A COMPARISON OF FOUR METHODS OF WEANING PATIENTS FROM MECHANICAL VENTILATION

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Abstract

Background. Weaning patients from mechanical ventilation is an important problem in intensive care units. Weaning is usually conducted in an empirical manner, and a standardized approach has not been developed.

Methods. We carried out a prospective, randomized, multicenter study involving 546 patients who had received mechanical ventilation for a mean (±SD) of 7.5±6.1 days and who were considered by their physicians to be ready for weaning. One hundred thirty patients had respiratory distress during a two-hour trial of spontaneous breathing. These patients were randomly assigned to undergo one of four weaning techniques: intermittent mandatory ventilation, in which the ventilator rate was initially set at a mean (±SD) of 10.0±2.2 breaths per minute and then decreased, if possible, at least twice a day, usually by 2 to 4 breaths per minute (29 patients); pressure-support ventilation, in which pressure support was initially set at 18.0±6.1 cm of water and then reduced, if possible, by 2 to 4 cm of water at least twice a day (29 patients); intermittent trials of spontaneous breathing, conducted two or more times a day if possible (33 patients); or a once-daily trial of spontaneous breathing (31 patients).

Although often lifesaving, mechanical ventilation causes numerous life-threatening complications, making it important to discontinue ventilator support at the earliest possible time. More than 40 percent of the time that a patient receives mechanical ventilation is spent trying to wean the patient from the ventilator. Considering the proportion of staff time devoted to weaning, it is surprising that the process continues to be managed empirically and that a standardized approach has not been developed.

Weaning techniques differ considerably from one another. Traditionally, intermittent trials of spontaneous breathing, conducted one or more times a day, have been used. Intermittent mandatory ventilation was introduced amid claims that it was superior to the traditional weaning approach. It allows the patient to breathe spontaneously between ventilator-delivered breaths; thus, weaning can be considered to begin with the institution of mechanical ventilation. In the 1980s, pressure-support ventilation became available; it provides a titratable pressure boost to every inspiratory effort, and weaning is accomplished by gradually decreasing the level of the pressure boost.

Efficacy studies of weaning techniques can be faulted for having a retrospective design, inappropriate study...
populations, and poorly standardized protocols; in addition, most were conducted before the use of pressure-support ventilation became widespread. Accordingly, we performed a prospective, randomized study involving patients who were deemed ready to discontinue mechanical ventilation. In a subgroup of patients who were difficult to wean we compared the length of time required for weaning with the use of four techniques: intermittent mandatory ventilation, pressure-support ventilation, intermittent trials of spontaneous breathing conducted several times a day, and a once-daily trial of spontaneous breathing.

METHODS

Patients

The study was conducted between October 1992 and October 1993 in the medical–surgical intensive care units of 14 teaching hospitals in Spain. The study population consisted of 546 patients (378 men and 168 women), with a mean (±2 SD) age of 58.2±18.4 years. All received mechanical ventilation for more than 24 hours because of acute respiratory failure. The following underlying conditions were present: chronic obstructive pulmonary disease with acute respiratory failure in 128 patients, acute lung injury in 319, neurologic or neuromuscular disorders in 85, and miscellaneous causes in 14. The acute lung injury was a result of surgery in 74 patients, infection in 168, traumatic injury in 98, acute respiratory distress syndrome in 23, and other pulmonary causes in 29. On admission, most were conducted before the use of pressure-support ventilation, intermittent trials of spontaneous breathing, and a once-daily trial of spontaneous breathing. The patients were assigned to the groups in a blinded fashion with the use of opaque, sealed, numbered envelopes, which were opened only when a patient did not successfully complete the two-hour trial of spontaneous breathing. All adjustments for each weaning technique were made by the primary physician.

