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Effect of Mechanical Ventilator Weaning Protocols on Respiratory Outcomes in Infants and Children

A Randomized Controlled Trial

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ACUTE RESPIRATORY, CARDIAC, and neurologic failure in infants and children lead to intubation, mechanical ventilator support, and pharmacological sedation. Despite the frequent use of mechanical ventilation, methods for weaning children from respiratory support have never been rigorously studied.¹ Weaning methods are extrapolated from studies in adult patients and prematurely born neonates. Extrapolation to infants and children may not be appropriate due to the unique as-

For editorial comment see p 2601.

Context Ventilator management protocols shorten the time required to wean adult patients from mechanical ventilation. The efficacy of such weaning protocols among children has not been studied.

Objective To evaluate whether weaning protocols are superior to standard care (no defined protocol) for infants and children with acute illnesses requiring mechanical ventilator support and whether a volume support weaning protocol using continuous automated adjustment of pressure support by the ventilator (ie, VSV) is superior to manual adjustment of pressure support by clinicians (ie, PSV).

Design and Setting Randomized controlled trial conducted in the pediatric intensive care units of 10 children's hospitals across North America from November 1999 through April 2001.

Patients One hundred eighty-two spontaneously breathing children (<18 years old) who had been receiving ventilator support for more than 24 hours and who failed a test for extubation readiness on minimal pressure support.

Interventions Patients were randomized to a PSV protocol (n=62), VSV protocol (n=60), or no protocol (n=60).

Main Outcome Measures Duration of weaning time (from randomization to successful extubation); extubation failure (any invasive or noninvasive ventilator support within 48 hours of extubation).

Results Extubation failure rates were not significantly different for PSV (15%), VSV (24%), and no protocol (17%) ($P=.44$). Among weaning successes, median duration of weaning was not significantly different for PSV (1.6 days), VSV (1.8 days), and no protocol (2.0 days) ($P=.75$). Male children more frequently failed extubation (odds ratio, 7.86; 95% confidence interval, 2.36-26.2; $P<.001$). Increased sedative use in the first 24 hours of weaning predicted extubation failure ($P=.04$) and, among extubation successes, duration of weaning ($P<.001$).

Conclusions In contrast with adult patients, the majority of children are weaned from mechanical ventilator support in 2 days or less. Weaning protocols did not significantly shorten this brief duration of weaning.

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pects of their pulmonary physiology, respiratory mechanics,² and epidemiology of acute lung injury. Discontinuing mechanical ventilation as soon as it is no longer needed is important to prevent respiratory complications³ and physiological dependence on the sedative and narcotic drugs required to keep ventilated children comfortable and safe.⁴

Studies in adult patients have shown that, compared with care guided by the individual practices of clinicians, use of protocols to guide the weaning of patients from mechanical ventilator support leads to improved patient outcomes.^{5,6} Pressure support ventilation (PSV) and volume support ventilation (VSV) are modes commonly used to wean children from mechanical ventilator support. The 2 modes are similar in that they are both patient-triggered spontaneous breathing modes that use pressure support. Using PSV, clinicians intermittently adjust the level of pressure support to achieve acceptable respiratory parameters⁷ with gradual weaning to a minimal amount of PSV.⁸ Volume-support ventilation is an automated mode where the amount of pressure support is continually adjusted by the ventilator to achieve a minimum minute ventilation goal.⁹ Because accepted protocols for applying these modes in children do not currently exist, there is great variability in clinical application.

The primary goals of this study were to evaluate whether weaning protocols are superior to standard care (no defined protocol) for infants and children with acute illnesses requiring mechanical ventilator support and whether a weaning protocol using continuous automated adjustment of pressure support by the ventilator (ie, VSV) is superior to manual adjustment of pressure support by clinicians (ie, PSV). The secondary goals of the study were to evaluate the performance of a set of extubation criteria on extubation success and failure and to study the relationship between sedative use during weaning and respiratory outcomes.

METHODS

Study Patients

The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network is a consortium of investigators at pediatric intensive care units (ICUs) across North America. Eligible children admitted between November 1999 and April 2001 in ICUs at 10 children's hospitals were enrolled. Children were eligible for the study if they required ventilator support for more than 24 hours. The study was approved by the institutional review board at each hospital. Consent was obtained from at least one parent or legal guardian before enrollment.

