Decrease in Ventilation Time
With a Standardized Weaning Process

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Objective: To test the hypothesis that standardizing the process of weaning from mechanical ventilation would decrease ventilation times and length of stay in a surgical intensive care unit.

Design: Comparison of historic ventilation times with physician-directed weaning with those obtained with protocol-guided weaning by respiratory therapists.

Setting: Urban, teaching surgical intensive care unit with open admission policy and no dominant diagnosis related group.

Results: From January 1, 1995, through December 31, 1995, 378 patients who underwent physician-directed weaning from a ventilator had 64,488 hours of ventilation, compared with 57,796 ventilation hours in 515 patients with protocol-guided weaning (April 1, 1996, through May 31, 1997). The mean hours of ventilation decreased by 58 hours, a 46% decrease (P<.001). The length of hospital stay decreased by 1.77 days (29% change), while the Acute Physiology and Chronic Health Evaluation III score remained at 50 to 51. The number of reintubations did not change. The marginal cost savings was $603,580.

Conclusion: Protocol-guided weaning from mechanical ventilation leads to more rapid extubation than physician-directed weaning and has great potential for cost savings.

Arch Surg. 1998;133:483-489

WEANING from mechanical ventilation is defined as the gradual reduction of mechanical support and replacing this support with spontaneous ventilation.1 Although a wide variety of techniques are available for weaning patients from mechanical ventilation, controversy and conflicting results exist in the literature over the best weaning method.2-4 Traditionally, surgeons use weaning techniques based on their training, experience, and preference, or consultative advice. Spontaneous breathing with or without continuous positive airway pressure (CPAP) is used in a single trial or serial timed trials for weaning. Intermittent mandatory ventilation (IMV) with rate reduction or pressure support ventilation (PSV) with gradual pressure reduction allow patients receiving mechanical ventilation to perform more of the work of breathing until the ventilator is not required.5,6

Typically in the surgical intensive care unit (SICU), weaning from mechanical ventilation is initiated by the surgeon and begins when the patient’s medical or surgical condition has improved or stabilized. Surgical patients with easily reversible disease processes require mechanical ventilation for a short time in the perioperative period. These patients can readily sustain spontaneous ventilation and are easily weaned and extubated. Sepsis, complex surgical repairs, acute lung injury, closed head injury, and spinal cord trauma complicate SICU management and increase the duration of mechanical ventilation and length of stay in the SICU. Surgical patients with a prolonged requirement for mechanical ventilation are more difficult to wean and may have physiological limitations that prolong the weaning process.6

The approach to weaning, if poorly organized, adds additional hours or days to the duration of ventilation. Ventilation management teams and protocols are reported to improve the coordination and communication for the weaning process and decrease the ventilation time.7,8 Protocol-directed weaning is successfully used in the cardiac surgery patient population, where large numbers of patients un-
PATIENTS AND METHODS

This study was performed in a large urban teaching hospital with a level I trauma center. The 16-bed SICU has an open admission policy, multiple admitting surgical services, and no dominant diagnosis related group. There is an active critical team with residents, fellows, and surgical critical care staff. The critical care team provides critical care services by consultation.

Traditionally, weaning from mechanical ventilation is surgeon directed. The RT examines the patient every 12 hours and checks the ventilator settings more frequently. Ventilator settings and pressures, consistency of secretions and frequency of suctioning, breath sounds, patient anxiety and pain, heart rate, blood pressure, and oxygen saturation are monitored. Negative inspiratory force by manometer, tidal volume, vital capacity, and minute ventilation are the respiratory measures evaluated in response to the surgeon’s request. During morning rounds, patient readiness to wean is evaluated on the basis of a fraction of inspired oxygen less than 50%, positive end-expiratory pressure of 5 cm H2O or less, acceptable arterial blood gas values, and stable or improved medical condition. Respiratory measures, if available, are reviewed or ordered. Surgeon preference determines the mode of weaning (IMV, PSV, or CPAP). Orders are given to the RT for the ventilatory changes for weaning. Weaning occurs during hours or days, depending on the frequency of surgeon orders for ventilation changes. The duration of mechanical ventilation was 6.8 days in 1994 and increased to 8.3 days in the last 3 months of 1995 with surgeon-directed weaning.