Intermittent Mandatory Ventilation

In the group that received intermittent mandatory ventilation, the ventilator rate was initially set at half the frequency used during assist–control ventilation; this initial rate was 10.0±2.2 breaths per minute, and mechanical breaths were synchronized with inspiratory effort. We attempted to decrease the ventilator rate, usually by two to four breaths per minute, at least twice a day. The ventilator rate was decreased more rapidly if tolerated by the patient, as reflected by clinical assessment and blood gas monitoring. Patients who tolerated a ventilator rate of five breaths per minute for two hours without signs of distress were extubated. A continuous positive airway pressure of ≤3 cm of water was permitted.

Pressure-Support Ventilation

In the group that received pressure-support ventilation, pressure was titrated to achieve a frequency of ≤25 breaths per minute. Pressure support was initially set at 10.0±6.1 cm of water, and we attempted to reduce this level of support by 2 to 4 cm of water at least twice a day. The pace was increased if the patient did not have signs of distress (the same criteria were applied as in the initial trial of spontaneous breathing, except that a respiratory frequency of ≤25 breaths per minute was required). Patients who tolerated pressure support at a setting of 3 cm of water for two hours with no apparent ill effects were extubated. A continuous positive airway pressure of ≤5 cm of water was permitted.

Intermittent Trials of Spontaneous Breathing

Patients assigned to intermittent trials of spontaneous breathing were disconnected from the ventilator and allowed to breathe spontaneously through either a T-tube circuit or a continuous-flow circuit designed to provide a continuous positive airway pressure of ≤5 cm of water. The duration of the trials was gradually increased, and they were attempted at least twice a day. Between the trials, assist–control ventilation was provided for at least one hour. Patients able to breathe on their own for at least two hours without signs of distress were extubated.

Once-Daily Trial of Spontaneous Breathing

Patients assigned to a once-daily trial of spontaneous breathing were disconnected from the ventilator and allowed to breathe spontaneously through a T-tube circuit for up to two hours each day. If signs of intolerance developed, assist–control ventilation was reintroduced for 24 hours, at which time another trial was attempted. Patients who tolerated a two-hour trial without signs of distress were extubated.

For all four methods, weaning was considered to have failed if reintubation was necessary within 48 hours after extubation or if...
Weaning was considered successful if extubation was achieved within the 14-day period and reintubation was not required within 48 hours of extubation.

**Statistical Analysis**

The chi-square test was used to compare categorical data, and the Kruskal–Wallis test was used to compare continuous variables among the groups. The Kaplan–Meier method was used to determine the probability of the success of a particular method of weaning over time. The relative probability of success over time was examined by a Cox proportional-hazards model. Base-line covariates included in the model were the weaning technique, age, APACHE II score, ratio of PaO$_2$ to FiO$_2$, maximal inspiratory pressure, spontaneous respiratory frequency, spontaneous tidal volume per kilogram, duration of previous ventilator support, and the length of time to the failure of the initial trial of spontaneous breathing. Backward elimination was used to reduce the model to the subgroup of factors that made statistically significant contributions to variation in the time required for successful weaning. Data were censored on 2 patients who died during the study, 2 patients in whom weaning was interrupted because of intercurrent illness, 23 patients who required reintubation within 48 hours of extubation, and 11 patients who were still receiving ventilator support on day 14. We calculated that 31 patients were needed in each group to detect at a power of 80 percent a difference in weaning time between groups of two days, with a two-tailed alpha error of 0.05. Data are presented as means ± SD, medians, or proportions, as appropriate.

**RESULTS**

Of the 546 study patients, 416 (76.2 percent) successfully underwent a two-hour trial of spontaneous breathing, and 372 (69.4 percent) of them were immediately extubated. Of these 372 patients, 58 (15.6 percent) required reintubation within 48 hours. Extubation was postponed for 24 hours in 44 patients, primarily because of concern about their ability to maintain clear airways. These patients breathed through a T-tube circuit for up to 24 hours, but 16 (36.4 percent) required reinstitution of mechanical ventilation during this period. The remaining 28 (63.6 percent) were extubated within this 24-hour period, and only 2 required reintubation within the subsequent 48 hours.

