ability of the lung to recover structurally and functionally after a severe insult seems an important prognosis factor in ARDS, but assessment of the potential reversibility of the pulmonary injury is difficult. Gasometric or pulmonary mechanics parameters are poor predictive factors. In contrast, the response to a TO strategy appeared, using stepwise logistic regression, as the most predictive factor for mortality. Such an approach could also be used in the future to select subgroups of patients for investigational trials.

ACKNOWLEDGMENTS: The authors wish to thank Dr. Eric Vicaut for his statistical advice.

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