A Multicenter Randomized Trial of Computer-driven Protocolized Weaning from Mechanical Ventilation

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Rationale and Objectives: **Duration of weaning from mechanical ventilation may be reduced by the use of a systematic approach. We assessed whether a closed-loop knowledge-based algorithm introduced in a ventilator to act as a computer-driven weaning protocol can improve patient outcomes as compared with usual care.**

Methods and Measurements: **We conducted a multicenter randomized controlled study with concealed allocation to compare usual care for weaning with computer-driven weaning. The computerized protocol included an automatic gradual reduction in pressure support, automatic performance of spontaneous breathing trials (SBT), and generation of an incentive message when an SBT was successfully passed. One hundred forty-four patients were enrolled before weaning initiation. They were randomly allocated to computer-driven weaning or to physician-controlled weaning according to local guidelines. Weaning duration until successful extubation and total duration of ventilation were the primary endpoints.**

Main Results: **Weaning duration was reduced in the computer-driven group from a median of 5 to 3 d ($p = 0.01$) and total duration of mechanical ventilation from 12 to 7.5 d ($p = 0.003$). Reintubation rate did not differ (23 vs. 16%, $p = 0.40$). Computer-driven weaning also decreased median intensive care unit (ICU) stay duration from 15.5 to 12 d ($p = 0.02$) and caused no adverse events. The amount of sedation did not differ between groups. In the usual care group, compliance to recommended modes and to SBT was estimated, respectively, at 96 and 51%.**

Conclusions: **The specific computer-driven system used in this study can reduce mechanical ventilation duration and ICU length of stay, as compared with a physician-controlled weaning process.**

Keywords: computers; extubation; knowledge-based system; mechanical ventilation, weaning protocols

The weaning process accounts for approximately 40% of the total duration of mechanical ventilation (1, 2). Undue prolongation of mechanical ventilation can lead to an increased risk of infectious complications, mainly nosocomial pneumonia (3, 4), but premature extubation followed by reintubation is associated with increased morbidity and mortality (5). Thus, a major goal is to recognize readiness for extubation as soon and as reliably as possible. Clinical judgment is far from perfect and often tends to prolong mechanical ventilation (6–8). Thus, studies have shown that the duration of mechanical ventilation, and most notably of the weaning period, can be shortened by using a systematic approach for reducing the level of assistance and testing the possibility to resume spontaneous breathing (6, 9).

A closed-loop knowledge-based system has been developed and tested over the last few years as a method for driving pressure-support ventilation (PSV) (10). This system interprets clinical data in real time and provides continuous adjustment of the level of assistance delivered to intubated or tracheotomized patients. The system has been described elsewhere (10–14). In brief, it is embedded in a standard ventilator and adapts the level of pressure support to continuously recorded data on the patient's ventilatory needs, with the goal of keeping the patient within a "comfort" zone. Comfort is defined primarily as a respiratory rate that can vary freely in the range of 15 to 30 breaths/min (up to 34 in patients with neurologic disease), a tidal volume above a minimum threshold, and an end-tidal CO_2 level below a maximum threshold. The level of pressure support is periodically adapted by the system (10, 13) in steps of 2 to 4 cm of water. The system automatically tries to reduce the pressure level to a minimal value. At this value, a trial of "spontaneous breathing" with the minimal low-pressure support is performed. When successful, a message on the screen recommends separation from the ventilator.

It therefore adapts and reduces the level of assistance at a pace tailored to the individual patient's needs and evaluates the patient's ability to be separated from the ventilator. Such a system has previously been shown to reduce the duration of ventilation spent with excessive levels of respiratory work (13), and to improve prediction of extubation readiness (11). Such a system can be used safely over prolonged periods of mechanical ventilation (15).