Exclusion criteria were: age 18 years or older, corrected gestational age less than 38 weeks, diaphragmatic hernia or paralysis, ventilator use prior to admission when the patient was at baseline health status (including use of noninvasive ventilator support), cyanotic congenital heart disease with unrepaired or palliated right-to-left intracardiac shunt, history of single ventricle defect at any stage of repair, significantly diminished lung capacity (estimated resting tidal volume <6 mL/kg), decreased lung vascularity, anatomical obstruction of lower airways, primary pulmonary hypertension or anticipated need for nitric oxide after extubation, previous bone marrow or lung transplant, spinal cord injury above the lumbar region, tracheal or upper airway obstructive conditions, status asthmaticus in children 2 years or older, and progressive neuromuscular weakness. Children currently enrolled in another trial in which the intervention potentially influenced a patient's respiratory outcome were excluded. Children were also excluded if a decision to withdraw or limit life support was in place.

Data were collected prospectively. Pediatric Risk of Mortality III (PRISM III) scoring was performed in all patients during the first 24 hours of admission to assess illness severity.¹⁰

Extubation Readiness Test—Final Eligibility Criterion

Mechanically ventilated patients in the pediatric ICUs were prospectively

evaluated and screened daily to test for extubation readiness. Eligibility criteria for testing were: spontaneous respiratory effort; gag or cough with suctioning; pH of 7.32 to 7.47 on most recent blood gas analysis; positive end-expiratory pressure (PEEP) of 7 cm H₂O or lower and fraction of inspired oxygen (F_IO₂) of 0.6 or less; level of consciousness acceptable for extubation; attending physician's approval; no clinical need for increased ventilator support in the last 24 hours; no planned operative procedures requiring heavy sedation in the next 12 hours; and no excessive leak around the endotracheal tube (ETT) requiring ventilator manipulations. Enteral feeding was stopped for testing.

The extubation readiness test (ERT) consisted of changing the F_IO₂ to 0.5 (left at current setting if already <0.5 with saturation by pulse oximetry [SpO₂] reading ≥95%) and decreasing the PEEP to 5 cm H₂O (left at current setting if already <5 cm H₂O with SpO₂ reading ≥95%). Patients unable to maintain SpO₂ of 95% or higher failed the test; those who maintained SpO₂ of 95% or higher had their ventilator mode changed to PSV and were placed on minimal PSV. Minimal pressure support was adjusted for the ETT size because of increasing resistance with lower ETT size¹¹ (ETT size 3.0-3.5=pressure support of 10 cm H₂O; ETT size 4.0-4.5=pressure support of 8 cm H₂O; ETT size ≥ 5.0=pressure support of 6 cm H₂O). Exhaled tidal volumes were measured at the ETT using a CO₂SMO Plus monitor (Novametric Medical Systems Inc, Wallingford, Conn) with neonatal, pediatric, or adult sensors. Patients were monitored during the test for 2 hours.

Patients were classified as failing the test if at any time in the 2-hour period their SpO₂ was less than 95%, their exhaled tidal volume was less than 5 mL/kg ideal body weight, or their respiratory rate was outside of the acceptable range for their age (for age <6 months, 20-60/min; 6 months-2 years, 15-45/min; 2-5 years, 15-40/min; >5 years, 10-35/min). Ideal body weight

was estimated as the 50th percentile for age and sex from National Center for Health Statistics growth charts¹² and was the weight used for adjustment of all respiratory parameters during the test and within the protocol groups of the study. As soon as any criteria for failure were met, the patient was removed from the test, placed back on previous ventilator settings, and randomized to PSV, VSV, or no protocol.

Randomization

Randomization was performed using a permuted blocks design, stratified by ICU, with random block sizes of 3, 6, or 9. Packets were placed in opaque envelopes with a second paper barrier and signed over the unbroken seal to ensure that the assignment was concealed.

Ventilator Management

Ventilator management prior to weaning was at the discretion of the physician. During weaning, all patients were placed on a Servo 300 ventilator (Siemens-Elma, Solna, Sweden). Children were evaluated for 48 hours after they were extubated, and the time of extubation was recorded as the primary end point.

In the no protocol group, weaning was at the discretion of the physician and no management recommendations were made. Ventilator management followed the protocols determined for the PSV and VSV groups. Both protocols used the CO₂SMO Plus monitor attached to a neonatal, pediatric, or adult sensor at the ETT for all measurements of exhaled tidal volume. The patient's physician was responsible for implementing the ventilator weaning protocols, obtaining blood gas tests when clinically indicated, and deciding when temporary cessation of the protocol was required for procedures or due to clinical deterioration. Physicians were encouraged to evaluate sedation and analgesia if the patient's respiratory rate was outside of the goal for age.