One hundred thirty patients (23.8 percent) had signs of poor tolerance during the initial trial of spontaneous breathing, which lasted a mean (±SD) of 50.1±31.2 minutes (range, 5 to 110). These patients were randomly assigned to intermittent mandatory ventilation (29 patients), pressure-support ventilation (37), intermittent trials of spontaneous breathing (33) involving the use of a T-tube (27) or continuous positive airway pressure (6) interspersed with assist–control ventilation, or a once-daily trial of spontaneous breathing alternating with assist–control ventilation (31). The groups were similar with respect to the patients’ characteristics, the indications for mechanical ventilation, and respiratory function; the only significant difference was in the duration of ventilatory support before weaning was begun, which was shorter in the patients who received intermittent mandatory ventilation than in the other groups (Table 1).

Kaplan–Meier plots of the probability of successful weaning with the use of each technique are shown in Figure 1, and the associated median times to successful extubation are listed (with first and third quartiles) in Table 2. Cox proportional-hazards regression analysis revealed four factors that predicted the time to successful extubation are listed (with first and third quartiles) in Table 2. Cox proportional-hazards regression analysis revealed four factors that predicted the time.
The adjusted rate of successful weaning with pressure-support ventilation was not significantly different from that with intermittent mandatory ventilation (rate ratio, 1.38; 95 percent confidence interval, 0.68 to 2.79; P = 0.32).

Table 4 lists outcomes for the various techniques. More patients in the group that received intermittent mandatory ventilation required continued ventilatory support on the 14th day than in the groups that received once-daily trials (P = 0.07) or intermittent trials (P = 0.06) of spontaneous breathing. The rates of extubation and reintubation did not significantly differ between the four groups.

**DISCUSSION**

This study has two major findings. First, in a selected group of patients who were difficult to wean from mechanical ventilation, the rate of successful weaning depended on the technique employed: a once-daily trial of spontaneous breathing led to extubation about three times more quickly than intermittent mandatory ventilation and about twice as quickly as pressure-support ventilation. There was no significant difference in the rate of success between a once-daily trial and multiple daily trials of spontaneous breathing or between intermittent mandatory ventilation and pressure-support ventilation. Second, ventilator support was discontinued without any special weaning technique in two thirds of an unselected group of patients, and only a small proportion required reintubation within 48 hours.

**Intermittent Mandatory Ventilation**

Several advantages have been claimed for intermittent mandatory ventilation as a weaning technique: it is supposed to prevent a patient from “fighting” the ventilator, reduce respiratory-muscle fatigue, and expedite weaning. However, there are few data to support these claims. Intermittent mandatory ventilation is usually delivered in a synchronized manner with demand-valve circuitry, which increases the work of breathing. The intermittent nature of assistance also poses a problem. It was previously assumed that the degree of respiratory-muscle rest was proportional to the level of machine assistance. However, recent evidence indicates that respiratory-sensor output does not adjust to breath-to-breath changes in respiratory load, and intermittent mandatory ventilation may therefore contribute to the development of respiratory-muscle fatigue or prevent recovery from it.

Studies of the efficacy of intermittent mandatory ventilation in weaning have serious limitations. Schachter et al. compared it with conventional ventilation and noted no difference between the two techniques in the duration of ventilator support. Their study suffers from a retrospective design, nonuniform study groups, and inadequate description of the protocol. Hastings et al. compared trials of spontaneous breathing with intermittent mandatory ventilation at a fixed rate (4 breaths per minute) in patients in stable condition after cardiac surgery. The length of time to extubation was similar in

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**Table 2.** The Length of Time from the Initiation of Weaning to Successful Extubation in the Four Groups.