Applying guidelines to real-life clinical practice has been found difficult (16, 17). The closed-loop system constitutes an automated, continuous, protocol-driven ventilation and weaning process that may help to improve compliance with guidelines, including a prompt to physicians when readiness testing is successful. Although it may not outperform a strictly followed and aggressive weaning protocol, it may be better than usual care. We tested this hypothesis in a multicenter randomized controlled trial versus usual weaning processes. This work has been presented in abstract form (18).

METHODS

A detailed METHODS is available in the online supplement.

Patients

This study was conducted in five teaching hospital medical–surgical intensive care units (ICUs) in Barcelona (Spain), Brussels (Belgium),

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Créteil (France), Geneva (Switzerland), and Paris (France). Each center obtained approval of the study from the ethics committee. Signed informed consent was obtained from each patient or next of kin.

Patients under mechanical ventilation for at least 24 h and ventilated using an assisted mode were screened for eligibility at an early stage, before usual criteria for weaning readiness were present (Figure 1). Enrollment criteria required absence of the following: a do-not-resuscitate order, expected poor short-term prognosis, tracheostomy, and cardiac arrest with a poor neurologic prognosis. Inclusion criteria were pulse oximetry greater than 90%, with an FI_{O_2} of 50% or less; positive end-expiratory pressure level of 8 cm or less of water; no need for epinephrine or norepinephrine at a rate greater than 1 mg/h; body temperature between 36°C and 39°C; and a stable neurologic status, with little or no sedation.

Study Protocol

As soon as patients met the inclusion criteria, a preinclusion test with pressure support at 15 cm or more of water was performed to assess the patient's ability to tolerate this mode. The test was positive at 30 min if the patient remained clinically stable, with no hemodynamic or respiratory distress.

Patients were then allocated at random to ventilation with an Evita 4 ventilator (Dräger, Lübeck, Germany) equipped with the system or to the usual care (control) group. In the usual care arm, weaning was conducted according to usual local practice (guidelines were available in four units). In all centers, weaning was conducted based on written guidelines, as follows: (*1*) once daily or more, screening for criteria to decide for a spontaneous breathing trial (SBT; T-piece or PSV ± positive end-expiratory pressure) had to be performed; (*2*) SBT might be performed as soon as criteria were present; and (*3*) after succeeding an SBT, standardized extubation criteria were used. These principles and the local guidelines are detailed in the online supplement. We did not assess compliance to guidelines not to influence practice. In this group, ventilatory settings were chosen by the physician in charge of the patient.

Randomization was concealed and generated by an electronic-mail system. The randomization was stratified by center and on the presence of an underlying disease (chronic obstructive pulmonary disease, central neurologic disease, or none).

Identical criteria were used in both groups to switch back to assist-control ventilation in case of worsening. The patient was then retested, and returned to the same arm when the test was positive.

Endpoints

The primary endpoints were the time to successful extubation, defined as the time from inclusion until successful extubation (followed by 72 h without ventilator support), and the total duration of mechanical ventilation.

Secondary endpoints were the duration of ventilatory support until first extubation, length of ICU and hospital stay, number of complications in the ICU, number of nosocomial pneumonia cases, and mortality rates in the ICU and hospital.

Statistical Analysis

The sample size of 75 in each group was chosen to give a power of 0.80 to detect a reduction in weaning time of 2 d (from 7 to 5 d, 30%), assuming a standard deviation of 5 d and a two-sided test at the 0.05 level. The analysis was performed in the two groups as treated. Results are given as medians (25th–75th interquartile ranges). Proportions were compared using the χ^2 test or the Fisher exact test when required. The Mann-Whitney U test was used to analyze mechanical ventilation durations or length of stay. The cumulative probability of remaining on mechanical ventilation was analyzed by the Kaplan-Meier method, and a log-rank test was used to assess differences. p values smaller than 0.05 were considered significant. All the p values were two-sided.