A protocol was developed that organized the RT’s usual assessment and the surgeon’s usual weaning practices. The protocol standardized the RT examination of patients receiving mechanical ventilation and was performed every 2 hours when the fraction of inspired oxygen was less than 50%, positive end-expiratory pressure was 5 cm H2O or less, and there was no arrhythmia or vasopressor use. The standardized evaluation included negative inspiratory force of −22 cm H2O or more, tidal volume of 5 mL/kg or more, vital capacity at 2 times the tidal volume, minute ventilation less than 10 L/min, and acceptable arterial blood gas values and patient vital signs. The patient was awake with a cough and gag, was able to lift the arm or head from the bed, and had minimal secretions. Heart rate less than 130/ min, PaO2 of 65 mm Hg or more, pH of 7.4, and Paco2 of 44 mm Hg or less were considered acceptable. If the patient receiving mechanical ventilation passed the assessment, he or she was given CPAP for 1 hour and reexamined by the therapist. If the respiratory rate was less than 30/min, the work of breathing was minimal, and respiratory measures and arterial blood gas values remained acceptable, the surgeon was notified that the patient was ready for extubation. Extubation was performed by surgeon order. If the patient failed 3 CPAP trials with 2 hours between trials, mechanical ventilation was resumed and the patient was reexamined in 8 hours. A determination with the surgeon decided whether an alternative weaning method (IMV or PSV) was used.

A trial period of 1 month was used to test and modify the protocol. During this time, the RT assessment skills and our ability to follow the protocol were evaluated. The protocol was reviewed by the surgeons and critical care team. Permission to use the RT protocol–guided weaning in patients receiving mechanical ventilation was given by the responsible surgeon.

Historic mechanical ventilation times with surgeon-directed weaning from January 1 through December 31, 1995, were compared with ventilation times during RT protocol–guided weaning from April 1, 1996, to May 31, 1997. Ventilation time was measured in hours from intubation and ventilation to extubation. Length of stay in the SICU was compared. Acute Physiology and Chronic Health Evaluation (APACHE) III was performed on SICU day 1. Accidental extubation and reintubation, which was defined as intubation within 24 hours of extubation, were measured. Crude mortality rates were calculated. The t test (StatView, Abacus Concepts Inc, Berkeley, Calif) was used to determine statistical significance, and results are reported as mean±SD. The marginal cost of a ventilator day is the cost of directly providing health care services to the patient, eg, nursing time and direct patient supplies would be included in marginal costs. Marginal costs do not include “fixed” or “overhead” costs, such as depreciation, interest, or management salaries. Therefore, marginal costs accurately show how much expense or savings will be incurred with moderate increases or decreases in the number of patient ventilator days. The marginal cost of reduction of 24 hours of ventilation was multiplied by the mean reduction in hours to determine savings.
Ventilation times of subsets of patients were compared to determine the effect of the organized weaning approach. Ventilation times of 168 hours (1 week) or less, more than 168 hours, and 24 hours or less were compared. Reduction in ventilation hours with RT protocol-guided weaning occurred in patients with ventilation times of 168 hours or less and patients with ventilation time greater than 168 hours but not in patients who received mechanical ventilation for 24 hours or less (Figure 2).

For patients who received mechanical ventilation for 168 hours or less, the ventilation times were longer with surgeon-directed weaning (Figure 2, A). The 279 patients with surgeon-directed weaning received support for 14 296 hours. The mean duration of mechanical ventilation was 51.2 ± 41.2 hours compared with 43.8 ± 41.0 hours in the 369 patients with protocol-guided weans (P < .001). Total ventilation hours with the protocol-guided wean were 15 951. The median ventilation time decreased from 38 hours for the physician-directed wean to 25 hours for the protocol-guided wean (Figure 2, A). The percentage of patients who received mechanical ventilation for 168 hours or less was similar in both surgeon-directed and protocol-guided weaning.

A reduction in duration of ventilation in patients who received mechanical ventilation for more than 168 hours occurred with the protocol-guided wean (Figure 2, B). The range of ventilator hours in the 99 patients with physician-directed weaning was 173.6 to 2152.2 hours, and mean ventilation time was 507 ± 413 hours (Figure 2, B). During protocol-guided weaning, 146 patients had a mean ventilation time of 346.0 ± 199.9 hours (range, 169.9-1438.8 hours) (P < .001). The median hours of ventilation decreased from 333 to 305 hours. The 99 patients with surgeon-directed weaning had 50 190 hours of ventilation, while the 146 patients with RT protocol-guided weaning had 41 845 hours of ventilatory support.