For both protocols, FIO₂ and PEEP were adjusted to maintain SpO₂ at 95% or higher using the following recom-

mended methods: decrease PEEP by 1 cm H₂O every 4 hours if the SpO₂ is 95% or higher with FIO₂ less than or equal to 0.6, weaning FIO₂ to 0.5 or less once PEEP is 5 cm H₂O or lower; and, if SpO₂ is lower than 95% at any time, increasing FIO₂ by 10% and increasing PEEP if necessary. The PSV and VSV protocols were developed at 1 site, refined during a 2-day consensus meeting of all investigators, tested on 10 patients, then pretested at each site by randomizing 2 patients to each protocol. Data on protocol compliance were monitored using a specially designed time-sensitive form and protocol deviation forms. Patients in the protocol groups had to pass the ERT prior to extubation.

PSV Protocol. In the PSV protocol, the amount of pressure support was adjusted to achieve an exhaled tidal volume goal of 5 to 7 mL/kg. Instructions for weaning were: (1) Every 4 hours, decrease the pressure support by 2-cm H₂O increments if the patient maintains tidal volume within the goal range and decrease pressure support earlier if tidal volumes are consistently over 7 mL/kg. If tidal volumes are consistently less than 5 mL/kg, increase pressure support by 2-cm H₂O increments to achieve the tidal volume goal. (2) Perform an ERT once pressure support is decreased to 16 cm H₂O and patient tolerates this level for 2 hours with an SpO₂ of 95% or higher (with PEEP ≤5 cm H₂O and FIO₂ ≤0.5) and a respiratory rate within goal range for age. (3) If the child fails the ERT, return to the previous pressure support setting, hold for 4 hours, then decrease the pressure support stepwise by 2-cm H₂O increments every 4 hours until the level used in the ERT is reached.

VSV Protocol. In the VSV protocol, the ventilator in volume support mode automatically adjusted the level of pressure support to achieve an exhaled tidal volume of 5 to 7 mL/kg. Instructions for weaning were: (1) Adjust initial set inspired tidal volume to achieve exhaled tidal volume of 6 mL/kg (measured at the ETT) and set backup respiratory rate according to age (for age <6 months, 16/min; 6 months-2 years, 14/min; 2-5

years, 12/min; >5 years, 10/min). (2) Monitor tidal volumes at the ETT for the first 30 minutes and every 12 hours to ensure that they remain between 5 to 7 mL/kg. (3) Perform an ERT (maximum of 2 tests in 24 hours) when peak inspiratory pressure is 20 cm H₂O or lower, SpO₂ is 95% or higher (on PEEP ≤5 cm H₂O and FIO₂ ≤0.5), and respiratory rate is within the goal for age.

Sedation Score

Many children received multiple sedative drugs and some received intermittent paralytic agents for procedures. All sedative use was recorded prospectively. The amount of sedation given in the first 24 hours of weaning was calculated using a score for which 1 point was given for the amount of each drug that would be equivalent to 1 hour of sedation in a nontolerant subject. The relative potency scale for opiates and benzodiazepines used by Wilson et al¹³ was modified for children with the help of the pediatric pharmacology staff at Children's Hospital, Boston, Mass. All opiates were converted to morphine equivalents using the following conversions to equal 1 mg of morphine sulfate: 15 µg fentanyl citrate, 0.15 mg hydromorphone hydrochloride, 0.3 mg methadone hydrochloride, 20 mg codeine. All benzodiazepines were converted to midazolam equivalents using the following conversions to equal 1 mg of midazolam: 2 mg diazepam, 0.33 mg lorazepam. For the sedation scoring, 1 point was given for each of the following: morphine or midazolam equivalents of 0.1 mg/kg, pentobarbital 2 mg/kg, chloral hydrate 50 mg/kg, any propofol use, any phenobarbital use. Use of any antihistamines received a point score of 0.5. For example, a child weighing 5 kg who, during the first 24 hours of weaning, received a total of 4 mg of morphine sulfate, 3 mg of lorazepam (converted to 9 mg midazolam), and a 30-minute infusion of propofol for a procedure would have a sedative use score of 27 (ie, 8+18+1).

Statistical Methods

Our first hypothesis was that the time to successful extubation for children re-

ceiving protocol-directed weaning (PSV and VSV combined) was equivalent to or less than those receiving traditional physician-directed weaning (no protocol). Decreasing the time to extubation from 4 days (based on data from a pilot study) to 2.65 days (33% less) was considered clinically important. Using a hazard ratio of 0.67, a 2-sided α of .05, and a 2:1 ratio of children randomized to protocol-directed wean-

ing vs physician-directed weaning, a total of 306 weaning times (204 in the protocol-directed weaning group and 102 in the traditional weaning group) were required for 80% power.

