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Original Research

CRITICAL CARE MEDICINE

Outcomes of Patients Ventilated With Synchronized Intermittent Mandatory Ventilation With Pressure Support

A Comparative Propensity Score Study

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Background: **Few data are available regarding the benefits of one mode over another for ventilatory support. We set out to compare clinical outcomes of patients receiving synchronized intermittent mandatory ventilation with pressure support (SIMV-PS) compared with assist-control (A/C) ventilation as their primary mode of ventilatory support.**

Methods: **This was a secondary analysis of an observational study conducted in 349 ICUs from 23 countries. A propensity score stratified analysis was used to compare 350 patients ventilated with SIMV-PS with 1,228 patients ventilated with A/C ventilation. The primary outcome was in-hospital mortality.**

Results: **In a logistic regression model, patients were more likely to receive SIMV-PS if they were from North America, had lower severity of illness, or were ventilated postoperatively or for trauma. SIMV-PS was less likely to be selected if patients were ventilated because of asthma or coma, or if they developed complications such as sepsis or cardiovascular failure during mechanical ventilation. In the stratified analysis according to propensity score, we did not find significant differences in the in-hospital mortality. After adjustment for propensity score, overall effect of SIMV-PS on in-hospital mortality was not significant (odds ratio, 1.04; 95% CI, 0.77-1.42; *P* = .78).**

Conclusions: **In our cohort of ventilated patients, ventilation with SIMV-PS compared with A/C did not offer any advantage in terms of clinical outcomes, despite treatment-allocation bias that would have favored SIMV-PS.**

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Abbreviations: A/C = assist-control ventilation; CMV = controlled mechanical ventilation; CPAP = continuous positive airway pressure; IMV = intermittent mandatory ventilation; PS = pressure support; SIMV = synchronized intermittent mandatory ventilation; SIMV-PS = synchronized intermittent mandatory ventilation with pressure support

Synchronized intermittent mandatory ventilation (SIMV) is a mode of mechanical ventilation that allows patients to breathe spontaneously between mandatory machine-cycled breaths.[1] Respiratory efforts in excess of the mandatory set rate are spontaneous breaths on continuous positive airway pressure (CPAP) with or without pressure support (PS). SIMV, originally designed as a mode for weaning from mechanical ventilation,[2] has also been proposed as a primary mode of ventilatory support.[3,4] Compared with controlled mechanical ventilation (CMV) or assist-control (A/C) ventilation, proponents have claimed that SIMV has clinical advantages based on its allowance for spontaneous breathing.[1] However, some studies[5,6] that have evaluated physiologic variables comparing SIMV with other modes of ventilation did not find advantages of this mode of ventilation in terms of work of breathing. To unload inspiratory muscle work during the spontaneous breathing cycles the addition of PS has been proposed.[7]

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SIMV was first used in adult patients as method for discontinuing mechanical ventilation.[2] Two randomized controlled trials[8,9] showed that SIMV was associated with significant increases in weaning duration compared with daily T-piece trials or gradual reductions in PS. Additionally, Jounieaux et al[10] found no difference in weaning success when comparing weaning with SIMV alone with SIMV with PS (SIMV-PS) in patients with COPD.

However, despite these negative studies, investigators have documented that SIMV (with or without PS) continues to be used frequently as a mode of ventilation and for weaning.[11-15] To our knowledge, there are no published studies that have evaluated the use of SIMV-PS (vs A/C) on clinical outcomes, including mortality. Using the data of an international prospective cohort study of mechanical ventilation,[14] we set out to compare clinical outcomes (duration of ventilatory support, ICU mortality, in-hospital mortality) of patients receiving SIMV-PS vs A/C ventilation as their primary mode of ventilatory support.

Materials and Methods

Patients

We analyzed data from a cohort of 4,968 mechanically ventilated adult patients in 349 ICUs from 23 countries[14] (see the list of the investigators in Appendix 1). The study protocol was approved by the Institutional Review Board at each of the participating centers with a waiver for consent. For the purpose of this study we selected patients who were ventilated only with SIMV-PS or only with A/C during their total time of ventilatory support. We excluded patients ventilated with SIMV-PS who received neuromuscular blockers (n = 17).

Full details of the methodology are shown in Appendix 2. Briefly, for each patient enrolled we collected baseline data on demographics, severity of illness, and reason for initiation of ventilation. Daily we collected data related to ventilatory parameters, organ failures (cardiovascular, respiratory, renal, hepatic, hematologic) defined as a Sequential Organ Failure Assessment score >2 points for at least 2 consecutive days, and complications (barotrauma, ventilator-associated pneumonia, sepsis, ARDS) arising during ventilation. The onset of weaning was the time that the physician in charge considered the patient likely to resume and sustain spontaneous breathing after a patient met standard criteria for weaning readiness. Weaning was classified as simple weaning (extubation on the first attempt of spontaneous breathing); difficult weaning (patients who required up to 7 days from the first spontaneous breathing trial to achieve successful weaning); or prolonged weaning (patients who required >7 days of weaning after the first spontaneous breathing trial).[15] Patients were prospectively followed to hospital discharge.

