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# Characteristics and Outcomes in Adult Patients Receiving Mechanical Ventilation

## A 28-Day International Study

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INFORMATION ABOUT THE MORTALITY of patients requiring mechanical ventilation is important because it allows for better counseling of patients and their families. Investigators have evaluated the outcome in patients receiving mechanical ventilation for specific indications. For example, among 362 patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) selected from the APACHE III database, Seneff et al<sup>1</sup> found hospital survival was 68% in patients receiving mechanical ventilation. Survival of patients with acute respiratory distress syndrome (ARDS) has also been addressed.<sup>2-8</sup> In the control group of these clinical trials,<sup>2-6</sup> survival is considerably more (50%-65%) than in the cohort studies (approximately 40%),<sup>7-10</sup> perhaps re-

**Context** The outcome of patients receiving mechanical ventilation for particular indications has been studied, but the outcome in a large number of unselected, heterogeneous patients has not been reported.

**Objective** To determine the survival of patients receiving mechanical ventilation and the relative importance of factors influencing survival.

**Design, Setting, and Subjects** Prospective cohort of consecutive adult patients admitted to 361 intensive care units who received mechanical ventilation for more than 12 hours between March 1, 1998, and March 31, 1998. Data were collected on each patient at initiation of mechanical ventilation and daily throughout the course of mechanical ventilation for up to 28 days.

**Main Outcome Measure** All-cause mortality during intensive care unit stay.

**Results** Of the 15757 patients admitted, a total of 5183 (33%) received mechanical ventilation for a mean (SD) duration of 5.9 (7.2) days. The mean (SD) length of stay in the intensive care unit was 11.2 (13.7) days. Overall mortality rate in the intensive care unit was 30.7% (1590 patients) for the entire population, 52% (120) in patients who received ventilation because of acute respiratory distress syndrome, and 22% (115) in patients who received ventilation for an exacerbation of chronic obstructive pulmonary disease. Survival of unselected patients receiving mechanical ventilation for more than 12 hours was 69%. The main conditions independently associated with increased mortality were (1) factors present at the start of mechanical ventilation (odds ratio [OR], 2.98; 95% confidence interval [CI], 2.44-3.63;  $P < .001$  for coma), (2) factors related to patient management (OR, 3.67; 95% CI, 2.02-6.66;  $P < .001$  for plateau airway pressure  $> 35$  cm H<sub>2</sub>O), and (3) developments occurring over the course of mechanical ventilation (OR, 8.71; 95% CI, 5.44-13.94;  $P < .001$  for ratio of PaO<sub>2</sub> to fraction of inspired oxygen  $< 100$ ).

**Conclusion** Survival among mechanically ventilated patients depends not only on the factors present at the start of mechanical ventilation, but also on the development of complications and patient management in the intensive care unit.

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flecting restrictive, inclusion criteria enrolling less severely-ill patients. For example, 88% of patients screened for the ARDS Network trial were excluded; mortality in these patients was higher than those included in the trial.<sup>11</sup>

Vasilyev et al<sup>12</sup> conducted an international multicenter prospective study to determine the hospital survival rates of patients with acute respiratory failure (ARF) managed in the intensive care unit (ICU). Of 1426 patients admitted to ICUs from 11 centers in the United States and 14 centers in Europe, 633 patients (44%) died in the hospital. Univariate analysis revealed that the most important predictors of hospital survival were severity of lung dysfunction, etiology of ARF, and multiorgan dysfunction. Another prospective study<sup>13</sup> in 132 ICUs from Sweden, Denmark, and Iceland determined that 1231 patients required mechanical ventilation for more than 24 hours within the first week after ICU admission; the 90-day mortality was 41%. Age, acute physiology score of more than 15, a nonpulmonary origin of respiratory failure, more than 2 quadrants with infiltrates, and immunosuppression were independently associated with outcome. A retrospective cohort<sup>14</sup> of 61 113 patients in 904 US hospitals yielded a 31-day hospital mortality rate of 31%. The multivariate analysis showed that factors independently associated with an increased mortality were age, multiorgan system failure, human immunodeficiency virus infection, chronic liver disease, and cancer.

The objective of this study was to determine the survival and the relative importance of many factors influencing survival of mechanically ventilated patients, such as baseline characteristics at the start of mechanical ventilation, ventilatory settings, and organ failure developing over the course of mechanical ventilation.

## METHODS

### Study Design

We conducted a prospective cohort study of consecutive adult patients admitted to 361 ICUs in 20 countries and

who received mechanical ventilation for more than 12 consecutive hours between March 1, 1998, and March 31, 1998. Before data collection, the study protocol was reviewed and approved by institutional review committees of each hospital.

To minimize behavior change as a result of being observed, only the investigator and research coordinator in each ICU were aware that the study was under way. Each investigator and research coordinator was provided with a manual describing data collection and definitions. Each country had a national coordinator who was able to answer questions regarding data collection. Before the initiation of the study, forms were completed for 10 patients in 3 different ICUs to evaluate their comprehensibility and reproducibility. Based on difficulties detected during this initial evaluation, forms were modified before commencing the study. Each questionnaire was checked by 3 study coordinators to identify omissions and inconsistent data were corrected.