There were 269 patients in the subset of patients who received 24 hours or less of mechanical ventilation (Figure 2, C). Median and mean ventilation time did not change with the protocol-guided wean. Of the 378 patients who underwent surgeon-directed weaning, 99 (26.2%) received ventilatory support for 1356.3 hours (mean, 13.7 ± 6.0 hours). Although a larger percentage of RT protocol-guided patients (34% [175/515]) received ventilation for 2277.8 hours (mean, 13 ± 6 hours), there was no demonstrated decrease in ventilation times.

Table 1. Patient Demographics

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<td>Operating room</td>
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<tr>
<td>Emergency department</td>
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<td>15</td>
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<tr>
<td>Floor</td>
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<td>13</td>
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<tr>
<td>Other hospital</td>
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<td>2</td>
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</tbody>
</table>

* APACHE indicates Acute Physiology and Chronic Health Evaluation.

Table 2. Hours of Mechanical Ventilation

<table>
<thead>
<tr>
<th>No. of patients who received mechanical ventilation</th>
<th>Surgeon-Directed Wean</th>
<th>Protocol-Guided Wean</th>
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<tbody>
<tr>
<td>Total ventilation time, h</td>
<td>64 488</td>
<td>57 796</td>
</tr>
<tr>
<td>Mean ± SD ventilation time, h</td>
<td>170.6±294.0</td>
<td>112.6±164.0</td>
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Accidental extubation, reintubation after weaning, and mortality rate were examined. There was a trend toward a decrease in accidental extubation. During 1995, with surgeon-directed weaning, there were 14 accidental extubations with 6 reintubations performed 5 minutes to 8 hours after the accidental extubation. During protocol-guided weaning, there were 10 accidental extubations, and 2 patients required reintubation 5 minutes to 1 hour after this occurrence. These numbers were too small to obtain significance. The rate of reintubation after weaning from mechanical ventilation remained at 1.7 per month from 1995 through 1997. There were no patient deaths associated with the protocol. There were 55 deaths in 1995 (5.6% mortality rate) and 63 deaths during the protocol period (5.6% mortality rate). Crude mortality rates were similar.

The decrease in ventilation times with the RT protocol–guided weaning was associated with a decrease in the SICU length of stay. The length of stay per month and the number of patients admitted to the SICU per month are shown in Figure 3. Overall, the length of stay decreased by 29%, or 1.77 days, while patient admissions remained stable. In 1997, a trend of decreasing admissions occurred. The patient acuity, as shown by APACHE III scores, had not changed (Table 1).

On the basis of our hospital cost, a decrease of 24 hours in ventilation time provided a marginal cost savings of $520 in nursing costs and $66 in RT costs, for a total of $586. There was a 58-hour, or 2.42-day, reduction in mean ventilation time with the use of the protocol. The marginal cost savings for the protocol was calculated as 2 days×$586×515 patients and was $603 580. Two days was used in the calculation because marginal cost was based on 24 hours and not fractions of a day. In 1996, using the protocol, we saved $406 684. The projected savings for 1997 was $440 525 as ventilation time continued to decrease.

The results of this study show a decrease in the duration of mechanical ventilation achieved in a diverse surgical patient population when an organized weaning process is implemented. Ventilatory management teams and protocol-guided weaning both decrease total ventilation time.7-9 Respiratory therapist–directed weaning in patients with similar anesthetic techniques and operations decreases the hours of mechanical ventilation.7 Cohen and associates8 reduced mechanical ventilation days, length of stay in the intensive care unit, and arterial blood gas testing in a diverse patient population by means of a ventilatory management team with an organized approach.

Figure 2. A, Ventilation time in the subset of patients who received mechanical ventilation for 168 hours or less (P<.001). B, Ventilation time in the subset of patients who received mechanical ventilation for more than 168 hours (P<.001). C, Ventilation time in the subset of patients who received mechanical ventilation for 24 hours or less.