RESULTS

Patients

Patients were enrolled from September 1, 2002, to July 12, 2003. Mean duration of participation per center was 171 d; 40 patients were enrolled in Brussels, 39 in Barcelona, 34 in Créteil, 18 in Geneva, and 16 in Paris. Figure 1 shows the number of patients receiving invasive mechanical ventilation in the study centers, and the 147 patients included. Two patients were extubated before being randomized to the computer-driven weaning group, due to a delay in the electronic randomization procedure, and one control group patient was excluded because the family withdrew their consent. This left 144 patients for the data analysis, 74 in the intervention group and 70 in the control group.

Patient characteristics at baseline are shown in Table 1. Patients were similar for most characteristics, including the number

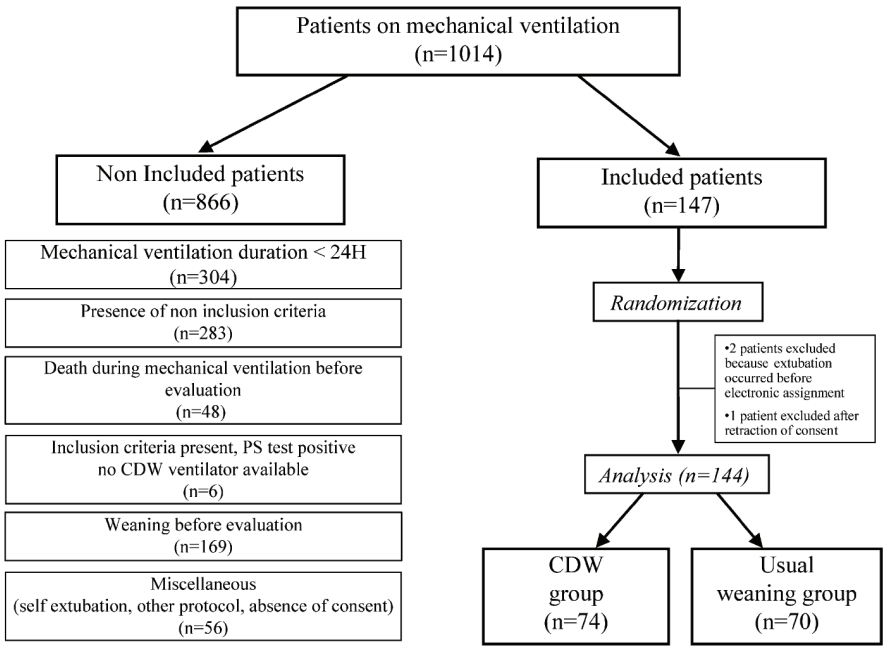

Figure 1. Flow chart of the study. This chart shows the results of daily screening for study inclusion in the five participating centers during the study period. Mean duration of center participation was 171 d (range, 79 to 284 d). PS denotes pressure support and CDW computer-driven weaning.

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY PATIENTS

Variable	CDW Group (*n* = *74*)	Usual Weaning Group (*n* = *70*)	p Value
Age, yr	60 (51–74)	62 (52–72)	0.76
Sex, male/female, n	47/27	45/25	0.99
SAPS II at admission	49 (39–57)	47.5 (38–50)	0.89
LODS at admission	7 (5–9)	7 (5–10)	0.65
LODS at inclusion	5 (3–7)	5 (3–7)	0.65
McCabe, n (%)			
1	38 (51)	37 (53)	
2	31 (42)	28 (40)	0.97
3	5 (7)	5 (7)	
Admission type, n (%)			
Medical	51 (68)	47 (67)	0.93
Elective surgery	11 (15)	10 (14)	
Emergent surgery	12 (16)	13 (19)	
Comorbidities, n (%)			
COPD	16 (22)	13 (19)	0.68
Restrictive respiratory insufficiency	3 (4)	4 (6)	0.71
Asthma	2 (3)	1 (1)	0.99
Ischemic heart disease	12 (16)	6 (9)	0.21
Hypertensive heart disease	5 (7)	6 (9)	0.76
Valvular heart disease	5 (7)	7 (10)	0.56
Peripheral neurologic disorder	1 (1)	4 (6)	0.20
Central neurologic disorder	8 (11)	5 (7)	0.56
Psychiatric disorder	9 (12)	5 (7)	0.40
Immunosuppression	8 (11)	9 (13)	0.79
At least one comorbidity	51 (69)	43 (63)	0.48
PS test at inclusion			
Level of PS, cm H_2O	18 (15–20)	16 (15–20)	0.14
Level of PEEP, cm H_2O	5 (5–6)	5 (5–6)	0.52
Level of $F_{I_{O_2}}$, %	35 (30–40)	35 (30–40)	0.95
Duration of invasive mechanical ventilation before inclusion, d*	3.5 (2–6)	4 (3–7)	0.08