Statistical Analysis

Data are expressed as mean (standard deviation), median (interquartile range), or proportions as appropriate. We used Student *t* test and the Mann-Whitney *U* test to compare continuous variables, and used a χ^2 test or Fisher exact test to compare proportions as appropriate.

Propensity Score Development: Because the use of SIMV-PS was not randomly assigned, we attempted to deal with treatment-indication bias by developing a propensity score for the use of SIMV-PS. For this purpose, we performed a multivariate analysis using a backward stepwise logistic regression model. Based on a univariate association with a P value $<.10$, we entered the following variables in the analysis: Simplified Acute Physiology Score II, geographical area, reason for initiation of ventilation (chronic obstructive pulmonary disease, asthma, coma, neuromuscular disease, postoperative acute respiratory failure, sepsis, trauma, or congestive heart failure), and complications arising during ventilation (barotrauma, ARDS, sepsis, ventilator-associated pneumonia, renal failure, hematologic failure, cardiovascular failure). We assessed goodness-of-fit of the model using the Hosmer-Lemeshow test and model discrimination by evaluating the area under the receiver operator curve.

Estimation of the Effect of the Mode of Ventilation: Patients were stratified into quintiles according to their predicted probability of ventilation with SIMV-PS. Patients in quintile 1 were least likely to receive ventilation with SIMV-PS (4% of SIMV-PS patients were located in this quintile), whereas those in quintile 5 were most likely to receive ventilation with SIMV-PS (48% of SIMV-PS patients were located in this quintile). Within each quintile, the absolute and relative effects on mortality in the hospital were determined. In addition, the overall effectiveness of mode of ventilation on mortality in the hospital was assessed by logistic regression to adjust by propensity score strata. Within each quintile, a univariate analysis was used to compare the secondary outcomes: use of sedatives, days of ventilatory support, length of stay in the ICU, and mortality in the ICU.

Validation of the Propensity Score: We explored graphically, using box-plots, the within-quintile residual imbalance in the estimated propensity score. Comparison of propensity score in each quintile was performed with nonparametric Kolmogorov-Smirnov

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*A complete list of study participants is located in the Appendix.
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test. We used SPSS 17.0 (SPSS Inc.; Chicago, IL) to conduct analyses and considered a P value $< .05$ to indicate statistical significance.

Results

Among the 4,968 patients included in the original cohort, we identified 350 patients who were ventilated only with SIMV-PS and compared them with 1,228 patients ventilated continually with A/C (Fig 1). Baseline characteristics for both groups are shown in Table 1.

Factors Associated With SIMV-PS Use

Table 2 shows univariate and multivariate analyses of the factors associated with SIMV-PS use. Patients receiving SIMV-PS were less likely to be from Latin America or Europe, had lower severity of illness, and were more frequently ventilated postoperatively or for trauma; they were less likely to be ventilated because of asthma or coma or to have developed complications, such as sepsis or cardiovascular failure, during mechanical ventilation. The model obtained (right-hand column of Table 2) showed an adequate goodness-of-fit ($\chi^2 = 12.04$; $P = .15$) and moderate discrimination (area under receiver operator curve = 0.76; 95% CI, 0.73-0.79; $P < .001$).

Estimation of Treatment Effect: Stratifying on the Quintiles of the Propensity Score

There were no significant differences for in-hospital mortality across propensity strata (Table 3). After adjustment for propensity score, overall effect of SIMV-PS on mortality was also not significant (odds ratio 1.04; 95% CI, 0.77-1.42; $P = .78$).

In Table 4 we show secondary outcomes according to propensity score quintiles. There was a trend toward a lower sedation (statistically significant in the third quintile) in patients ventilated with SIMV-PS.

Box plots of the estimated propensity score for both groups are depicted in Figure 2. The distribution of the propensity score was similar within each quintile of the propensity score excepting the fifth quintile. The Kolmogorov-Smirnov test indicated that distributions were comparable between two groups in each quintile ($P = .41$; $P = .59$; $P = .68$; $P = .23$; respectively) excepting in the fifth quintile ($P < .001$). Thus, there is some evidence of residual imbalance in observed characteristics between patients ventilated with SIMV-PS and with A/C within the last quintile.

Weaning

In the A/C group, 638 patients (52%) were weaned successfully compared with 245 patients (70%) in the SIMV-PS group ($P < .001$). We compared weaning modes in the overall cohort without stratification (Table 5). In both groups, 60% of patients had a simple weaning. In the subgroups of both difficult and prolonged weaning, there were no differences in the duration of weaning between patients receiving SIMV-PS vs A/C. In these subgroups the most common method of weaning was a gradual reduction of ventilatory support. In the SIMV-PS group, the method most common was SIMV with or without PS (55 of 109 patients; 55%), whereas in the A/C group, PS was used most frequently (109 of 242 patients; 45%). There were no differences in the rate of reintubation (9% in SIMV-PS group vs 9% in A/C group; $P = .78$) or tracheostomy (9% in SIMV-PS group vs 9% in A/C group; $P = .84$).