Our second hypothesis was that the time to successful extubation for children randomized to the VSV protocol was less than for those randomized to the PSV protocol, because in VSV the pressure support level was continu-

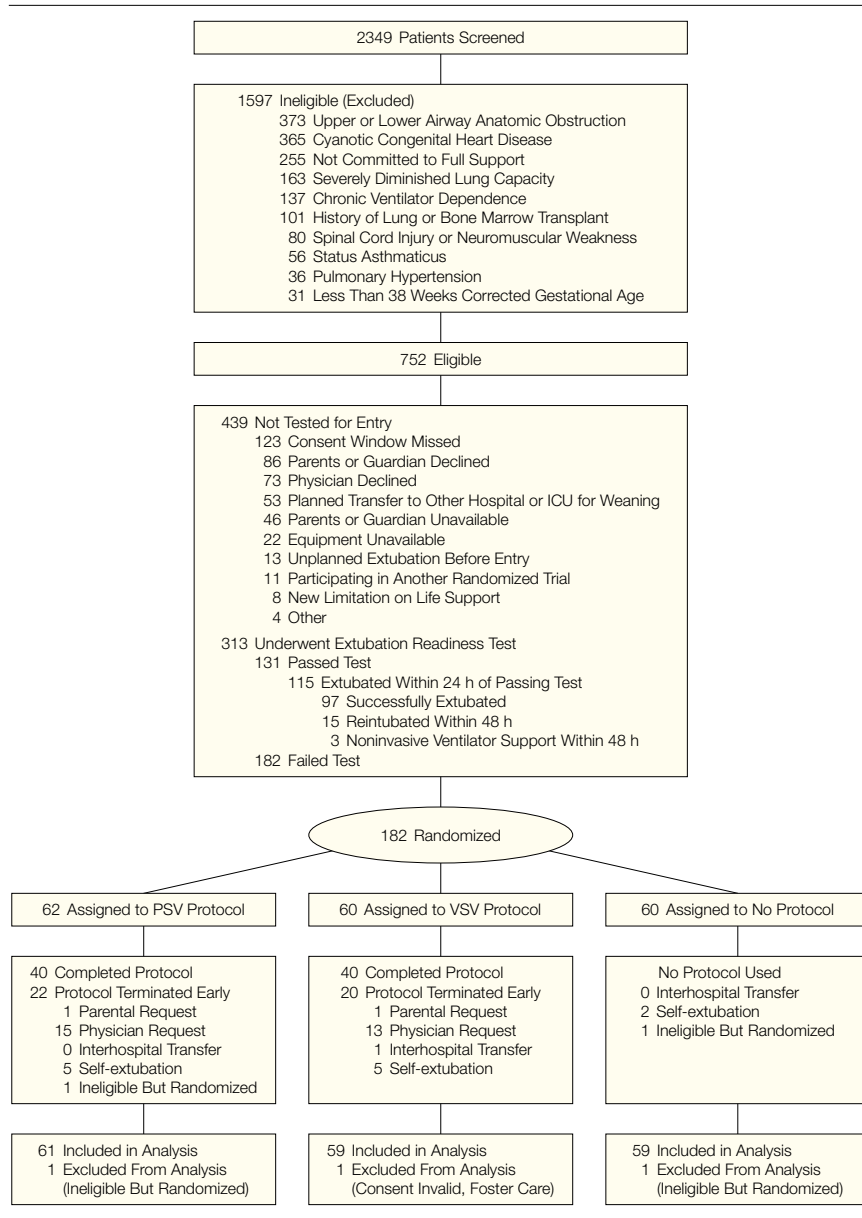
ally adjusted as the patient improved. Decreasing the median time to extubation from 3 days to 2 days (33% less) was considered clinically important. Using a hazard ratio of 0.67, a 2-sided α of .05, and a 1:1 ratio of children randomized to PSV and VSV, a total of 328 weaning times (164 in each group) were required for 80% power.

A priori, clinicians determined that a clinically important difference between trial groups was a minimum of 1 day. An interim analysis was scheduled at 306 patients. At this point, the data and safety monitoring board (DSMB) was instructed to recommend ceasing enrollment in the no protocol group if care provided using a protocol was proven equivalent to or better than care provided without a protocol. They were also instructed to recommend increasing the sample size if necessary but to stop the study for lack of efficacy if the differences in weaning times between study groups were unlikely to exceed 1 day.

The study was analyzed on an intention-to-treat basis. The primary efficacy variables were weaning success and, among the subset of patients who were weaning successes, the duration of time to weaning. Weaning failure was defined as either the reinstatement of mechanical ventilator support within 48 hours of extubation (through an ETT or noninvasively) or failure to wean within 28 days of randomization. All patients were prospectively evaluated to hospital discharge or transfer to another institution. Patients who died or were transferred before completing the study were treated as weaning failures.