The following information was collected in each patient: age, sex, weight, simplified acute physiology score II (SAPS II) at the time of admission to the ICU, chronic functional status, indication for the initiation of mechanical ventilation, and modality of ventilatory support (noninvasive or conventional mechanical ventilation).<sup>15</sup> The following events were assessed daily during the course of mechanical ventilation for a maximum of 28 days: need for tracheal intubation in patients receiving noninvasive mechanical ventilation, ARDS, barotrauma, pneumonia, sepsis, renal failure, hepatic failure, and coagulopathy. Because sepsis, pneumonia, and ARDS could be reasons for the initiation of mechanical ventilation, they were considered as events only if they appeared more than 48 hours after mechanical ventilation was started. Acute respiratory distress syndrome was defined according to the criteria of the American-European consensus conference.<sup>16</sup> Sepsis and shock were defined according to the criteria of the American College of Chest Physicians-

Society of Critical Care Medicine consensus conference.<sup>17</sup> Barotrauma refers to the development of at least 1 of the following: interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema. Ventilator-associated pneumonia was defined according to the modified Centers for Disease Control and Prevention criteria,<sup>18</sup> which require a new radiographic infiltrate persistent for 48 hours or more plus a body temperature more than 38.5°C or less than 35.0°C, a leukocyte count of more than 10 000/ $\mu$ L or less than 3000/ $\mu$ L, purulent sputum or change in character of sputum, or isolation of pathogenic bacteria from an endotracheal aspirate. Renal failure was defined as an acute increase in creatinine of more than 2 mg/dL (177  $\mu$ mol/L), double the baseline value in a patient with underlying chronic renal failure, and/or the need for acute hemodialysis or acute use of any form of dialysis. Hepatic failure was defined as an acute change in bilirubin to more than 2 mg/dL (34  $\mu$ mol/L) with transaminase and lactic dehydrogenase levels at least twice the upper limit of normal. Coagulopathy was defined as a decrease in the platelet count of 25% or more from the baseline with an increase in prothrombin time at least twice the control value.

The first arterial blood gas measurement and corresponding ventilator settings were recorded daily while patients received mechanical ventilation for a maximum of 28 days. The use of neuromuscular blockers, sedatives, and vasoactive drugs (given for  $\geq$ 3 hours during a 24-hour period) was recorded daily for a maximum of 28 days.

Duration of mechanical ventilation was defined as the time elapsed from the initiation of ventilatory support to the onset of weaning.<sup>19-21</sup> The onset of weaning was the time that the physician in charge considered the patient likely to resume and sustain spontaneous breathing. Weaning was performed by either a reduction in the level of ventilator support or a trial of spontaneous breathing. The need for reintubation within 48 hours after extuba-

tion and the time of reintubation were recorded. All patients were followed up until hospital discharge.

### Statistical Analysis

The primary outcome measure was all-cause mortality during ICU stay. All variables were grouped in 3 categories: factors present at the start of mechanical ventilation, factors related to patient management, and events occurring over the course of mechanical ventilation. The categorical variables, such as presence of particular manifestations, were coded as 0 (absence) or as 1 (presence). With respect to those variables grouped in the categories of factors related to patient management and events occurring over the course of mechanical ventilation, a patient was considered to have any of the above conditions if present for at least 2 consecutive days. For the PaO<sub>2</sub>/FIO<sub>2</sub> ratio, the lowest value was selected. Some continuous variables (such as age, SAPS II score, PaO<sub>2</sub>/FIO<sub>2</sub> ratio, positive end-expiratory pressure, tidal volume) were coded as dummy variables that compare all categories with that category having the lower mortality. The remaining continuous variables were dichotomized using cutoff points that were clinically relevant with previously published threshold values. For the univariate analysis, frequencies were compared by the  $\chi^2$  test and adjusted odds ratios, and 95% confidence intervals (CIs) were calculated. Comparison among groups according to the reason for the initiation of ventilation were made using 1-way analysis of variance for continuous variables. The Kaplan-Meier method was used to determine the probability of survival over duration of ventilation.

To estimate the simultaneous effects of multiple variables on ICU mortality, a multivariate analysis was performed using a conditional logistic regression model and a forward stepwise selection method to correct for collinearity. The criterion for entering variables tested in the model were selected if  $P < .10$ . We used a logistic regression analysis in place of a Cox proportional hazards model because a large number of the variables did not satisfy the assumption of propor-

tional hazards. Statistical analysis was performed with SPSS version 8.0 (SPSS Inc, Chicago, Ill).

### RESULTS

Seventy-seven percent of the 361 ICUs included in the study were medical/surgical, 19% were medical, and 4% were surgical. Ninety percent of the participant ICUs were located at postgraduate teaching hospitals and 69% at pregraduate teaching hospitals. In the 361 ICUs, 15 757 patients were admitted during the study period and 5183 (33%) received mechanical ventilation for more than 12 hours. A total of 5131 (99%) patients were followed up during their entire course of mechanical ventilation and 52 (1%) were followed up for the first 28 days of ventilation. Demographic characteristics and the reasons for instituting mechanical ventilation are listed in TABLE 1.

Mechanical ventilation was delivered through an orotracheal tube in

4614 (89.0%) patients, a nasotracheal tube in 211 (4.1%) patients, a facial mask in 256 (4.9%) patients (16.9% among patients ventilated because of an exacerbation of COPD), and a tracheostomy in 102 (2.0%) patients. Of the 256 patients who initially received noninvasive ventilation, 81 (31.6%) needed tracheal intubation. Eighty-five patients with COPD received noninvasive ventilation and 22 (25.9%) subsequently required tracheal intubation. Of the 148 patients with ARF who received noninvasive ventilation, 54 (36.5%) subsequently required tracheal intubation.