Discussion

Our main finding is that ventilation with SIMV-PS did not have any significant advantage or disadvantage over ventilation with A/C. For a similar probability of ventilation with SIMV-PS, patients ventilated with A/C had a similar duration of mechanical ventilation and mortality.

SIMV has been evaluated in small studies with physiologic variables as outcomes in most of the studies. More than 20 years ago, Marini et al[5] published a study whose purpose was to measure the work of breathing done by 12 patients during spontaneous and SIMV-assisted breaths. There was very little difference between the muscular force generated during spontaneous and assisted breaths, regardless of the level of assistance. Measurement of muscular force output was done through registration of the development of respiratory work per liter of ventilation or through the pressure-time product. These investigators demonstrated that the ventilatory pump remained active during both types of ventilatory support, and there was an increased work of breathing that occurred almost immediately after patients were switched from A/C to SIMV. Their conclusion was that SIMV resulted in significantly less respiratory muscle rest than A/C. This finding was corroborated by Imsand et al[6] in a study including five patients during acute exacerbations of COPD. These authors evaluated assisted and spontaneous breaths at different levels of assistance offered by the ventilator. This was done by measuring intrapleural pressure with an esophageal balloon and assessing muscular activity through electromyograms of the diaphragm and the sternomastoid muscles. A slight reduction of the esophageal pressure-time index was found in pressure-control SIMV-assisted breaths. During conventional volume-control SIMV, patients responded to increases in the level of assistance with reductions in the amplitude of the neural inspiratory impulse, although its duration remained stable. It was found that the degree of inspiratory muscle rest offered by

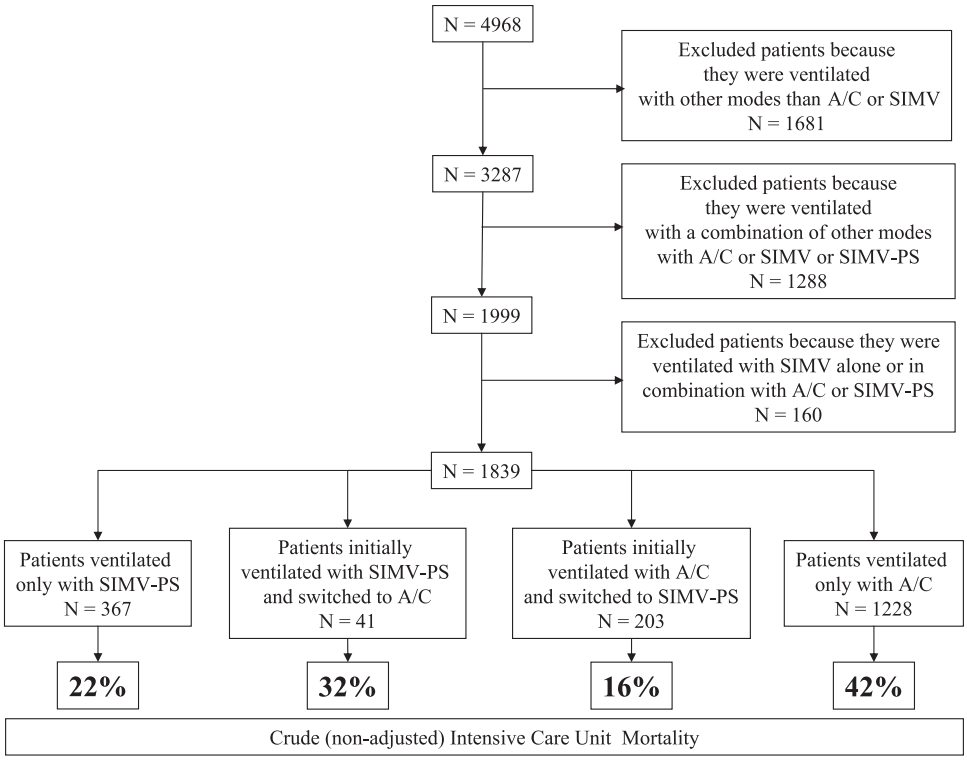

FIGURE 1. Crude mortality of patients according to mode of ventilation. The group of patients ventilated only with SIMV-PS includes the 17 patients excluded from analysis because they received neuromuscular blockers. A/C = assist-control; SIMV = synchronized intermittent mandatory ventilation; SIMV-PS = synchronized intermittent mandatory ventilation with pressure support.

SIMV is not proportional to the level of assistance given by the ventilator. In addition, Leung et al[7] undertook a comparison, in 11 ventilator-dependent patients, of patient-ventilator interactions with four ventilator modes: A/C, IMV, PS, and a combination of IMV and PS. Progressive increases in IMV rate and PS level each decreased inspiratory pressure-time product. When a pressure support of 10 cm H_2O was added to a given level of IMV, greater reductions in pressure-time product were achieved not only during intervening breaths but also during mandatory breaths; this additional unloading during mandatory breaths was proportional to the decrease in respiratory drive observed during intervening spontaneous breaths. These studies provide a physiologic demonstration of potential detrimental effects of SIMV on respiratory muscles and central drive.