Figure 3. A, Average length of stay during the study; numbers in parentheses are average length of stay by year. B, Number of patient admissions during the study; numbers in parentheses are numbers of patients by year.
Weaning decreases ventilation times, while Esteban et al identified similar management problems. Our physician-directed weaning practice resulted in a mean duration of ventilation longer than a week (170.6 hours). This ventilation time was similar to that in patients in the Spanish Lung Failure Collaborative Trial of 6 to 11.3 days but 70 hours longer than the time reported by Kollef et al with physician-directed weaning of 102.0 ± 169.1 hours. Our length of mechanical ventilation contributed to the 6.07-day length of stay in the SICU during 1995.

Weaning guided by RT protocol decreased both total hours of ventilation and mean ventilation hours over time (Figure 1). The protocol provided a consistent RT evaluation for readiness to wean and a standardized process for weaning. We examined total time and not the benefits of the individual steps of the protocol. Ely and colleagues reported on the benefits of routine standardized screening of patients receiving mechanical ventilation. In a randomized controlled trial, 300 adult medical patients were screened for weaning readiness. The intervention group was given a trial of spontaneous breathing following by physician notification. Ely and coworkers standardized screening process and trial of spontaneous breathing decreased the duration of mechanical ventilation by 1.5 days compared with the control group. Standardizing our process decreased our duration of ventilation by 2.4 days.

Our study protocol was heavily weighted toward extubation after a trial of spontaneous breathing. If this failed, other methods were used. Conflicting results are reported from randomized trials comparing weaning modes. Tomlinson et al reported no difference in weaning times when IMV was compared with T-piece weaning. Two European studies compared patients in whom a spontaneous breathing trial failed and reported different outcomes. Brochard and associates concluded that PSV weaning decreases ventilation times, while Esteban et al reported a spontaneous breathing trial most effective at decreasing ventilation time. Kollef et al performed a randomized controlled trial with unit-specific protocols in 2 medical and 2 surgical units. No difference between modes of weaning was found, but patients who underwent protocol-guided weaning had shorter time of mechanical ventilation than those in the physician-directed weaning group. These investigators speculated that the method of weaning is more important than the specific weaning mode.

By the design of our protocol, we anticipated that ventilation time would decrease in patients who received mechanical ventilation for a week or less and 24 hours or less. Although the mean and median ventilation times decreased in the patients who received ventilation for 168 hours or less, the amount of change in mean ventilation was small (7.4 hours). This change represented mean ventilation times of more than 2 days to ventilation times of less than 2 days. The decrease in median time represents a shift of ventilation time toward 24 hours or less, which was confirmed by a higher percentage of patients in the subset of ventilation times of 24 hours or less. The anticipated decrease in ventilation times of 24 hours or less did not occur with the protocol-guided wean. The reluctance to extubate patients during the midnight shift contributed and is reflected in the ventilation times of 24 hours or less. For many clinicians, patients who received ventilation for more than 168 hours are considered more difficult to wean. We did not anticipate these ventilation times to change, although the more organized approach to weaning had some effect similar to the experience of Cohen et al. Factors other than the protocol played a role in these patients. Acceptance of the futility of medical care, withdrawal of support, and transfer to long-term care facilities are practice changes not measured in this study that would influence results.

A decrease in SICU length of stay accompanied the decrease in duration of mechanical ventilation in this study. Kollef et al reported a decrease in hospital stay (1.5 days) but provided no information on intensive care unit stay. Cohen and associates found a decreased length of stay associated with decreasing days of ventilation. Clearly, factors other than ventilation time influence intensive care unit stay. The amount of nursing interventions for medical or surgical conditions, specialized monitoring, vasopressor use, availability of other monitoring areas, and availability of beds in a general practice unit also influence length of stay.

There are limitations associated with this study. It was not a randomized controlled study. Since our goal was to decrease the time of mechanical ventilation, not to determine the best mode, we used historical data and introduced a practice change with an organized approach to weaning. Changes other than the RT protocol-guided wean may have influenced results. Pathways, vasopressor use, sedation protocol, optimization philosophy, and transfer policies could have influenced our results. We used weaning methods familiar to and accepted by our surgeons. Because this protocol standardized our surgeons’ approach to weaning, it may not be generalizable to other intensive care unit environments.