TABLE 2 lists the duration of mechanical ventilation until weaning, the duration of weaning, length of ICU stay, and length of hospital stay according to the reason for initiating mechanical ventilation; the times for mechanical ventilation and weaning are exclusive of each other. The ventilator modes and settings at the time of obtaining blood

**Table 1.** Characteristics of the Studied Patients on Admission to the Intensive Care Unit (ICU)\*

Characteristic	No. (%) of Patients Mechanically Ventilated (N = 5183)
Age, mean (SD) [median {IQR}], y	59.2 (17.3) [63 {48-73}]
Sex, females	1985 (38.7)
SAPS II score, mean (SD) [median {IQR}]	44.1 (17.0) [43 {32-54}]
Prior functional status, limited activity	2016 (38.9)
Medical/surgical	3428 (66.1)/1755 (33.9)
Reason for the initiation of mechanical ventilation	
Acute respiratory failure	3564 (68.8)
Coma	864 (16.7)
Acute respiratory failure on chronic pulmonary disease	
COPD	522 (10.1)
Asthma	79 (1.5)
Chronic respiratory disease (non-COPD)	60 (1.2)
Neuromuscular disease	94 (1.8)
Cause of acute respiratory failure†	
Postoperative	1080 (20.8)
Pneumonia	721 (13.9)
Congestive heart failure	539 (10.4)
Sepsis	458 (8.8)
Trauma	407 (7.9)
ARDS	231 (4.5)
Aspiration	129 (2.5)
Cardiac arrest	100 (1.9)
Other	367 (7.1)

\*IQR indicates interquartile range; SAPS II, simplified acute physiology score II; COPD, chronic obstructive pulmonary disease; and ARDS, acute respiratory distress syndrome.

†More than 1 cause of acute respiratory failure per patient was permitted.

gases in the morning are listed in TABLE 3 according to the reason for initiating mechanical ventilation. FIGURE 1 shows the ventilator modes in the whole group over time.

A total of 5199 weaning attempts were undertaken in 3640 (70.2%) patients using the following methods: once-daily weaning trial in 2833 (77.8%) attempts, multiple weaning trials in 510 (14.0%) attempts, gradual reduction of pressure support in 752 (20.7%) attempts, gradual reduction of synchronized intermittent mandatory ventilation in 311 (8.5%) attempts, and

gradual reduction in the simultaneous use of synchronized intermittent mandatory ventilation and pressure support in 793 (21.8%) attempts. The trials of weaning were performed with a T-tube in 1725 (51.6%) attempts, continuous positive airway pressure in 643 (19.2%) attempts, pressure support of about 7 cm H<sub>2</sub>O in 943 (28.2%) attempts, and flow-by in 32 (1.0%) attempts.

Deliberate extubation was performed in 2858 (55.1%) patients; of these patients, 350 (12.2%) required reintubation within 48 hours (56.5% in

the first 12 hours, 18.7% between 12 and 24 hours, 24.7% between 24 and 48 hours). Unplanned extubation was reported in 179 (3.4%) patients; of these patients, reintubation was required in 74 (41.3%) with 79.7% occurring in the first 12 hours after extubation, 9.5% between 12 and 24 hours, and 6.7% between 24 and 48 hours (time of reintubation of 3 patients was unknown).

Patients experienced the following during mechanical ventilation: barotrauma, 154 (3.0%); ARDS, 218 (4.4%); pneumonia, 439 (9.8%); sepsis, 457 (9.7%); shock, 1145 (22.1%); acute re-

**Table 2.** Duration of Ventilator Support Until the Start of Weaning, Duration of Weaning, and Length of Stay in the Intensive Care Unit (ICU) and Hospital in Studied Patients\*

	Duration, Mean (SD) [Median {IQR}], d			P Value
	Overall	COPD	ARDS	
Duration of mechanical ventilation	5.9 (7.2) [3 {2-7}]	5.1 (5.3) [4 {2-6}]	8.8 (8.5) [6 {3-11}]	<.001
Duration of weaning	4.2 (7.2) [2 {1-4}]	4.7 (7.8) [2 {1-5}]	5.0 (5.6) [3 {1-6}]	.55
Length of stay in ICU	11.2 (13.7) [7 {4-14}]	11.2 (10.6) [8 {5-13}]	14.3 (17.7) [9 {5-20}]	.01
Length of stay in hospital	22.5 (23.7) [16 {9-29}]	21.2 (17.7) [17 {10-27}]	24.5 (24.8) [19 {9-31}]	.07

\*COPD indicates chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; and IQR, interquartile range. P values are for comparisons between COPD and ARDS patients.

**Table 3.** Ventilator Modes and Monitored Variables on Days 1, 3, and 7 of Mechanical Ventilation in Patients With an Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) or Acute Respiratory Distress Syndrome (ARDS)\*