<table>
<thead>
<tr>
<th>Weaning Technique</th>
<th>Median</th>
<th>First Quartile</th>
<th>Third Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent mandatory ventilation</td>
<td>5</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Pressure-support ventilation</td>
<td>4</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Intermittent trials of spontaneous breathing</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Once-daily trial of spontaneous breathing</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 3.** Rate of Successful Weaning with the Various Techniques and According to Base-Line Characteristics.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Rate of Successful Weaning (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weaning technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once-daily trial of spontaneous breathing vs. intermittent mandatory ventilation</td>
<td>2.83 (1.36–5.89)</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Once-daily trial of spontaneous breathing vs. pressure-support ventilation</td>
<td>2.05 (1.04–4.04)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Once-daily trial of spontaneous breathing vs. intermittent trials of spontaneous breathing</td>
<td>1.24 (0.64–2.41)</td>
<td>0.54</td>
</tr>
<tr>
<td>Duration of ventilator support before weaning began (1-day increments)</td>
<td>0.94 (0.90–0.98)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Time to failure of first trial of spontaneous breathing (10-min increments)</td>
<td>1.15 (1.07–1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (10-yr increments)</td>
<td>0.83 (0.71–0.96)</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*Proportional-hazards regression analysis was used to estimate the 95 percent confidence interval of the relative rate of successful weaning.
the two groups — approximately 2.6 hours. Their study provides little insight, however, because 24 hours had already elapsed since the operation and the patients had good pulmonary function; thus, little difficulty in weaning was anticipated. In patients in stable condition who received ventilator support for 3.6 days, Tomlinson et al.3 found that the duration of weaning was similar with spontaneous-breathing trials and intermittent mandatory ventilation — approximately 3.6 hours. This study was weighted toward patients who received short-term ventilatory support, and two thirds of those weaned within 2 hours were patients who received ventilatory support for less than 72 hours postoperatively.

In contrast, we studied difficult-to-wean patients who had received mechanical ventilation for 6.5±4.5 days. Although most patients could theoretically have met the extubation criteria within 24 hours of study entry, 17 percent were receiving ventilatory support after 14 days. Weaning took longer than in either of the trials of spontaneous breathing.7,8 Despite the use of randomization, the patients in the group assigned to intermittent mandatory ventilation had received ventilation for a shorter time than the patients in the other groups. This actually resulted in a bias in their favor, since weaning was accomplished more rapidly in patients receiving short-term support.

Pressure-Support Ventilation

Pressure-support ventilation is commonly used to counteract the work of breathing imposed by endotracheal tubes and ventilator circuits. Theoretically, this should help with weaning, because a patient who is comfortable at the compensatory level of pressure support should be able to sustain ventilation after extubation. However, the level of pressure support necessary to eliminate the work imposed by endotracheal tubes and ventilator circuits varies considerably (from 3 to 14 cm of water)18,19; thus, any prediction of a patient’s ability to sustain ventilation after extubation is likely to be misleading.

Brochard et al.20 recently reported that the duration of weaning was significantly shorter with pressure support (5.7±3.7 days) than with intermittent mandatory ventilation (9.9±8.2 days) or trials of spontaneous breathing (8.5±8.3 days). In contrast, we found that weaning with pressure-support ventilation took longer than weaning with a once-daily trial of spontaneous breathing and was not superior to weaning with intermittent mandatory ventilation. We suspect that the apparent superiority of pressure support in the study by Brochard et al., was due to the constrained manner in which they used other techniques. Patients had to tolerate an intermittent mandatory ventilation rate of 0–4 breaths per minute for at least 24 hours before being extubated. This poses a considerable ventilatory challenge and is not the usual approach to this technique.3,4,14,21 In contrast, we extubated patients when they tolerated a ventilator rate of five breaths per minute for two hours. In the study by Brochard et al., physicians could request up to three trials of spontaneous breathing over a 24-hour period, each lasting 2 hours, before deciding to extubate a patient. Again, this is a considerable ventilatory challenge — especially in patients who have already had difficulty in weaning. We consider the findings of their study and ours to be complementary. Both show that the pace of weaning depends on the manner in which a technique is employed. When intermittent mandatory ventilation and spontaneous-breathing trials are used in a constrained manner, weaning is slower than with pressure-support ventilation.20 Weaning is expedited when a trial of spontaneous breathing is attempted once a day. In both studies, the results pertain to specific regimens for each weaning technique and cannot be extrapolated to other regimens using these techniques.