The Fisher exact test was used to compare the proportion of weaning failures between groups. Logistic regression was used to assess the effects on weaning of sedation received during the first 24 hours, after controlling for study site, age, race, sex, PRISM III score, and days intubated prior to randomization. Age groups were defined as neonate (younger than 30 days), infant (younger than 1 year), child (younger than 12 years), and adolescent (younger than 18 years). Quartiles were used to

Figure 1. Flow of Patients Through the Trial



ICU indicates intensive care unit; PSV, pressure support ventilation; and VSV, volume support ventilation.

define levels for sedation score and days intubated prior to randomization.

Weaning-time analyses considered only cases that were successfully extubated.^{14,15} Kaplan-Meier survival curves and log-rank tests were used to compare the weaning times of the groups. Proportional hazards regression was used to assess the effects of covariates on weaning times. SAS v8.0 (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Enrollment in the trial began at the first site in November 1999. The first interim analysis was performed in February 2001, after 105 patients were randomized. The second interim analysis was performed after 182 patients were randomized. On April 30, 2001, the DSMB stopped the trial due to lack of efficacy.

A total of 313 eligible patients underwent the ERT. Of these, 182 (58%) failed the test and were randomized (FIGURE 1). Reasons for failing the test were related to exhaled tidal volume in 52 children (28.6%), to SpO₂ in 10 (5.5%), to respiratory rate in 32 (17.6%), and to more than 1 criterion in 88 (48.4%). Of the 131 patients (42%) passing the test, 115 (88%) were extubated within 24 hours. Of these, 97 (84%) were successfully extubated, 15 (13%) were reintubated, and 3 (3%) required use of noninvasive ventilator support.

Of the 182 children randomized in the study, 62 were randomized to the PSV protocol, 60 to the VSV protocol, and 60 to no protocol or standard care (Figure 1). The number of children enrolled at each center ranged from 4 to 31. One child was excluded from the analysis after randomization (to the VSV protocol) because social services determined that the foster mother was not eligible to give consent for a study. Two ineligible patients were randomized: a 20-year old with trisomy 21 (to no protocol) and an infant with repaired congenital diaphragmatic hernia (to the PSV protocol). Both were analyzed as extubation failures. The tables do not include the 1 patient excluded after randomization or the 2 in-

eligible patients, and report the results of the other 179 patients. Further analyses were performed including the 2 ineligible patients' data, and the results are reported in the text.

Baseline variables did not differ by treatment group with regard to history of chronic illness, admission diagnosis, age, sex, or length of time receiving ventilation prior to randomization (TABLE 1). Neonates comprised 17.3% of the study population, with 87% of these originating from home and 13% transferred after birth for persistent pulmonary hypertension of the newborn. Follow-up was complete for all subjects except for 1 child in the VSV protocol who was transferred to another hospital. This child was treated as an extubation failure. Four children died after randomization but before hospital discharge (2 VSV, 2 PSV). All 4 had redirection of care and withdrawal of support because of a change in prognosis due to their underlying diseases.

Protocol Compliance

Although the overall analysis was by intention to treat, we monitored protocol compliance prospectively. The number of children completing the protocol was 39 of 59 (66%) in the VSV group and 40 of 61 (66%) in the PSV group. One child in the VSV group was transferred prior to extubation. Of the 12 children whose extubations were unplanned (5 VSV, 5 PSV, 2 no protocol), none failed extubation. Of the 16 children extubated by their physician before passing the ERT (6 VSV, 10 PSV), 5 (31%) failed extubation (2 were reintubated and 3 received noninvasive ventilator support).

Two children were removed from the protocol at parental request (1 VSV, 1 PSV) but the attending physicians caring for these children reported acceptable protocol performance. Twelve children (10%) were removed from the protocols at physician request (7 VSV, 5 PSV). Four had persistent apneic episodes, 2 had excessive ETT leaks in-

Table 1. Baseline Characteristics of the Study Population*

Characteristic	Pressure Support (n = 61)	Volume Support (n = 59)	No Protocol (n = 59)
Age group, No. (%)			
Neonate (<30 d)	13 (21)	9 (15)	9 (15)
Infant (<1 y)	26 (43)	22 (37)	24 (41)
Child (<12 y)	18 (30)	16 (27)	18 (31)
Adolescent (12-17 y)	4 (7)	12 (20)	8 (14)
Male sex, No. (%)	39 (64)	31 (53)	36 (61)
Race, No. (%)			
Black	13 (21)	12 (20)	17 (29)
White	32 (52)	34 (58)	32 (54)
Hispanic	11 (18)	9 (15)	5 (8)
Other	5 (3)	4 (2)	5 (3)
Any chronic condition, No. (%)	27 (44)	27 (46)	25 (42)
Primary reason for admission, No. (%)			
Pulmonary	50 (82)	41 (69)	42 (71)
Pneumonia	12 (24)	12 (29)	11 (26)
Bronchiolitis	22 (44)	17 (41)	14 (33)
ARDS	7 (14)	3 (7)	7 (17)
Other pulmonary	9 (18)	9 (22)	10 (24)
Cardiac	7 (11)	4 (7)	4 (7)
Neurologic	3 (5)	5 (8)	5 (7)
Sepsis	1 (2)	5 (8)	4 (7)
Other	0	4 (7)	4 (7)
PRISM III score, mean (SD)	9.5 (7.1)	10.4 (7.3)	10.8 (7.8)
Days intubated prior to randomization, mean (SD)	7.1 (7.4)	6.0 (6.3)	7.6 (9.2)