	COPD			ARDS		
	Day 1 (n = 522)	Day 3 (n = 283)	Day 7 (n = 85)	Day 1 (n = 231)	Day 3 (n = 174)	Day 7 (n = 82)
Ventilator modes, No. (%)						
A/C	344 (65.9)	180 (63.6)	57 (67.1)	155 (67.0)	111 (63.8)	50 (61.0)
SIMV/PS	50 (9.6)	32 (11.3)	9 (10.6)	24 (10.4)	20 (11.5)	8 (9.8)
PS	40 (7.6)	24 (8.5)	10 (11.8)	3 (1.4)	6 (3.4)	3 (3.7)
PCV	20 (3.9)	11 (3.9)	2 (2.4)	24 (10.4)	23 (13.2)	13 (15.9)
SIMV	24 (4.6)	10 (3.5)	2 (2.4)	10 (4.2)	4 (2.3)	2 (2.4)
Other	39 (8.5)	26 (9.2)	1 (1.2)	15 (6.6)	10 (5.7)	6 (7.3)
Monitored variables, mean (SD) [median {IQR}]						
Peak pressure, cm H <sub>2</sub> O	31 (9) [31 {25-38}]	31 (9) [32 {25-37}]	32 (9) [32 {25-38}]	34 (9) [34 {28-40}]	33 (8) [32 {27-39}]	33 (9) [34 {27-40}]
Plateau pressure, cm H <sub>2</sub> O†	22 (6) [20 {17-26}]	22 (6) [21 {17-27}]	23 (7) [23 {18-28}]	28 (7) [28 {23-33}]	27 (7) [27 {21-30}]	26 (7) [25 {21-30}]
Tidal volume, mL	586 (133) [580 {500-692}]	564 (128) [550 {500-640}]	589 (135) [600 {500-670}]	616 (135) [600 {500-700}]	607 (131) [600 {500-700}]	613 (141) [600 {500-700}]
Tidal volume, mL/kg	8.4 (2.3) [8.3 {6.7-10.0}]	8.0 (2.3) [7.8 {6.4-9.6}]	8.1 (2.6) [7.9 {6.0-10.0}]	8.7 (2.0) [8.6 {7.4-10.0}]	8.5 (2.0) [8.4 {7.3-10.0}]	8.5 (2.0) [8.2 {6.9-10.0}]
Respiratory rate, breaths/min	17 (6) [16 {14-20}]	17 (5) [16 {14-20}]	17 (5) [18 {12-20}]	20 (6) [18 {15-22}]	21 (7) [20 {16-20}]	20 (6) [20 {16-22}]
FiO <sub>2</sub>	52 (18) [50 {40-60}]	46 (13) [40 {40-50}]	50 (18) [40 {40-60}]	74 (21) [70 {59-100}]	63 (21) [60 {50-80}]	59 (22) [50 {40-74}]
Patients without PEEP, No. (%)	218 (47.6)	128 (45.2)	33 (38.8)	34 (16.0)	14 (8.0)	8 (9.7)
PEEP, cm H <sub>2</sub> O	5 (2) [5 {4-5}]	5 (2) [5 {5-6}]	6 (3) [5 {4-7}]	8 (4) [8 {5-10}]	9 (3) [10 {6-12}]	9 (3) [9 {5-12}]

\*A/C indicates assist/control ventilation; SIMV, synchronized intermittent mandatory ventilation; PS, pressure support; PCV, pressure-controlled ventilation; IQR, interquartile range; and PEEP, positive end-expiratory pressure.

†Plateau pressure only recorded in patients ventilated with A/C.

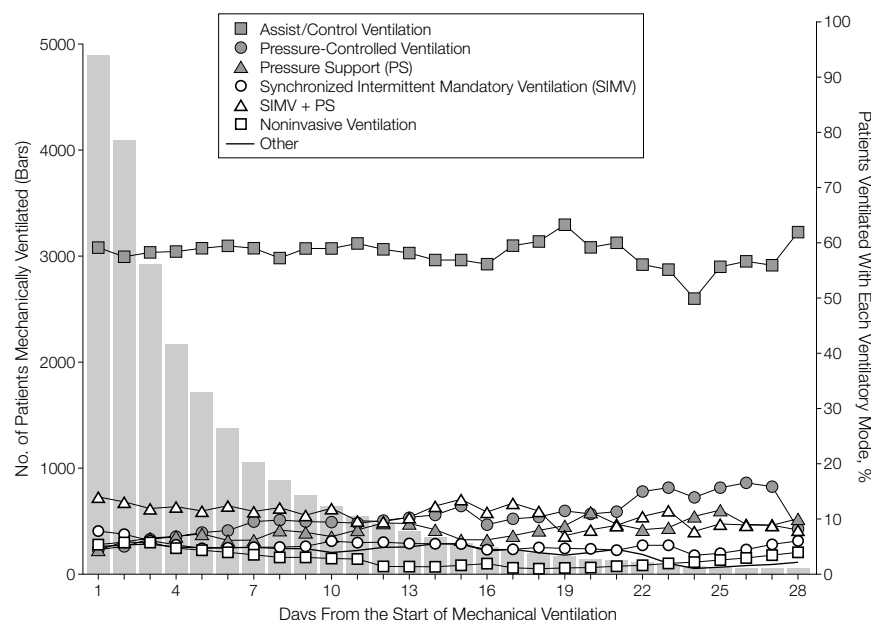
nal failure, 971 (18.7%); hepatic failure, 326 (6.3%); coagulopathy, 552 (10.6%); respiratory acidosis, 288 (5.6%); and metabolic acidosis, 311 (6.0%).

Among the 5183 studied patients, 1590 died in the ICU (overall unit mortality: 30.7%). Of 4718 patients with known vital status at hospital discharge, 1876 were alive (hospital mortality: 39.2%). FIGURE 2 shows the Kaplan-Meier curves of the probability of survival over time of patients mechanically ventilated because of COPD, asthma, ARDS, and non-ARDS causes of ARF.