Despite these data, SIMV (with or without PS) continues to be used as a mode of ventilation and as a weaning mode. In a survey by Venus et al,[11] 72% of the responders indicated that IMV was their primary mode of ventilatory support. In contrast, more recent epidemiologic studies[12-14] have reported a decrease in the use of SIMV, especially alone without PS. However, although use of SIMV as a weaning mode may be decreasing, it remains the second most commonly used mode for ongoing ventilatory support in our cohort studies.[13,14] Moreover, a recent survey carried out in 55 ICUs in Australia and New Zealand[16] revealed that SIMV, with or without PS, is the mode preferred by specialists in that region.

We observed that physicians were more likely use SIMV-PS as a preferred mode in patients with a lower baseline illness severity, whereas A/C was preferred for those who were more severely ill and likely to develop complications over the course of mechanical ventilation. This is consistent with the observed raw mortality rates, wherein patients ventilated continually with SIMV-PS had a lower mortality than patients initially ventilated with SIMV-PS and later switched to A/C, or those ventilated continually with A/C (Fig 1).

One of the most important advantages of SIMV-PS could be the reduction in the need for sedation.[17] We only found significant differences in the proportion of patients with sedatives in the third quintile. However, in practice this difference did not translate into any significant differences in outcomes (duration of mechanical ventilation, weaning, stay in the ICU).

The efficacy of IMV as a weaning technique was initially evaluated in three small studies[18-20] with methodological limitations. In the mid-1990s two large randomized controlled trials[8,9] compared the most popular methods of weaning and found that the use of SIMV prolonged the time of weaning vs pressure

Table 1—*Baseline Characteristics of Patients Included in the Analysis*

Characteristic	A/C (n = 1,228)	SIMV-PS (n = 350)	*P* Value
Geographical area, No. (%)			< .001
Latin America	488 (40)	60 (17)	
Europe	373 (30)	81 (23)	
United States-Canada	331 (27)	173 (49)	
Other (Saudi Arabia, Tunisia, Turkey)	36 (3)	36 (10)	
Age, mean (SD), y	57 (18)	58 (18)	.47
Female sex, No. (%)	486 (40)	126 (36)	.23
Simplified Acute Physiology Score II, mean (SD), points	46 (18)	40 (17)	< .001
Medical problem, No. (%)	833 (68)	133 (38)	< .001
Main reason for mechanical ventilation, No. (%)			
COPD	52 (4)	8 (2)	.09
Asthma	21 (2)	1 (0.3)	.04
Other chronic lung disease	13 (1)	4 (1)	.89
Coma	359 (29)	50 (14)	< .001
Neuromuscular disease	17 (1)	1 (0.3)	.15
Acute respiratory failure			
Postoperative	182 (15)	133 (38)	< .001
Pneumonia	112 (9)	20 (6)	.04
Sepsis	132 (11)	25 (7)	.05
ARDS	27 (2)	4 (1)	.21
Congestive heart failure	67 (5.5)	11 (3)	.08
Cardiac arrest	61 (5)	17 (5)	.93
Trauma	36 (3)	39 (11)	< .001
Aspiration	34 (3)	7 (2)	.42
Other cause of acute respiratory failure	115 (9)	30 (9)	.65
Complications over the course of mechanical ventilation, No. (%)			
Ventilator-associated pneumonia	60 (5)	6 (2)	.009
Sepsis	98 (8)	5 (1)	< .001
ARDS	60 (5)	3 (1)	.001
Barotrauma	32 (3)	7 (2)	.52
Organ dysfunction during mechanical ventilation, No. (%)			
Cardiovascular failure	386 (31)	57 (16)	< .001
Respiratory failure	428 (35)	73 (21)	< .001
Renal failure	98 (8)	22 (6)	.29
Hepatic failure	53 (4)	15 (4)	.98
Hematologic failure	93 (8)	11 (3)	.003
Outcomes			
Duration of ventilatory support, median (interquartile range), d	4 (2-7)	3 (2-5)	< .001
Tracheostomy, No. (%)	105 (9)	31 (9)	.84
Mortality in the ICU, No. (%)	514 (42)	76 (22)	< .001
Mortality in the hospital, No. (%)	546 (44)	93 (26.5)	< .001

A/C = assist-control; SIMV-PS = synchronized intermittent mandatory ventilation with pressure support.

support[8] or vs trials with T-piece.[9] These results have influenced how clinicians treat difficult-to-wean patients, and there has been a decrease in the use of SIMV as a method of weaning in recent years.[13,14] In the current study, it is relevant to note that more than half of the patients who were ventilated with SIMV-PS during the acute phase of their illness were still undergoing weaning with SIMV-PS, a mode that has not been shown to be more effective.[10]

Our study has several limitations. First, this is an observational study, the assignment of ventilatory mode was not random, and the regression analysis model for developing the propensity score showed only moderate discrimination and calibration. It is probable that some confounder variables, which could influence the decision of choosing SIMV-PS as the mode of ventilation, were not taken into account in our model. In these cases it is important to consider the direction in which this residual confounding would potentially bias results. Patients in the A/C group were clearly significantly sicker than those receiving SIMV-PS; thus we would expect residual confounding to lead to results favoring SIMV-PS. Therefore, the fact that we did not find any significant advantages to the use of SIMV-PS, which is in the opposite direction of this potential bias, is likely to be robust. Second, we included patients from many countries. Although this is clearly adds to the generalizability of our results, different local practices may have influenced our results. We tried to minimize this issue by including the geographical area in the model, considering similar practices in areas with cultural