*Protocol differences were tested using the Fisher exact test for categorical variables and Kruskal-Wallis tests for ordered categorical and continuous variables. P>.20 for all. The 2 patients who were ineligible but randomized, and the patient excluded after randomization, are not included. PRISM III indicates Pediatric Risk of Mortality III; ARDS, acute respiratory distress syndrome.

Table 2. Weaning Outcomes

	Pressure Support (n = 61)	Volume Support (n = 59)	No Protocol (n = 59)	P Value
Weaning failure, No. (%)	9 (15)	14 (24)	10 (17)	.44*
Weaning times among successes, median (interquartile range), d	1.6 (0.9-4.1)	1.8 (1.0-3.2)	2.0 (0.9-2.9)	.75†

*By Fisher exact test.

†By log-rank test.

terfering with effective ventilation, 5 had respiratory deterioration and the physicians elected not to reenter them in the protocol when they were ready to wean again, and 1 died after redirection of care due to poor prognosis.

Extubation was delayed more than 4 hours in 25 children (8 VSV, 17 PSV). The reasons for these delays were clinical team not available (5), neurologic status (5), apnea (4), no ETT leak (2), and other (9).

Ventilator Management in the No Protocol Group

In the no protocol group, a total of 9 modes of ventilation available on the ventilator were used at least once with single modes of ventilation used in 32 patients (55.2%), 2 modes in 18 (31%), 3 modes in 7 (12.1%), and 4 modes in 1 patient. In 22% of patients, the ventilator mode was changed 3 or more times during weaning. Modes commonly used were pressure control with pressure support (39 children, [67%]) and volume control with pressure support (15 children [27%]). Pressure support ventilation was used as the single mode of ventilation during weaning in only 5 children (8.5%), but was the last mode used prior to extubation in 26 children (43.3%) with a mean (SD) extubation pressure support level of 7.6 (2.1) cm H₂O. Volume support ventilation was used at least once in 5 children (8.5%) and in only 1 child as the single mode of ventilation during weaning and prior to extubation. In the 27 (45.8%) patients extubated from a mode with a set ventilator rate, the mean (SD) set respiratory rate at extubation was 5.7 (2.8) per minute.

Extubation Success and Failure

Weaning failure rates are summarized in TABLE 2. All weaning failures were

due to extubation failure, redirection of care and death, or patient transfer. Recorded reasons for extubation failure were: lower respiratory tract problems (54.2%), upper airway obstruction and stridor (25%), apnea (8.3%), cardiovascular insufficiency (4.2%), and other (8.3%). There were no significant differences in failure rates in the 3 groups ($P=.44$). Inferences were unchanged when 2 randomized but ineligible patients were included, or when comparing groups using logistic regression adjusting for study site.

Using logistic regression, a child's sex was identified as a significant predictor of extubation failure, with failure occurring more often in boys ($P<.001$) (TABLE 3). Overall there were 33 failures, of which 29 (87%) occurred in boys. For boys, the failure rates in the PSV, VSV, and no protocol groups were 21%, 45%, and 19%, respectively. For girls, they were 5%, 0%, and 13%. In addition to child's sex, sedation during the first 24 hours of weaning also significantly predicted extubation failure ($P=.04$; $df=3$). Extubation failure rates for the lowest to the highest sedation quartiles were 20%, 14%, 7%, and 32%, respectively; children in the highest quartile for sedation had more extubation failures than those in the middle quartiles ($P<.03$ for each). Sedative use was measured for the first 24 hours of weaning but not at the time of extubation. This may explain why the odds ratios for the sedation use score quartiles do not suggest a linear relationship. Inferences were unchanged when children who were removed from the protocol at physician or parent request, and the 4 children who died, were excluded from the analysis. The model was also unchanged when age was used as a continuous variable or when the presence of a chronic pulmo-

nary condition or a chronic neurologic condition was added separately to the model (all were nonsignificant as independent predictors). There was no significant interaction between age and sex.