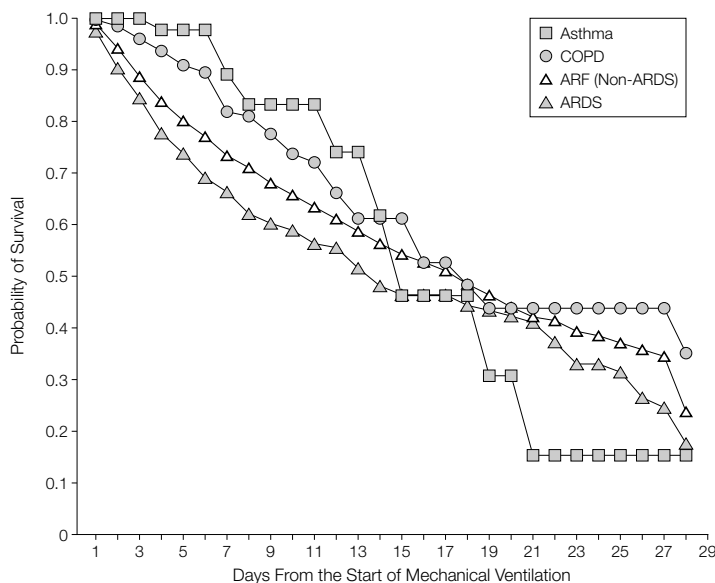
The ICU mortality associated with reintubation was 32.4% in patients with unplanned extubation and 22.6% in patients with planned extubation. The ICU mortality was 14.3% in patients with successful noninvasive ventilation and 42.0% in patients needing tracheal intubation after a failed attempt at noninvasive ventilation. Among patients with COPD ventilated because of ARF, ICU mortality was similar in those intubated after a failed attempt at noninvasive ventilation and in those treated with invasive ventilation (27.3% vs 23.8%,  $P = .91$ ). Conversely, among patients ventilated for ARF secondary to conditions other than COPD, those patients failing an attempt at noninvasive ventilation had a higher ICU mortality than those treated with invasive ventilation (48.1% vs 31.0%,  $P = .01$ ).

TABLE 4 lists both the univariate and multivariate analysis of factors associated with ICU mortality. The following were factors independently associated with an increased mortality: age, SAPS II score at ICU admission, prior functional status characterized by limited activity, initiation of mechanical ventilation because of coma, ARDS, or sepsis, use of vasoactive drugs, use of neuromuscular blockers, peak pressure higher than 50 cm H<sub>2</sub>O, plateau pressure higher than 35 cm H<sub>2</sub>O, barotrauma, ARDS or sepsis developed after initiation of mechanical ventilation, PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 200, and development of any of the following organ failures: cardiovascular (shock),

**Figure 1.** Ventilator Modes Used Each Day During the Course of Mechanical Ventilation



**Figure 2.** Kaplan-Meier Curves of the Probability of Survival Over Time of Mechanical Ventilation



No. at Risk	1	3	5	7	9	11	13	15	17	19	21	23	25	27	28
Asthma	79	53	14												1
COPD	522	377	117												9
ARF (non-ARDS)	3313	2116	838												52
ARDS	231	195	103												8

COPD indicates chronic obstructive pulmonary disease; ARF, acute respiratory failure; ARDS, acute respiratory distress syndrome.  $P < .001$  for the log-rank test. Numbers at risk are for days 1, 3, 7, 14, 21, and 28.

**Table 4.** Univariate and Multivariate Analysis of Factors Associated With Intensive Care Unit (ICU) Mortality in Ventilated Patients\*