Table 2—*Factors Associated With Ventilation Using SIMV-PS: Univariate and Multivariate Logistic-Regression Analysis*

Factor	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Geographical area		< .001		< .001
Latin America	1		1	
Europe	1.76 (1.23-2.53)		1.64 (1.12-2.40)	
United States-Canada	4.25 (3.07 -5.88)		3.41 (2.40-4.83)	
Other (Saudi Arabia, Tunisia, Turkey)	8.13 (4.77-13.87)		8.58 (4.77-15.44)	
Simplified Acute Physiology Score II, points	0.98 (0.97-0.99)	< .001	0.99 (0.98-0.99)	.02
Main reason for mechanical ventilation				
COPD	0.59 (0.31-1.13)	.09	…	…
Asthma	0.20 (0.03-1.38)	.06	0.12 (0.02-0.94)	.04
Coma	0.48 (0.36-0.63)	< .001	0.56 (0.38-0.82)	.003
Acute respiratory failure				
Postoperative	2.46 (2.06-2.93)	< .001	2.58 (1.85-3.60)	< .001
Sepsis	0.69 (0.48-1.01)	.05	…	…
Pneumonia	0.66 (0.44-1.00)	.04	…	…
Congestive heart failure	0.62 (0.36-1.09)	.08	…	…
Trauma	2.51 (1.98-3.19)	< .001	3.59 (2.09-6.18)	< .001
Complications during the mechanical ventilation				
ARDS	0.21 (0.07-0.63)	.001	…	…
Sepsis	0.21 (0.09-0.49)	< .001	0.28 (0.11-0.73)	.009
Ventilator-associated pneumonia	0.40 (0.18-0.86)	.009	…	…
Cardiovascular failure	0.49 (0.38-0.65)	< .001	0.66 (0.46-0.94)	.02
Respiratory failure	0.57 (0.45-0.72)	< .001	…	…
Hematologic failure	0.46 (0.26-0.81)	.003	…	…

See Table 1 for expansion of abbreviation.

and economic similarities. Third, we only collected data on total respiratory rate and we did not know the proportion of mandatory vs spontaneous breaths in the SIMV-PS group, or the proportion of assisted vs controlled breaths in the A/C group. It is therefore possible that some patients assigned as SIMV-PS could have received full-support ventilation without any differences from A/C. However, the differences observed between the baseline characteristics of groups clearly suggest clinicians were targeting distinctly different patients for SIMV-PS vs A/C and we believe it is likely they would have selected SIMV-PS when patients were making at least some spontaneous efforts.

Regarding our chosen methodology for developing the propensity scores in this study, we considered the patient on mechanical ventilation to be a patient undergoing a dynamic and changing process. We therefore decided to take variables that were available before and after initiating respiratory support into consideration in the model; we believe that the evolution of the patient could influence the decision either to remain on SIMV-PS or switch away from it. We based this decision partly on recommendations proposed by several studies using the propensity score method,[21] which suggest including both baseline variables at admission and variables related to the outcome.

In conclusion, in a large cohort of mechanically ventilated patients, ventilation with SIMV-PSV compared with A/C was more likely to be used in less severely ill patients, either because of trauma or postoperatively. However, when baseline differences between groups were accounted for using a propensity score analysis, no differences were observed in clinically relevant outcomes, such as duration of mechanical ventilation or mortality, despite biases that would have favored SIMV-PS.

Table 3—*Univariate Analysis of Effect of SIMV-PS on In-Hospital Mortality Across the Propensity Score Strata*

Quintile	Mortality in the Hospital (%)		Absolute Effect, %	Relative Effect, %	Odds Ratio (95% CI)	*P* Value
	A/C	SIMV-PS				
First	68.3	70.6	−2.3	−3.4	1.03 (0.75-1.42)	.84
Second	56.3	42.1	14.2	25.2	0.75 (0.51-1.10)	.10
Third	42.5	55.1	−12.6	−29.6	1.30 (0.97-1.73)	.10
Fourth	31.1	25.7	5.4	17.4	0.83 (0.53-1.28)	.38
Fifth	12.5	11.8	0.7	5.3	0.95 (0.52-1.74)	.86

See Table 1 for expansion of abbreviations.