Length of Time in Weaning

For the 146 successfully weaned cases, we compared the weaning times of treatment groups. The mean weaning times for the PSV, VSV, and the no protocol groups were 3.3, 2.5, and 3.2 days, respectively. The medians were 1.6, 1.8, and 2.0 days (Table 2). Weaning times did not differ significantly between treatment groups ($P=.75$).

Using proportional hazards regression, sedation during the first 24 hours of weaning significantly predicted weaning times ($P<.001$; $df=3$). Mean weaning times for the lowest to highest sedation score quartiles were 1.5, 2.9, 2.8, and 5.2 days. Median weaning times for the lowest to highest sedation score quartiles were 1.0, 1.9, 1.9, and 3.0 days (FIGURE 2). Inferences were unchanged when 10 successfully extubated patients who did not complete their assigned protocol were excluded from the analysis.

COMMENT

Limiting the duration of airway intubation and mechanical ventilator support to the shortest possible time is of utmost importance for reducing risk of nosocomial infection, tracheal irritation and injury, and sedative dependency. Shortening the duration of mechanical ventilator support should also decrease ICU length of stay and associated costs. The prevalent philosophy is that it is necessary to gradually wean children experiencing respiratory failure from the mechanical ventilator to retrain their respiratory muscle strength. The findings of our study, the largest study performed to date in infants and children with acute respiratory failure, suggest that gradual weaning may not be indicated for the majority of infants and children. More than a third of the children whose physicians determined that they were ready to begin the weaning process, in fact, already met bed-

side extubation readiness criteria and most were successfully extubated within 24 hours. More than half of the children not meeting these criteria were successfully extubated within 2 days. At the time that study enrollment was terminated, there was no difference in weaning between the protocol and nonprotocol groups, and no clinically important difference was likely to be seen if the study went to completion. In contrast to previous studies in adults that found that protocols shortened duration of weaning,^{5,6} use of weaning protocols had no impact on the duration of mechanical ventilator support in this multicenter cohort of children.

Sedative use in the first 24 hours of weaning appears to strongly influence both length of time on the ventilator and extubation failure in infants and children. This is consistent with findings in adult patients.¹⁶ Cognitive immaturity impedes the ability of children to be awake and tolerate having an ETT in place. Although sedative drugs are required to prevent unplanned extubation and associated adverse events, the need to maintain patient comfort may impede liberation from the ventilator.

Another major finding of our study was that the great majority of extubation failures were in male patients. The reasons for this are unclear. Male and female patients were equally distributed across the various diagnostic and age groups. Male sex has been associated with worse outcomes for neonatal respiratory distress syndrome¹⁷ and for community-acquired pneumonia in adult patients.¹⁸ Whether anatomical, hormonal, or other influences underlie the difference in outcome is entirely speculative.

This is the only controlled trial to date evaluating methods of weaning infants and children from mechanical ventilator support with extubation as the study end point. Schultz et al¹⁹ randomized 223 children to a weaning protocol or to physician-directed weaning but used the time at which minimum settings were achieved as the study end point. In addition, patients were not placed on minimal settings prior to weaning to ensure that they actually required weaning, and

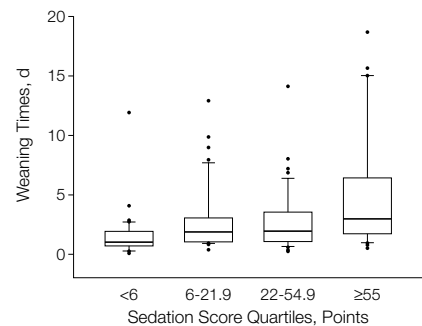
Table 3. Predictors of Weaning Failure and Weaning Times*

Characteristic	Weaning Failure (n = 179)		Weaning Time (Among n = 146 Successes)	
	OR (95% CI)	P Value	HR (95% CI)†	P Value
Treatment assignment				
Pressure support	0.81 (0.27-2.41)	.70	0.85 (0.56-1.29)	.44
Volume support	2.27 (0.78-6.63)	.13	1.10 (0.70-1.72)	.67
No protocol	Reference		Reference	
Age group				
Neonate (<30 d)	Reference		Reference	
Infant (<1 y)	1.54 (0.40-5.86)	.53	1.15 (0.70-1.89)	.59
Child (<12 y)	2.19 (0.54-8.86)	.27	0.79 (0.47-1.43)	.38
Adolescent (12-17 y)	1.49 (0.29-7.69)	.64	0.84 (0.46-1.55)	.58
White	0.55 (0.23-1.32)	.18	1.22 (0.85-1.74)	.28
Male	7.86 (2.36-26.2)	<.001	1.05 (0.71-1.53)	.81
PRISM III score (per point)	1.03 (0.97-1.09)	.33	1.00 (0.98-1.03)	.84
Sedation score (points)				
Quartile 1 (<6)	0.41 (0.44-5.25)	.52	4.11 (2.29-7.41)	<.001
Quartile 2 (6-21.9)	0.24 (0.07-0.83)	.03	2.01 (1.16-3.49)	.01
Quartile 3 (22-54.9)	0.16 (0.04-0.71)	.02	1.84 (1.06-3.20)	.03
Quartile 4 (≥55)	Reference		Reference	
Time intubated prior to randomization (d)				
Quartile 1 (0-2)	1.23 (0.34-4.41)	.75	1.25 (0.71-2.20)	.45
Quartile 2 (3-4)	0.99 (0.26-3.82)	.99	1.12 (0.66-1.91)	.66
Quartile 3 (5-7)	1.51 (0.44-5.25)	.52	1.53 (0.85-2.77)	.16
Quartile 4 (≥8)	Reference		Reference	