This study shows a decrease in ventilation time and an associated decrease in length of stay in the SICU after implementation of an organized approach to weaning from mechanical ventilation. On the basis of the results of this study, we recommend protocol-guided weaning. Protocol-guided weaning leads to more rapid extubation than physician-directed weaning from mechanical ventilation and has great potential for cost savings.
John A. Weigelt, MD, St. Paul, Minn: You may want to ignore this paper as representing the dark side of the transformation of medicine. Call it a paradigm shift, call it a critical pathway, call it clinical guidelines, reengineering, or operation improvement. I would hope that you would not dismiss this paper in those terms. This paper is about reducing variation. It clearly shows what we may not like to admit, but individual physician or surgeon variation results in inefficiencies. That message needs to be recognized as the major solid conclusion of this paper. We should all think about using this principle in our practices.

I do have a few questions for the authors related to their methods and their conclusions. Would your data be more valuable to us if you reported true weaning duration and not total ventilatory time? We felt that total ventilatory time vs weaning duration was the most meaningful time for ventilation support and the more individuals involved, the more disparate the results.

Frederick A. Moore, MD, Houston, Tex: Having visited Henry Ford, I recognize its commitment to surgical critical care.

What you have shown is that a multidisciplinary critical care team does a better job than the individual attending surgeon in taking care of patients. The ICU is an expensive cost center that must be controlled. You have developed a system that permits the RT to do what the surgeon cannot do, that is, be at the bedside to play with the ventilator and observe the patient's response and then work with the critical care attending to develop a rational way to get the patient off the ventilator. How did you get the individual attending surgeons to participate in this program?

Bruce M. Wolfe, MD, Sacramento, Calif: In the last 3 years, the development of the University of California–Davis health care system has established a large primary care network, which has resulted in a substantial change in the patient population that we see, whereby there are many more routine general surgical patients passing through our intensive care unit for short intervals. So, any historical comparison of ICU patients would be hazardous based on the change in the patient population that we are treating.

C. Edward Hartford, MD, Denver, Colo: We have started to enter the area of RT-directed protocol in weaning patients from ventilatory support. We have had a bit of difficulty getting started with it, however. I wonder if the results that have been described by the authors can be attributed to the Hawthorne effect. We all know the effects of historical controls on outcome. For instance, what changes in general management occurred during these 2 periods? In our program, I recall dramatic effect when the cardiac anesthesiologist used a benzodiazepine-based anesthetic during cardiac procedures, and of course large doses result in prolonged half-life of that drug. When we changed that, there was a dramatic decrease in the ventilation time postoperatively. Why were the cardiac patients excluded? Is there a learning curve in this process? There was a rather dramatic progressive change that occurred during this study. I also want to know how many individual surgeons were involved in the historical control data because there are so many confounding variables in determining the need for ventilatory support and the more individuals involved, the more disparate the results.

William R. Schiller, MD, Phoenix, Ariz: I have 3 questions I would like to ask. One, what was the starting point of your weaning program? In other words, what point did the patient have to get to before they were entered into the weaning protocol? Second, you mentioned in your paper that there was a lot of variation in the way physicians and surgeons did this, but you did not give us any information about what the variations were and what the extent of it was.

Lastly, I would like for you to give some thought to the notion that if the respiratory technicians do this, they tend to do it 24 hours a day, whereas physicians tend to be more intense at some parts of the day and less intense at other parts of the day. Your improvement looked like it was about a 30% improvement. I am wondering if that has to do with an 8-hour period of time when maybe surgeons are trying to sleep. So, the question I am bringing up is, is this really a difference in intensity of effort, or is it a difference in the quality of the way this is done?

Robert F. Wilson, MD, Detroit, Mich: I would like to ask about the role of tracheostomy in the management of these patients. Since there was such a wide variety of physicians involved, my guess is that some physicians beat the protocol, and I would like to have more data on that particular point.

Frank R. Lewis, MD, Detroit: Dr Weigelt, we totally agree with you that this is basically about decreasing variation, and we think that the significance is real. You asked first about weaning duration vs total ventilatory time. We felt that total ventilatory time was the most meaningful since that is really where the resource consumption occurs, and there are a lot of different ways of defining the weaning time, particularly because it may start and stop and one can change the starting and ending points. We thought that was a softer number to document, whereas it is pretty definite whether the tube is in or out and one can use that as the most meaningful time for ventilation and the one that is easiest to measure.