Definition of abbreviations: CDW = computer-driven weaning; COPD = chronic obstructive pulmonary disease; LODS = logistic organ dysfunction score; PEEP = positive end-expiratory pressure; PS = pressure support; SAPS II = simplified acute physiologic score II.

Values are expressed as medians (interquartile range), or numbers (percentage).

* The duration of invasive mechanical ventilation before inclusion is the time on endotracheal mechanical ventilation prior to study inclusion.

with chronic obstructive pulmonary disease or central neurologic disorders. Duration of mechanical ventilation before inclusion was similar in the two groups. The values used for the pressure-support test, including the positive end-expiratory pressure and fraction of inspired oxygen, were also similar.

Outcome

The main results are shown in Table 2. The weaning time was greatly reduced with the computer-driven weaning as compared with usual weaning, whether or not the time on postextubation noninvasive ventilation was counted. The total duration of mechanical ventilation and the duration of the ICU stay were also significantly reduced with the computer-driven weaning, when considering the total population as well as patients alive at ICU discharge (Table E1 of the online supplement). No difference was found for hospital length of stay.

Mortality in the ICU was similar in the computer-driven weaning group and the usual group (21.6 vs. 22.9%, p = 1.0), as was hospital mortality (37.8 vs. 28.6%, p = 0.29). Mortality while connected to the ventilator during the weaning phase was also similar in the computer-driven weaning and control groups (six and five patients, respectively; p = 0.70).

TABLE 2. COMPARISON OF OUTCOME BETWEEN STUDY GROUPS

Outcome	CDW Group (*n* = *74*)	Usual Weaning Group (*n* = *70*)	p Value
Time to first extubation*	2.00 (1.75–6.25)	4.00 (2.00–8.25)	0.02
Duration of mechanical ventilation until first extubation*	6.50 (3.00–12.25)	9.00 (5.75–16.00)	0.03
Time to successful extubation†	3.00 (2.00–8.00)	5.00 (2.00–12.00)	0.01
Total duration of mechanical ventilation†	7.50 (4.00–16.00)	12.00 (7.00–26.00)	0.003
Intensive care length of stay	12.00 (6.00–22.00)	15.50 (9.00–33.00)	0.02
Hospital length of stay	30.00 (17.00–54.75)	35.00 (21.00–60.25)	0.22

Definition of abbreviation: CDW denotes computer-driven weaning.

* The time to first extubation is the time from study inclusion (first positive pressure-support test) to first extubation.

† The time to successful extubation is the time from study inclusion (first positive pressure-support test) to last successful extubation. Total duration of mechanical ventilation is the time from intubation to first or last successful extubation.

Data are expressed as median number of days (25th–75th interquartile range).