Table 4—*Comparison of Secondary Outcomes According to Stratification by the Propensity Score*

Outcome	First Quintile n = 315		Second Quintile n = 317		Third Quintile n = 315		Fourth Quintile n = 317		Fifth Quintile n = 314	
	A/C n = 297	SIMV-PS n = 18	A/C n = 279	SIMV-PS n = 38	A/C n = 265	SIMV-PS n = 50	A/C n = 245	SIMV-PS n = 72	A/C n = 142	SIMV-PS n = 172
Use of sedatives, % patients	73	56	68	53	77[a]	54[a]	73	68	76	71
Days of sedatives, median (interquartile range)	4 (2-7)	2.5 (2-6)	3[b] (2-6)	2[b] (1-3)	2 (1-4)	2 (1-3)	2 (1-4)	2 (1-3)	2 (1-3)	2 (1-3)
Days of ventilatory support (including duration of weaning), median (interquartile range)	5 (2-8)	2.5 (1-7)	4 (2-8)	3 (2-4)	3 (2-5)	2 (2-7)	3 (2-6)	3 (2-4)	2 (2-4)	3 (2-4)
Length of stay in the ICU, median (interquartile range)	7 (4-12)	5.5 (3-13)	6 (3-13)	5 (3-8)	6 (3-11)	7 (3-11)	6 (4-10)	5 (4-8)	4.5 (3-8)	5 (3-10)
Mortality in the ICU, No. (%)	192 (65)	11 (61)	144 (52)	14 (37)	96 (36)	24 (48)	66 (27)	12 (17)	16 (11)	15 (9)

See Table 1 for expansion of abbreviations.
[a]$P = .002$.
[b]$P = .04$.

Appendix 1: Ventila Group Member Collaborators

Argentina: Coordinators: Carlos Apezteguia (Hospital Prof. A. Posadas, El Palomar, Buenos Aires) and Pablo Desmery (Sanatorio Mitre, Buenos Aires).

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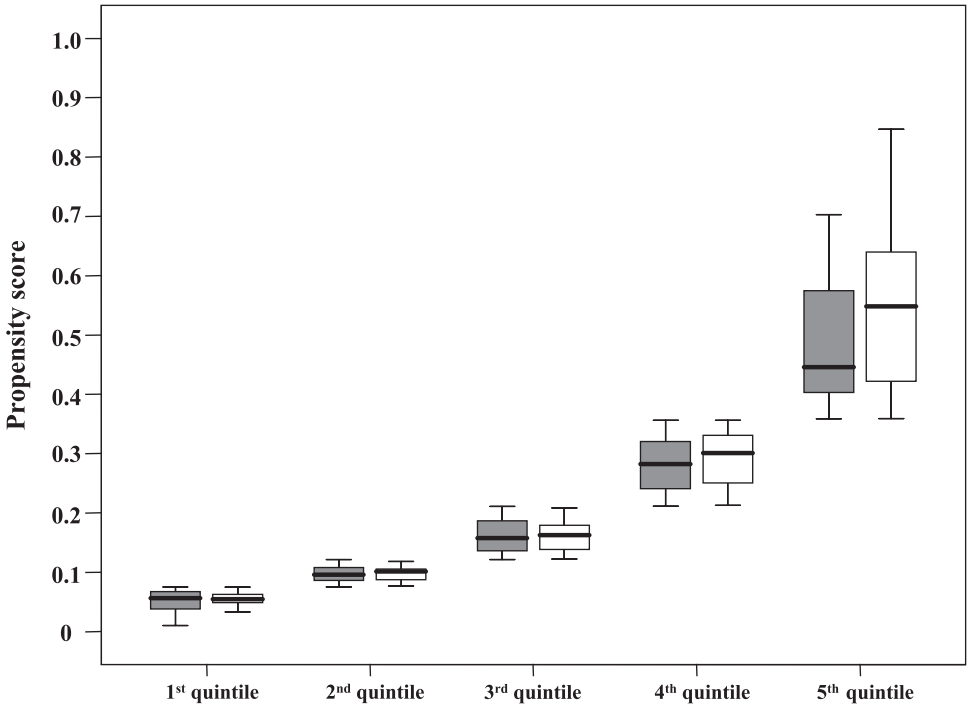

Figure 2. Comparison of propensity score in each quintile. Gray box plots correspond to the A/C group and white box plots correspond to the SIMV-PS group. The black vertical line at the center of each box denotes the median value. The lower and upper limits of the box denote the 25th and 75th percentile, respectively. The vertical lines indicate the extremes values. See Figure 1 for expansion of abbreviations.

Table 5—*Methods Used for Weaning From Mechanical Ventilation*

	A/C (n = 638)	SIMV-PS (n = 245)	*P* Value
Simple weaning, No. (%)	395 (62)	146 (60)	.57
Methods of weaning			
Spontaneous breathing trial, No. (%)	374 (95)	129 (88)	.01
T-piece, No.	255	44	…
CPAP, No.	68	42	…
Pressure support < 7 cm H_2O, No.	48	39	…
Other, %	3	4	…
Gradual reduction, No. (%)	21 (5)	17 (12)	.01
SIMV, No.	…	1	…
SIMV-PS, No.	2	12	…
PS, No.	19	4	…
Difficult weaning, No. (%)	215 (34)	89 (36)	.59
Days of weaning, mean (interquartile range)	2 (2-3)	2 (2-4)	.95
Methods of weaning			
Spontaneous breathing trial, No. (%)	82 (38)	22 (25)	.008
T-piece, No.	47	4	…
CPAP, No.	22	10	…
Pressure support < 7 cm H_2O, n	12	7	…
Other, %	1	1	…
Gradual reduction, No. (%)	133 (62)	67 (75)	.008
SIMV, No.	7	3	…
SIMV-PS, No.	32	35	…
PS, No.	94	29	…
Prolonged weaning, No. (%)	27(4)	10 (4)	.99
Days of weaning, mean (interquartile range)	8 (7-11)	9 (8-11.5)	.47
Methods of weaning			
Spontaneous breathing trial, No. (%)	9 (33)	2 (20)	.70
T-piece, No.	4	…	…
CPAP, No.	3	1	…
Pressure support < 7 cm H_2O, No.	2	1	…
Other, %	…	…	…
Gradual reduction, No. (%)	18 (66)	8 (80)	.70
SIMV, No.	…	1	…
SIMV-PS, No.	3	3	…
PS, No.	15	4	…