You asked about a cost analysis. We did not tie this to any layoff of nurses. On the other hand, we think that the marginal cost analysis is real and, if anything, understates the cost savings. The cost analysis was performed purely by using the actual salaries of nursing time that was avoided and respiratory technician time. We did not include any overhead numbers, nor any supply numbers, nor any maintenance numbers relative to ventilatory equipment in the cost savings. All of those calculations were done to the nearest dollar.
The role of the admitting surgeons? I should say that in our critical care units we looked at 16 beds. We have another 16 beds that are used primarily by cardiothoracic, vascular, and general surgery, and we have a variety of management methods depending on the surgeon preference. For many of the subspecialty surgeons, they prefer to put the patient in the unit and have them managed totally by the intensive care team. For the trauma surgeons and the general surgeons, management is by a joint procedure in which the primary service and the ICU service both round on the patients, collaborate actively in determining management, and finally in the vascular service and the cardiothoracic service, they prefer to manage the ventilator entirely on their own and involve the intensive care team only by consultation. So, those patients were not included in this. The admitting surgeons are very actively involved, and this is done with their full participation and consent.

Dr. Moore, you asked how one gets the individual surgeons to participate. To a great extent, the group is the same. The trauma service consisting of 6 surgeons primarily is also the critical care service for the most part. When those surgeons are taking call in the critical care unit, they round exclusively there for 1 or 2 weeks at a time. Those same surgeons take call on the trauma service. So, it is not really a different group of surgeons; it is only a primary responsibility for the week they are on call. There is great collaborative interaction among them and, in essence, the people making the calls in the ICU are the same ones who are participating in another week when they are not primarily on ICU call but are taking trauma call. So, we are not really talking about different groups of people; all of these people are critical care certified in doing the trauma care and there is a tendency to have a great deal of mutual respect for decision making.

In addition, participation of enrollment of patients in the study was voluntary by the participating surgeons. The number who chose not to participate was very tiny because by and large, it was the same people involved.

Dr. Wolfe, we thank you for your comments.

Dr. Hartford, you asked about the Hawthorne effect. That may have some role here, but, in fact, this has been a very sustained effect and the data you saw for the first months of 1997 indicate that improvement is continuing. I do not know if it is due to the Hawthorne effect or something else, but whatever it is, we will take it because it seems to improve resource allocation and has not had adverse effects that we can see. Why were cardiac patients excluded? The answer is that they are in a separate ICU and the cardiac surgeons manage their own ventilatory status; they were on their own fast-track weaning protocol, which was slightly different from this, but has resulted also in significant shortening using protocol weaning. How many individual surgeons were involved? Again, the 6 trauma surgeons are the principal ICU rounders. There are another 12 or 13 general surgeons who participate, but do not make rounds in the ICU, and then there are a number of subspecialty surgeons (orthopedics, urology, and so forth) whose patients come into the unit sporadically. All of them participated.

Dr. Schiller, the starting point of the weaning protocol was defined. It is the general stability of the patient and fraction of inspired oxygen of less than 50%, positive end-expiratory pressure of less than 5 cm H2O, minute ventilation of less than 10 liters per minute, and overall stability or improvement of the patient. That is probably defined better in the manuscript than Mattie had time to review in the presentation. What variations were present in practice before? We did not really document those because the individual people making rounds in the ICU or the individual primary surgeons tended to have their own different patterns and there is no uniformity in defining the end points at which weaning would begin. I think that is common in many places. All we did was institute a common end point of saying when these are present, we should undertake the effort at weaning. Time of the day for weaning as a result of the effect? I do not think that had a big effect. In general, we never wean and extubate the patient on the 11 to 7 shift. That was true before and after; however, most of the other shifts are pretty fair game and it is true that the therapist is there 24 hours a day, but I do not think that is the primary cause of the effect.

Dr. Wilson, regarding the role of tracheostomy, I do not think it had a role here. In general, we perform tracheostomies fairly late, typically after about 2 weeks, if we see the patient is not likely to be extubatable in the immediate future. Most of these patients were extubated by that time, and you saw the mean period of ventilation was originally 6 to 7 days and decreased to about 4 days.

Correction

In the article titled “Transient Hypoadrenalism During Surgical Critical Illness,” published in the February issue of the Archives (1998;133:199-204), the pharmacologic doses of hydrocortisone and methylprednisolone in line 4 on page 200 were incorrectly stated. The correct values should read ≥300 mg/d of hydrocortisone and ≥50 mg/d of methylprednisolone.