	ICU Mortality, % (95% Confidence Interval)	Univariate Analysis		Multivariate Analysis	
		Odds Ratio (95% Confidence Interval)	P Value	Odds Ratio (95% Confidence Interval)	P Value
<b>Factors Present at the Initiation of Mechanical Ventilation</b>					
Geographical area					
United States and Canada	27 (25-29)	1.00	] <.001		
Europe	31 (29-33)	1.21 (1.04-1.40)			
Latin America	34 (31-37)	1.38 (1.17-1.63)			
Age, y					
<40	21 (19-24)	1.00	] <.001	1.00	] <.001
40-70	30 (28-32)	1.60 (1.33-1.91)		1.58 (1.27-1.98)	
>70	36 (34-39)	2.11 (1.75-2.55)		2.18 (1.71-2.76)	
Sex					
Male	30 (29-32)				
Female	31 (29-33)				
SAPS II score at ICU admission					
<20	15 (11-19)	1.00	] <.001	1.00	] <.001
20-39	19 (17-21)	1.31 (0.95-1.82)		0.93 (0.64-1.33)	
40-59	35 (33-37)	3.06 (2.23-4.20)		1.54 (1.08-2.21)	
60-80	50 (46-54)	5.72 (4.07-8.03)		1.95 (1.31-2.88)	
>80	72 (64-79)	14.53 (9.01-23.22)		3.87 (2.26-6.65)	
Medical problem	33 (31-35)	1.27 (1.16-1.39)	<.001		
Surgical problem	26 (24-28)	0.78 (0.71-0.86)	<.001		
Prior functional status					
Normal	30 (28-32)	1.00	] .04	1.00	] .03
Limited activity	32 (30-34)	1.09 (1.00-1.19)		1.18 (1.02-1.39)	
Reason for initiation of mechanical ventilation					
Acute respiratory failure	31 (29-32)				
Coma	36 (33-39)	1.31 (1.19-1.45)	<.001	2.98 (2.44-3.63)	<.001
COPD	22 (19-26)	0.70 (0.59-0.83)	<.001		
Asthma	11 (6-21)	0.37 (0.20-0.68)	<.001		
Neuromuscular disease	15 (9-24)	0.48 (0.30-0.78)	.001		
Cause of acute respiratory failure					
Postoperative	22 (20-25)	0.67 (0.59-0.76)	<.001	0.75 (0.61-0.91)	<.001
Pneumonia	38 (35-42)	1.29 (1.16-1.43)	<.001		
Congestive heart failure	28 (24-32)				
Sepsis	55 (51-60)	1.95 (1.77-2.14)	<.001	1.71 (1.34-2.20)	<.001
Trauma	20 (17-25)	0.64 (0.53-0.79)	<.001		
ARDS	52 (46-59)	1.76 (1.55-2.01)	<.001	1.44 (1.03-2.01)	.04
Aspiration	27 (20-36)				
Cardiac arrest	44 (34-54)	1.45 (1.15-1.81)	.004		
Other	28 (23-33)				
<b>Factors Related to Patient Management</b>					
Successful noninvasive ventilation	14 (10-21)	0.46 (0.32-0.66)	<.001		
Use of vasoactive drugs	48 (46-50)	2.41 (2.22-2.63)	<.001	1.77 (1.50-2.08)	<.001
Use of sedatives	33 (31-35)	1.22 (1.13-1.34)	<.001		
Use of neuromuscular blockers	50 (46-55)	1.75 (1.58-1.94)	<.001	1.39 (1.08-1.79)	<.001
Tidal volume, mL/kg					
<6	32 (28-41)	1.23 (0.91-1.63)	] .09		
6-10	30 (28-31)	1.00			
>10	33 (30-35)	1.14 (0.99-1.31)			
PEEP, cm H <sub>2</sub> O					
<5	28 (26-30)	1.00	] <.001		
5-10	31 (29-33)	1.15 (1.02-1.30)			
>10	50 (44-56)	2.52 (1.96-3.24)			
Peak pressure >50 cm H <sub>2</sub> O	65 (53-74)	2.15 (1.83-2.52)	<.001	2.67 (1.50-4.72)	<.001
Plateau pressure >35 cm H <sub>2</sub> O	78 (69-86)	2.64 (2.36-2.95)	<.001	3.67 (2.02-6.66)	<.001
Tracheostomy	20 (17-23)	0.62 (0.52-0.74)	<.001	0.45 (0.35-0.58)	<.001

(continued)

**Table 4.** Univariate and Multivariate Analysis of Factors Associated With Intensive Care Unit (ICU) Mortality in Ventilated Patients (cont)\*

	ICU Mortality, % (95% Confidence Interval)	Univariate Analysis		Multivariate Analysis	
		Odds Ratio (95% Confidence Interval)	P Value	Odds Ratio (95% Confidence Interval)	P Value
<b>Factors Developing During Mechanical Ventilation</b>					
Barotrauma	50 (42-58)	1.66 (1.41-1.96)	<.001	1.99 (1.33-2.97)	<.001
ARDS	63 (56-70)	2.16 (1.94-2.42)	<.001	1.66 (1.15-2.38)	<.001
Pneumonia	38 (35-41)	1.28 (1.18-1.42)	<.001		
Sepsis	55 (51-58)	2.07 (1.91-2.24)	<.001	1.57 (1.23-2.02)	<.001
Shock	61 (58-64)	2.76 (2.56-2.97)	.01	2.11 (1.75-2.54)	<.001
Renal failure	61 (58-74)	2.56 (2.38-2.76)	<.001	1.96 (1.62-2.38)	<.001
Hepatic failure	69 (63-74)	2.44 (2.24-2.66)	<.001	1.78 (1.29-2.45)	<.001
Coagulopathy	61 (56-65)	2.23 (2.05-2.42)	<.001	1.29 (1.01-1.68)	<.001
Metabolic acidosis	59 (53-65)	2.05 (1.85-2.27)	<.001	2.04 (1.52-2.74)	<.001
Respiratory acidosis	37 (32-43)	1.24 (1.05-1.43)	.01		
PaO <sub>2</sub> /FiO <sub>2</sub> ratio					
>300	24 (21-26)	1.00		1.00	
200-300	25 (23-28)	1.10 (0.92-1.33)	<.001	0.91 (0.74-1.13)	<.001
150-199	31 (28-35)	1.36 (1.16-1.61)		1.30 (1.08-1.58)	
100-149	47 (42-51)	2.29 (2.26-3.54)		2.15 (1.64-2.82)	
<100	83 (77-88)	15.73 (10.45-23.69)		8.71 (5.44-13.94)	

\*SAPS II indicates simplified acute physiology score II; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; and PEEP, positive end-expiratory pressure. Odds ratios are only shown for variables with  $P < .10$ .

renal failure, hepatic failure, coagulopathy, and metabolic acidosis.

## COMMENT

Survival in patients with respiratory failure who required mechanical ventilation for more than 12 hours was 69% and depended not only on factors present when initiating mechanical ventilation but mainly on the development of complications, changes in monitored variables, and patient management during the subsequent course.