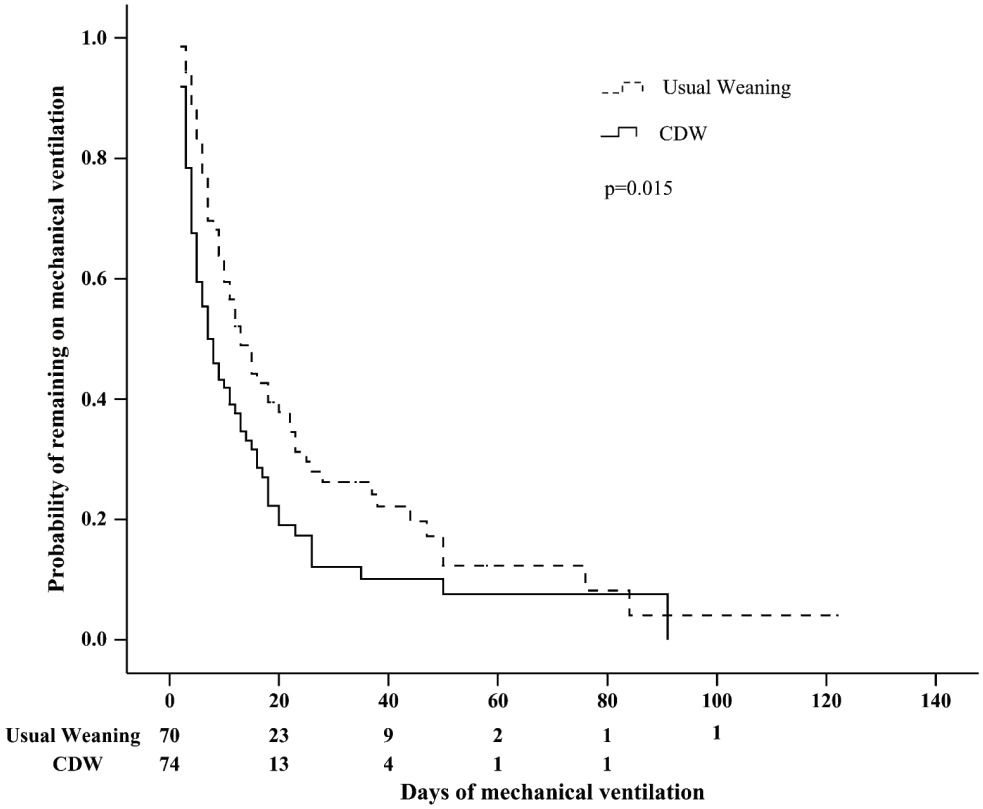

Figure 2. Kaplan-Meier analysis of weaning time until successful extubation or death after inclusion for all included patients in each study group.

The probability of remaining on mechanical ventilation is shown in Figure 2, and was significantly reduced with the computer-driven weaning (log-rank test, p = 0.015). Data concerning survivors only are shown in Table E1.

Complications

Complications are reported in Table 3. The need for noninvasive ventilation was almost halved in the group. The total number of ventilation-related complications (reintubation, self-extubation, need for noninvasive ventilation, mechanical ventilation longer than 21 d, and tracheotomy) was reduced by 30% in the computer-driven weaning compared with the usual group. In the computer-driven weaning and control groups, ventilator-associated pneumonia occurred in 13 and 11 patients, and pneumothorax in 0 and 2 patients, respectively.

Mechanical Ventilation

Patients were ventilated with pressure support for 392 d in the usual weaning group and 293 d in the computer-driven weaning group. The modes of ventilation recommended in the guidelines (pressure support for the weaning phase and ACV in case of worsening) were used 92 and 96% of the time after inclusion in the computer-driven weaning group and in the usual weaning group, respectively. Alternatively, synchronized intermittent mandatory ventilation (SIMV) was used 8 and 4% of the time (Table E2). A T-piece trial was performed 124 times in the usual weaning group and 12 times (in eight patients) in the computer-driven weaning group. In the usual care group, we estimated compliance to recommendations for using SBTs; T-piece trials were performed 51% of the days of ventilation with PSV or SIMV at FI_{O_2} below 50% in the usual weaning group. In the computer-driven weaning group, the mean time from display of the message recommending separation from the ventilator to extubation was 0.6 ± 2.65 d (median, 1 d; 25th–75th, 0–2 d), with a minimum of 0 d, and a maximum of 15 d. Only 42% of the patients were extubated the day of the message.