CPAP = continuous positive airway pressure; PS = pressure support; SIMV = synchronized intermittent mandatory ventilation. See Table 1 for expansion of other abbreviations.

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Appendix 2: Protocol of the Second International Study on Mechanical Ventilation

Objectives of Study

The main objective of this study was to obtain a better understanding of the spectrum of use of mechanical ventilation in ICUs.

1. To know the current status of mechanical ventilation in the ICU. Determine the number and percentage of patients who are admitted to an ICU and require mechanical ventilation. This protocol excluded patients admitted after elective surgery and who required mechanical ventilation for < 12 h (excepting patients who receive noninvasive ventilation).
2. To analyze the results obtained in this study in following aspects:

   a. Patient characteristics
   b. Modes of ventilation and setting
   c. Outcome of overall population
   d. Characteristics and outcome of patients with:

      i. Stroke or brain trauma
      ii. Asthma
      iii. COPD

   e. Epidemiology and outcome of noninvasive ventilation
   f. Outcome of weaning

Overview

This was a multicenter, international study that collected data of all patients who were admitted to the study ICUs and who met the inclusion/exclusion criteria between April 1, 2004, at 12:00 AM and the finish date of April 30, 2004, at 11:59 PM. Patients who were already mechanically ventilated prior to April 1 at 12:00 AM were not included in the study.

Study Population

1. Inclusion Criteria

a. Patients who were admitted to the ICU and required invasive mechanical ventilation (endotracheal tube or tracheostomy) for > 12 h
b. Patients who were admitted to the ICU and required noninvasive mechanical ventilation (bilevel pressure ventilation or CPAP with nasal or facial mask) for > 1 h
c. Patients in whom mechanical ventilation was started outside the study ICU at the same institution and/or a different institution, including emergency room or operating room, and were then transferred to the ICU
d. This study was conducted in ICUs that met the following criteria:

   i. Units that had six or more beds and/or average (during prior 12 months) > 30% of the patients admitted required mechanical ventilation
   ii. Units that had staff or visiting physicians with intensive care training and/or physicians who had > 5 years of intensive care experience

2. Exclusion Criteria

a. Patient < 18 y of age
b. Patients who were admitted to an ICU after elective surgery and required mechanical ventilation for < 12 h
c. The following ICUs were excluded:

   i. Pediatric ICU
   ii. Postoperative anesthesia recovery room

Study Protocol

Data from patients who met the inclusion criteria and who were enrolled in the study were followed according to the following situations, whichever occurred first: for 28 days after enrollment in the study or until discharge from the hospital and/or death within 28 days after inclusion in the study. The data were collected by the Investigator or Research Coordinator in each ICU. The Study Coordinator for each country was consulted regarding any protocol-related questions.

Data Collection:

1. Demographic data: age, sex, weight expressed in kilograms, height expressed in centimeters, Simplified Acute Physiology Score was calculated at admission to ICU, date of hospital admission, date of admission to the study ICU
2. Type of problem: medical or surgical (including scheduled and nonscheduled surgery)
3. Primary reason to start the mechanical ventilation:

   a. Acute-on-chronic respiratory disease:

      i. Acute exacerbation of COPD: Patient had the diagnosis of COPD and had an exacerbation that required mechanical ventilation
      ii. Asthma: Mechanical ventilation started because of status asthmaticus and/or acute exacerbation in a patient with prior history of reactive airway disease
      iii. Other chronic respiratory disease: Patient with diagnosis of chronic respiratory disease other than COPD or asthma (eg, pulmonary fibrosis)

   b. Acute respiratory failure: Any patient who required mechanical ventilation and had one of the following conditions:

      i. ARDS: Based on the criteria established by the American-European Consensus Conference of ARDS (acute onset, $Pao_2/Fio_2 < 200$, bilateral infiltrate on chest radiograph, absence of heart failure)
      ii. Postoperative: patients who underwent surgery and were not weaned from mechanical ventilation because of obesity, abdominal or thoracic surgery, advanced age, and so forth. Prior to surgery patients had not been on mechanical ventilation.
      iii. Acute pulmonary edema and/or congestive heart failure: patients with (1) acute cardiogenic pulmonary edema, (2) congestive heart failure with severe dyspnea with or without radiologic infiltrate, (3) cardiogenic shock
      iv. Aspiration: patients who had gastric contents in their airway or tracheal aspirate
      v. Pneumonia: patients with a new radiographic alveolar infiltrate or worsening of previous alveolar infiltrate associated with fever/hypothermia and leukocytosis/leukopenia