*OR indicates odds ratio; CI, confidence interval; HR, hazard ratio; and PRISM III, Pediatric Risk of Mortality III. †Compared with the reference groups, HRs >1 indicate shorter (<1, longer) weaning times.

the median time in weaning was 10 hours or less across groups. We believe that our study population is representative of the majority of infants and children requiring mechanical ventilation in pediatric ICUs for which a ventilator protocol would apply. Ten large pediatric ICUs contributed patients to this study. Diagnoses that could strongly influence ability to wean or successfully extubate, such as upper airway obstruction or asthma, were excluded. The great majority of patients were recovering from primary respiratory disease. In contrast to studies in adult patients, we attempted to enroll patients in weaning as early as they could tolerate spontaneous breathing. In adult studies, more than 75% of patients passed the initial extubation readiness screening test and were not eligible for entry,^{14,20} whereas in our pediatric study only 42% passed this initial test. Despite this, the duration of weaning was markedly shorter in these children compared with that reported in the adult studies. It is possible that infants and children recover more rapidly from a pul-

Figure 2. Weaning Times as a Function of Sedation Score for 146 Patients Weaned From Mechanical Ventilation



See "Methods" section for calculation of the sedation score. Middle bar indicates the median value, and the lower and upper boundaries indicate the interquartile range. Vertical lines indicate the 10th and 90th percentiles; dots, more extreme observations.

monary insult. Less than 10% of the children in this study had any chronic pulmonary disease, whereas in adult patients, chronic obstructive pulmonary disease was present in more than 25% of patients enrolled in adult weaning and extubation trials.^{14,15,21}

Both protocol groups used objective criteria to determine extubation readiness, in contrast to physician judgment in the no protocol group. Despite this, objective criteria were no more predictive than physician judgment in determining which children could be successfully extubated. The average extubation failure rate was 19% using an ERT and 17% using physician judgment. These failure rates are consistent with previous rates.²²⁻²⁴ The only potentially manipulable factor influencing failure rates was sedation use. Because male sex was a strong determinant of extubation failure, more stringent criteria for extubation readiness may be indicated for male patients.

We cannot rule out the possibility that ventilator weaning protocols may be beneficial in the subgroup of children whose weaning time is longer than 3 days. It is also possible, however, that daily testing^{15,21} and daily interruption of sedative medications¹⁶ are more effective in decreasing duration of mechanical ventilation. Like other protocols for care, physician compliance with these protocols was not perfect; however, many reasons for noncompliance were clinically justifiable. It is possible that strict compliance with a multifaceted protocol used for a prolonged period may not exceed 66% in the best circumstances. Given that the median duration of weaning was short (2 days or less) in all arms of the study, it is unlikely that improved protocol adherence would lead to a clinically important difference in weaning times.

Our findings underscore the need for more effective methods of achieving patient comfort without negative effects on ventilatory drive. Benzodiazepines and narcotics are the main agents used and their use is associated with physiological dependence and withdrawal in patients requiring them for 7 or more days.^{4,25} The long-term neurologic effects of exposure to those agents on developing brains are unclear. We found that, for the majority of infants and children receiving ventilator support for acute respiratory failure, ventilator weaning protocols had no effect on duration

of mechanical ventilation. Improved management of sedative drugs and daily testing for extubation readiness could potentially lead to shorter duration of mechanical ventilator support.

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Drafting of the manuscript: Randolph, Wypij, Forbes. *Critical revision of the manuscript for important intellectual content:* Randolph, Wypij, Venkataraman, Hanson, Gedeit, Meert, Luckett, Forbes, Lilley, Thompson, Cheifetz, Hibberd, Wetzel, Cox, Arnold.

Statistical expertise: Wypij, Forbes, Hibberd.

Obtained funding: Randolph, Thompson.

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