Technical problems recorded with the computer-driven weaning were as follows. In five patients, a total of 11 episodes

TABLE 3. COMPLICATIONS OF MECHANICAL VENTILATION

Complication	CDW Group (*n = 74*)	Usual Weaning Group (*n = 70*)	p Value
Reintubation within 72 h	12 (16)	16 (23)	0.40
Any reintubation	17 (23)	23 (33)	0.20
Need for noninvasive ventilation	14 (19)	26 (37)	0.02
Self-extubation	8 (11)	7 (10)	0.99
Tracheostomy	12 (16)	13 (19)	0.83
Mechanical ventilation duration for > 14 d	12 (16)	20 (29)	0.11
Mechanical ventilation duration for > 21 d	5 (7)	11 (16)	0.11

For definition of abbreviation, *see* Table 2.
Values denote number of patients, with percentages in parentheses.

of transient system interruption occurred over a total of 293 d of ventilation using this system. During the interruptions, ventilatory assistance was delivered in standard pressure-support mode. In 10 patients, the system was voluntarily stopped because worsening of the clinical condition required assist-control ventilation. In five patients, a manual increase in pressure support was deemed necessary by the physician, and a manual decrease was necessary in three patients. Two instances of CO_2 sensor dysfunction requiring removal of the computer-driven weaning system occurred in one center.

The amount of sedatives used did not differ between the groups during the intubation-to-inclusion period and the inclusion-to-extubation period (*see* Table 4 and Table E3). Use of steroids and neuromuscular blocking agents before and after inclusion was also similar in the two groups.

DISCUSSION

In this study, a computer-driven weaning protocol performed better than usual care based on written weaning guidelines. Weaning time was nearly halved with the computer-driven weaning as compared with usual weaning. The system used in this study was developed several years ago and has been repeatedly evaluated since then (10–14). It ensures that the desired ventilation protocol is applied. In the usual weaning group, weaning was performed according to local guidelines, representing the usual care in these university centers involved in respiratory and weaning research. The reduction in weaning duration was associated with decreases in both the total duration of mechanical ventilation, and the ICU length of stay.

Weaning protocols or guidelines recommending a systematic approach have been shown to reduce the duration of weaning and mechanical ventilation (6, 9) and are often recommended (19). In a randomized controlled study, Ely and coworkers showed that routine daily screening and identification of the patients able to breathe spontaneously reduced weaning duration from a median of 3 to 1 d and the total duration of mechanical ventilation from 6 to 3.5 d (6). Kollef and colleagues also showed a reduction in the duration of mechanical ventilation in patients weaned using protocols, from a median of 1.8 to 1.4 d (9). The implementation of protocols, however, is time consuming (16), requires staff training, is not always followed faithfully (17), and varies in efficacy according to all these factors (20–22). Protocols may not even be necessary in well-staffed centers (20). In the present study, written weaning guidelines were compared with a closed-loop knowledge-based ventilation system. The duration of weaning was significantly decreased, from a median of 5 to 3 d in the computer-driven weaning group, and the total duration of mechanical ventilation decreased from 12 to 7.5 d. The duration of weaning was slightly longer in the present study than in the previously mentioned studies. This is in part because the type of patients was different (9), and also because patients were included at an early stage, as soon as they were able to tolerate moderate to high pressure-support levels and before they met criteria for readiness testing and weaning.