vi. Sepsis: based on the criteria established by Consensus Conference on Sepsis by American College of Chest Physicians/Society of Critical Care Medicine[22]: systemic inflammatory response syndrome (hyperthermia/hypothermia, tachycardia, tachypnea, leukocytosis/leukopenia) secondary to infection
vii. Trauma: mechanical ventilation because of chest, abdominal, or multiple trauma (this category did not include patients with only brain trauma)
viii. Cardiac arrest: mechanical ventilation because of sudden and unexpected cessation of cardiopulmonary functions
ix. Other: etiology of acute respiratory failure not mentioned above

c. Coma

i. Metabolic: due to primary metabolic event (eg, hepatic encephalopathy)
ii. Overdose/intoxication: secondary to accidental or voluntary ingestion of drugs or illegal substances
iii. Stroke: acute cerebrovascular accident of ischemic or hemorrhagic cause
iv. Brain trauma
v. Neuromuscular disease: respiratory failure due to primary impairment of peripheral neurologic system, muscle mass, and/or motor plaque

4. Monitoring

a. Arterial blood gases: Arterial blood gases immediately before mechanical ventilation (invasive or noninvasive) started and within the first hour after starting mechanical ventilation, if available, were documented. Arterial blood gases, if available, were documented daily (for a maximum of 28 days) while the patient continued receiving mechanical ventilation.
b. Mode of ventilator and settings: Ventilatory mode, settings (tidal volume, total respiratory rate, inspiratory fraction of oxygen, applied positive end-expiratory pressure) and ventilatory parameters (peak pressure and plateau pressure) were documented within the first hour after intubation and daily (for a maximum of 28 days) while patient continued receiving mechanical ventilation. Mode and ventilator settings at the time the arterial blood gases were obtained.
c. Prone position and noninvasive ventilation, when these techniques were used, were registered.

5. Complications: refers to conditions that developed after the patient was started on mechanical ventilation:

a. Barotrauma: if the patient had any air leaks (pneumothorax, subcutaneous emphysema, pneumomediastinum, pneumopericardium) considered secondary to ventilatory management. Barotrauma secondary to chest trauma or to insertion of central lines was not included in this category.
b. ARDS: based on the criteria established by the American-European Consensus Conference of ARDS (acute onset, $Pao_2/Fio_2 < 200$, bilateral infiltrate on chest radiograph, absence of heart failure): pulmonary origin when the initial injury was pneumonia, aspiration, chest trauma or inhalation. Extrapulmonary origin when the initial injury was sepsis, shock, multiple trauma, pancreatitis, blood product transfusions.
c. Sepsis: based on the criteria established by Consensus Conference on sepsis by American College of Chest Physicians/Society of Critical Care Medicine[22]: systemic inflammatory response syndrome (hyperthermia/hypothermia, tachycardia, tachypnea, leukocytosis/leukopenia) secondary to infection.
d. Ventilator-associated pneumonia: Values corresponding to diagnosis criteria were collected: (1) temperature $>38.5°C$ or $<36°C$, (2) white cell count $>12{,}000$ cells/μL or $<4{,}000$ cells/μL, (3) purulent bronchial secretions, (4) alveolar infiltrate.
e. Organ failure: Organ dysfunctions developed after the patient was started on mechanical ventilation. To estimate the influence of the grade of dysfunction associated with the outcome we have registered the absolute value of any of the variables related to organ failure.

i. Cardiovascular failure: if mean arterial pressure is <70 mm Hg during 2 consecutive h and if patient is receiving vasoactive drugs.
ii. Renal failure: value of creatinine in mg/dL
iii. Hepatic failure: value of bilirubin in mg/dL
iv. Hematologic failure: platelet count
v. Neurologic failure: Best Glasgow Coma Scale. If patients had received any sedative drugs or neuromuscular blockers for at least 3 h in the previous 24 h, the drug was indicated and the previous Glasgow Coma Scale to sedation and/or neuromuscular blocking was registered.

6. Weaning: The following data were collected:

a. Date when the patient met the following criteria: improvement of the cause of respiratory failure, $Pao_2/Fio_2 > 200$, positive end-expiratory pressure <5 cm H_2O and stable cardiovascular function (no vasoactive drugs)
b. Date of the first spontaneous breathing trial and the method (T-piece, CPAP, PS ≤ 7 cm H_2O) used for its performance
c. Date when started a gradual reduction of ventilatory support and the mode (SIMV with or without PS, gradual reduction of PS, other method) used for it
d. Date the patient is extubated. Type of extubation: scheduled or accidental
e. Reintubation: any reintubation that occurred within 48 h after extubation. The time elapsed from extubation to reintubation also was documented as 0 to 12 h, 12 to 24 h, or 24 to 48 h.
f. Tracheostomy: date the tracheostomy was performed and the method: percutaneous or surgical

7. Outcome:

a. Date of discharge from ICU and status: alive/dead
b. Date of hospital discharge and status: alive/dead

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