Several studies have addressed the outcome of patients receiving mechanical ventilation<sup>12-14</sup> but most of them have analyzed patients with a particular medical condition, such as ARDS<sup>7-10,22,23</sup> or acute exacerbation of COPD.<sup>1,24</sup> Three multicenter cohort studies evaluating patients requiring mechanical ventilation because of ARF of different etiologies have reported hospital mortality rates from 30% to 40%.<sup>12-14</sup> We recently published a study<sup>15</sup> involving a large and unselected sample of mechanically ventilated patients, which yielded valuable information concerning epidemiology of mechanical ventilation, ventilatory modes, and ventilatory settings, however mortality and morbidity were not

described. Strengths of the current study are that unselected mechanically ventilated patients were enrolled from different countries and 99% of the patients were screened daily over the duration of mechanical ventilation to evaluate the determinants of their outcome. Our study represents the largest study to our knowledge of a heterogeneous group of mechanically ventilated patients, which prospectively evaluates the effect of more than 30 variables potentially related to mortality after controlling for the effect of confounding factors.

A total of 25 published studies have reported the effect of age on the mortality of mechanically ventilated patients, but only 8 were prospective, 12 were based on populations with more than 100 elderly patients, and 9 had multivariate analysis. There are 6 prospective cohort studies evaluating whether age has an independent effect on the outcome of patients treated with mechanical ventilation after ICU admission<sup>7,13,14,25-27</sup> and 5 found that age was independently associated with hospital mortality.<sup>7,13,14,26,27</sup> Ely et al<sup>25</sup> studied 300 mechanically ventilated patients admitted to medical and coronary

ICUs and found that hospital mortality was 38.1% among patients older than 75 years and 38.8% among younger patients. The Cox proportional hazards analysis confirmed that survival did not differ between the 2 groups (relative risk for older patients, 0.82; 95% CI, 0.52-1.29). The study population, however, was small (67 patients >75 years) and represented a selected group enrolled in a clinical trial. The present study prospectively analyzes a number of unselected patients older than 70 years (n=1753) using a multivariate analysis to determine the effect of age on outcome. In the absence of a clearly defined threshold for elderly patients, the age cutoff has been arbitrarily chosen and has varied from more than 60 years to more than 85 years.<sup>25</sup> Our data illustrate, after adjustment for other factors related to the mortality of mechanically ventilated patients, 3 intervals of age (<40, 40-70, >70 years) have very different prognostic value.

As reported in other studies,<sup>14,15,28</sup> we found that men account for more than half of patients (61% males) receiving mechanical ventilation in the ICU. In a study combining surgical and medical

patients, Kollef et al<sup>26</sup> using multivariate analysis showed that the hospital mortality rate was greater for female patients compared with male patients despite similar severity of illness and numbers of organ system derangements at the start of mechanical ventilation. In 580 medical patients, Epstein and Vuong<sup>29</sup> showed that sex was not independently associated with hospital mortality after controlling for factors present at the start of mechanical ventilation and for development of acute hepatic failure and acute renal failure over the course of ventilation. The study by Luhr et al,<sup>13</sup> in 1231 patients with ARF and RDS, also demonstrated that sex was not independently associated with mortality. We have taken into account many baseline and time dependent factors associated with mortality in a multivariate analysis, and our results show that mortality is not independently associated with the patient's sex.

Clinicians may struggle with the decision to initiate invasive mechanical ventilation in patients with COPD because of concern about uncertain prognosis and prolonged mechanical ventilation. Our study found a hospital mortality of 28% in patients with COPD receiving mechanical ventilation due to an acute exacerbation of their disease. Two retrospective studies involving more than 150 patients with COPD requiring mechanical ventilation reported similar rates of hospital mortality of 32% and 28%.<sup>1,24</sup> The major risk factors for hospital mortality are the development and severity of nonrespiratory organ system dysfunction and acute illness, while severity of the underlying respiratory function substantially influences mortality following hospital discharge.<sup>1,24</sup> The univariate analysis in the present study showed that patients receiving mechanical ventilation due to an acute decompensation of COPD had significantly lower mortality than patients receiving mechanical ventilation because of ARF of other etiologies. However, when mortality was adjusted for the effect of organ system failures and variables related to both the acute severity of illness and patient management, the

mortality rate of patients with COPD was not different from that of patients mechanically ventilated due to other etiologies of ARF. Mechanically ventilated patients with COPD had not only better clinical course than other mechanically ventilated patients but also duration of ventilatory support, duration of weaning, and length of ICU stay were not higher in mechanically ventilated patients with COPD when compared with patients ventilated due to other reasons of ARF. Ely et al<sup>30</sup> have also reported that duration of mechanical ventilation of patients with COPD was similar to that of other ventilated patients (5.5 vs 5 days).

Randomized trials evaluating the influence of different ventilator strategies on the outcome of patients with ARDS and/or acute lung injury have revealed contrary findings.<sup>2-6</sup> Survival of control patients has ranged from 30% to 62%, whereas survival of patients in descriptive studies is about 40%,<sup>7-10</sup> which is similar to the present finding. Investigators have shown that nonpulmonary organ failure markedly decreases survival in ARDS.<sup>7-10,22,23,31</sup> Enrollment criteria that exclude patients with organ failure may partly explain the higher survival in clinical trials than in observational studies. Mortality may also differ depending on the type of organ failure. In the present study, cardiovascular failure (shock) and metabolic acidosis carried worse prognosis than coagulopathy. Most studies have used an organ system dysfunction index that scored each organ failure similarly; differences in survival rates among randomized trials and observational studies may be explained by imbalances resulting from the particular organ failure.