Trials of Spontaneous Breathing

Some physicians gradually increase the duration of spontaneous-breathing trials while reinstituting mechanical ventilation between trials. Other physicians go directly from offering a high level of ventilatory assistance to a trial of spontaneous breathing, and if the trial is successful, extubate the patient without any further weaning. In the present study, two thirds of the patients initially enrolled were extubated after their first trial of spontaneous breathing. A once-daily trial of spontaneous breathing also allowed speedier weaning than approaches offering partial ventilatory support. This approach simplifies management, since a patient’s ability to breathe spontaneously without ventilatory support needs to be assessed only once a day. In contrast, with intermittent mandatory ventilation and pressure-support ventilation, ventilator settings must be adjusted repeatedly and each adjustment is usually followed by an arterial-blood gas measurement.

An implied goal of the various weaning techniques is to recondition respiratory muscles that may have been weakened during the period of mechanical ventilation. Theoretically, a once-daily trial of spontaneous breathing and a prolonged period of rest may be the most effective method of eliciting adaptive changes22,23 This

| Table 4. Outcomes in Patients Who Were Difficult to Wean from Mechanical Ventilation. |
|--------------------------------------|-----------------------------------|
| SUCCESSFUL WEANING AND REINTUBATION | CONTINUED MECHANICAL VENTILATION AFTER 14 DAYS |
| (no. of patients (%)) | (no. of patients (%)) |
| Intermittent mandatory ventilation | 20 (69.0) 4 (13.8) 5 (17.2) |
| Pressure-support ventilation | 23 (62.2) 7 (18.9) 4 (10.8) |
| Intermittent trials of spontaneous breathing | 27 (81.8) 5 (15.2) 1 (3.0) |
| Once-daily trial of spontaneous breathing | 22 (71.0) 7 (22.6) 1 (3.2) |

*The percentages do not total 100 percent in the groups that received pressure-support ventilation and a once-daily trial of spontaneous breathing because one patient died in each group and weaning was interrupted because of an intercurrent illness in two patients in the pressure-support group.
approach meets the three principal requirements of a conditioning program: overload, specificity, and reversibility.22 During the trial, patients breathe against an elevated intrinsic load, thus satisfying the overload requirement. Specificity is also satisfied, in that the trial is an endurance stimulus and the desired objective is enhanced endurance. Finally, the use of a daily trial prevents regression of the adaptive changes. It must be emphasized that this reasoning is based on indirect evidence and that the effect of different weaning techniques on respiratory-muscle reconditioning has not been investigated.

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APPENDIX

The other members of the Spanish Lung Failure Collaborative Group are as follows: F. del Nogal and A. Algora (Hospital Severo Ochoa, Leganés); E. Palazón and M. Cerón (Hospital Universitario de Murcia, Murcia); J. Ibáñez and J.M. Raurich (Hospital Son Dureta, Palma de Mallorca); J. Gudín and J. Cebrián (Hospital La Fé, Valencia); G. González and J.A. Gómez Rubi (Hospital Virgen de la Arrixaca, Murcia); F. Iturbe (Hospital Arnau de Vilanova, Llíoda); A. Vázquez (Hospital del Mar, Barcelona); P. Saura (Hospital Parc Taulí, Sabadell); J. Gener (Hospital Germans Trias i Pujol, Badalona); D. Fontaneda (Complejo Hospitalario de León, León); V. Sagredo (Hospital General de Segovia, Segovia); and M.J. Prieto (Hospital del Río Ortega, Valladolid) — all in Spain.

REFERENCES