In our study, several reasons may explain the reduction of mechanical ventilation duration in the computer-driven weaning group. Automation of the weaning protocol may explain an essential part of the results. The system is designed to perform several tasks comparable to a weaning protocol 24 h a day and 7 d a week: to automatically and gradually reduce the ventilatory assistance, to automatically perform the equivalent of an SBT, and to display an incentive message when the patient is deemed ready to breathe spontaneously. Although the reduction in pressure support applied by the system is gradual, complete weaning can be obtained in less than 24 h, thus allowing rapid detection of readiness for extubation. This computer-driven weaning protocol has advantages compared with a human-driven protocol. The computer-driven weaning protocol does not depend on the willingness or availability of the staff, and full compliance with the weaning protocol is therefore ensured. A permanent evaluation and adjustment of ventilatory support cannot be continuously performed by caregivers, and the system has the ability to determine more easily and rapidly than usual care the time for a possible separation from the ventilator. It is likely that the message delivered by the system also constitutes a strong incentive for the clinician to consider a possible extubation. This visual prompt constitutes an important aspect of the computer-driven protocol.

Other specific features of the computerized protocol used in the study, which may differ from human-directed protocols, should be underlined. The computerized protocol used in the study takes into account the history of breathing pattern and the previous modifications of the assistance level to determine the setting. One important feature is that the decision process of the system is designed to accept transient instabilities, such as a short increase in respiratory frequency, without changing

TABLE 4. USE OF OPIOIDS, SEDATIVES, NEUROMUSCULAR BLOCKERS, AND CORTICOSTEROIDS*

	CDW Group (*n* = 74)	Usual Weaning Group (*n* = 70)	p Value
Sedative agents			
Cumulative daily dosage (midazolam-equivalent), mg			
Before inclusion	49 (25–81)	46 (28–81)	0.74
After inclusion	0 (0–8)	0.7 (0–16)	0.14
Opioids			
Cumulative daily dosage (fentanyl-equivalent), μg			
Before inclusion	100 (0–795)	170 (0–1,312)	0.51
After inclusion	0 (0–50)	0 (0–100)	0.08
Neuromuscular blockers			
Days with NMBs before inclusion, %	0 (0–0)	0 (0–0)	0.10
Days with NMBs after inclusion, %	0 (0–0)	0 (0–0)	0.25
Corticosteroids			
Days with corticosteroids before inclusion, %	0 (0–33)	0 (0–62)	0.49
Days with corticosteroids after inclusion, %	0 (0–0)	0 (0–34)	0.36

Definition of abbreviations: CDW = computer-driven weaning; NMBs = neuromuscular blockers.

Data are expressed as medians (25th–75th interquartile range).

* The use of sedatives was calculated as midazolam-equivalent (34), and the use of opioids as fentanyl-equivalent (35).

the ventilation classification. The system is also able to perform the final test at any time and to repeat it whenever possible, increasing the opportunity to find a successful test. This temporal reasoning may differ from an automated or even a human-driven approach where one single measurement or test is performed.

It is possible, however, that the rigor with which weaning assessment was performed in the control group was suboptimal (e.g., with less assessment on weekends or in case of major variations in overall workload in the units), as often observed in real life. Such a suboptimal approach could also contribute to the difference between the two groups, but our design did not address this question.

The need for reintubation within 72 h after extubation tended to be lower with the computer-driven weaning (16.2 vs. 22.9%), but not significantly. This failure rate is on the higher end of the reported range. In recent studies, reintubation rates were 11% (23), 15.7% (24), 23.5% (25), and 14.5% (26). A relatively high extubation rate was expected because patients on mechanical ventilation for less than 24 h were not included in the study. The need for noninvasive ventilation after extubation was reduced to 18.9% in the computer-driven weaning group as compared with 37.1% in the usual group. The rate of respiratory failure after extubation, with a potential need for noninvasive ventilation, was 23% in the study by Keenan and colleagues (27) and 22.5% in the study by Esteban and colleagues (28). The difference with our study may be ascribable to differences in patient selection, with higher severity scores in our population, and to the experience of the centers with this technique.