Another factor that may contribute to differences in reported outcomes is the point in the hospital course at which a patient develops ARDS. Croce et al<sup>32</sup> reported 2 distinct clinical entities of ARDS in trauma patients. One occurs within 48 hours of hospital admission and is associated with profound hemorrhagic shock, and the other occurs later and is associated with multiple system injury

and pneumonia. Despite these differences, the overall mortality between patients with early ARDS and patients with late ARDS was similar. In the present study, survival was 23% lower in patients who developed ARDS 48 hours after the start of mechanical ventilation than in patients who had it when ventilation was instituted. Accordingly, it may be important to take into account the onset of ARDS when allocating patients in a clinical trial.

The reason for the initiation of mechanical ventilation influences the outcome of ventilated patients. After adjusting for other variables, the only factors independently associated with decreased survival were coma, ARDS, and sepsis, and the only factor independently associated with increased survival was postoperative state. The above findings are consistent with the results of other studies. Epstein and Vuong<sup>29</sup> reported that both acute lung injury and sepsis leading to the initiation of mechanical ventilation were independently associated with an increased hospital mortality rate. Kollef et al<sup>26</sup> found that the presence of ARDS was independently associated with hospital mortality and that postoperative as an indication for mechanical ventilation was associated with a decreased mortality in the univariate analysis but not in the multivariate analysis. We have no information concerning whether patients included in the category of postoperative had urgent or elective surgery, but the finding that mortality is significantly decreased in postoperative patients seems to indicate that most patients had elective surgery.

Data from randomized trials of low tidal volumes in patients with ARDS have shown that increased survival with lower tidal volumes can be detected only when patients receiving traditional tidal volumes had mean plateau pressures more than 32 cm H<sub>2</sub>O.<sup>33</sup> Vasilyev et al<sup>12</sup> reported that a peak inspiratory pressure more than 50 cm H<sub>2</sub>O at entry into the survey was associated with a survival rate of less than 20% while peak inspiratory pressure less than 30 cm H<sub>2</sub>O was associated with a survival rate of

60%. A retrospective description of all patients with ARDS treated in a Finland hospital from 1993 through 1995 reported that both mean static end-inspiratory pressure and mortality decreased over the study period from 33 cm H<sub>2</sub>O and 50%, respectively, in 1993 to 28 cm H<sub>2</sub>O and 42% in 1994, and to 26 cm H<sub>2</sub>O and 32% in 1995.<sup>22</sup> Our study revealed an independent association between plateau pressure of more than 35 cm H<sub>2</sub>O and decreased survival but did not prove that plateau pressure is causally related with the outcome of patients receiving mechanical ventilation.

While development of nonpulmonary organ failures increased the risk of mortality in our study, development of pulmonary failure that resulted in a ratio of PaO<sub>2</sub>/FIO<sub>2</sub> less than 100 carried an even higher risk. However, we have not stratified the degree of renal or hepatic functional impairment in patients developing either renal or hepatic dysfunction over the course of mechanical ventilation, so it is possible that severe renal or hepatic failure carries a similar risk of mortality than a ratio of PaO<sub>2</sub>/FIO<sub>2</sub> less than 100.

The relationship between pulmonary failure and mortality has been extensively evaluated in studies involving patients receiving mechanical ventilation with ARDS, but results show considerable discrepancy.<sup>10,12,13,23,34-36</sup> Doyle et al<sup>10</sup> did not find any significant difference in hospital mortality between patients with a PaO<sub>2</sub>/FIO<sub>2</sub> ratio of less than 150 at the time of entry into the study and those with a PaO<sub>2</sub>/FIO<sub>2</sub> ratio between 150 and 299 (56% vs 59%). Krafft et al<sup>34</sup> evaluated 101 published studies investigating 3264 patients with ARDS and found that no correlation existed between PaO<sub>2</sub>/FIO<sub>2</sub> and mortality rates. On the contrary, Sloane et al<sup>35</sup> and Knaus et al<sup>36</sup> reported that mortality was higher in ARDS patients with an initial PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 150. Navarrete-Navarro et al<sup>23</sup> found that the PaO<sub>2</sub>/FIO<sub>2</sub> ratio on the third day after the onset of ARDS was independently associated with increased mortality. Vasilyev et al<sup>12</sup> reported that hospital sur-

vival rates increased as the PaO<sub>2</sub>/FIO<sub>2</sub> ratio decreased, in such a way that hospital survival rate was 19% in patients with a PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 100, 37.3% in patients with a PaO<sub>2</sub>/FIO<sub>2</sub> ratio between 100 and 174, 50.0% in patients with a PaO<sub>2</sub>/FIO<sub>2</sub> ratio between 175 and 224, and 70% in patients with a PaO<sub>2</sub>/FIO<sub>2</sub> ratio higher than 225. Luhr et al<sup>13</sup> reported that impaired oxygenation as manifested by a PaO<sub>2</sub>/FIO<sub>2</sub> ratio of less than 200 was not significantly associated with mortality in patients with ARF; however, in the group of patients with ARDS, an independent association could be shown between a PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 100 and mortality. Our study evaluates the effect of the pulmonary failure severity on the outcome of patients receiving mechanical ventilation with ARDS after controlling for the effect of a large number of other factors strongly associated with mortality, and also stratifies the severity of pulmonary failure according to mortality risk.

In summary, both factors at baseline and complications of critical illness over time influence the outcome of patients receiving mechanical ventilation. Future controlled trials of ventilator strategies evaluating mortality need to take into account not only variables evident at the time of randomization but also developments that occur later in the course of mechanical ventilation.

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