The trend for a reduction in reintubation and in the need for noninvasive ventilation in the computer-driven weaning group may be explained by physiologic benefits of the system previously demonstrated, because adjusting the level of assistance to the breathing pattern may avoid periods of excessive work of breathing. In a previous study (13), patients were ventilated successively with the computer-driven weaning and with standard pressure support. The time spent in the comfort zone of ventilation was 93 $\pm$ 8% with automatic pressure support and 66 $\pm$ 24% with standard pressure support ($p < 0.05$). The time spent with a high airway occlusion pressure (suggesting excessive work of breathing) was significantly lower with automatic pressure support. The level of pressure support was modified 56 $\pm$ 40 times over a 24-h period in the computer-driven weaning group versus 1 $\pm$ 2 times in the standard pressure-support group. Repeated periods of excessive workload during mechanical ventilation may slow recovery from diaphragmatic fatigue and/or aggravate diaphragm weakness, a frequent finding in difficult-to-wean patients (29).

This study has limitations. The results cannot be generalized to all patients because only a small proportion of eligible patients were randomized (14%). The rationale, however, extends at least to patients with a short weaning duration and further studies will be needed including this group. In a few patients, the closed loop was interrupted, either for technical reasons or because the clinicians disagreed with the settings. More work is needed to determine which patients may be poor candidates for ventilation with the system. Another limitation is that blinding of the investigators was not feasible, which may have favored the computer-driven weaning group. The selection of control subjects is an important issue in randomized trials of mechanical ventilation and has recently been a focus of debate (30). It has been suggested that usual care should be applied in the control group when feasible (31), as in the study by Ely and coworkers (6). The control group in our study was managed based on written weaning guidelines used routinely in each center. These guidelines had been in use for several years in all study centers and included daily screening and SBTs. Compliance with guidelines, however, was not evaluated in the usual weaning group, as our goal was to keep usual weaning practices unchanged. Compliance with weaning protocols is frequently relatively low (17, 22, 32). In the study by Ely and colleagues, after the training period, compliance was 81% in medical ICUs and 63% in surgical units, and poor compliance was often related to the T-piece trial (17). With the computer-driven weaning, T-piece trials are not required to test the patient's readiness for extubation, because the SBTs are automatically performed with low levels of pressure support. In the present study, 12 T-piece trials were nevertheless performed in the computer-driven weaning arm, as compared with 124 in the usual weaning group. In the usual weaning group, we estimated from the number of performed T-piece trials that compliance with recommendations for testing spontaneous breathing with trials was about 51%. This calculation, however, only takes into account SBTs performed with T-piece, and not those performed in pressure support, which were not recorded. The level of compliance may then have been underestimated by this calculation. In the future, comparison with protocolized weaning rather than usual care may be required.

In conclusion, we have shown in the present study that weaning duration from mechanical ventilation could be reduced using a system that automatically drives the level of pressure support, automatically performs SBTs, and displays an incentive message when the trial is successfully passed. Milic-Emili asked whether weaning was an art or a science (33). Science is gaining ground as knowledge accumulates from physiologic studies and randomized trials. We think that incorporation of this knowledge into a computer-driven weaning system is a step forward in a scientific approach to weaning.

Conflict of Interest Statement: F.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.M. received €1,500 for lecturing at Draeger Hispania, Investigation Foundation of the Sant Pau Hospital, where J.M. is currently working, and received €18,000 through a research contract with Draeger Medical AG for the conduct of this trial. P.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.D. is currently (2006) discussing with Draeger for consultant fees. B.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.M. is an employee of Draeger Medical AG & Co KG in Research and Development Department Critical Care, Lübeck Germany. L.B., as head of the clinical research group, has received grants through research contracts with Draeger for the conduct of clinical trials concerning the studied system, approximately €15,000 per year from 2001 to 2004. Draeger Medical has provided the centers with the equipment necessary for the study, including the ventilators EVITA 4 equipped with the Evita Weaning System, and has provided a grant necessary to cover insurance costs, ethics committees' administrative fees, and organization of meetings for the investigators and for monitoring purposes. Also, L.B. is currently (2006) discussing with Draeger for consultant fees.

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