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Weaning children from mechanical ventilation with a computer-driven protocol: a pilot trial

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Abstract *Purpose:* Duration of weaning from mechanical ventilation is decreased with the use of written protocols in adults. In children, the use of written protocols has not had such an impact. *Methods and measurements:* We conducted a single-center trial to assess the feasibility of conducting a multicenter randomized clinical trial comparing the duration of weaning from mechanical ventilation in those managed by a computer-driven explicit protocol versus usual care. Mechanically ventilated children aged between 2 and 17 years on pressure support and not receiving inotropes were included. After randomization, children were weaned either by usual care ($n = 15$) that was characterized by no protocolized decisions by attending physicians, or by a computer-driven protocol (Smartcare/PS^{TM}, Drager Medical) ($n = 15$). Weaning duration until first extubation was the primary outcome. For comparison, a Mann–Whitney U test was employed ($p < 0.05$). *Results:* Patients characteristics at inclusion were similar. The median duration of weaning was 21 h (range 3–142 h) in the SmartCare/PS^{TM} group and 90 h (range 4–552 h) in the usual care group, $p = 0.007$. The rate of reintubation within 48 h after extubation and the rate of noninvasive ventilation after extubation in the SmartCare/PS^{TM} and usual care groups were 2/15 versus 1/15 and 2/15 versus 2/15, respectively. *Conclusions:* A pediatric randomized trial on mechanical ventilation with a computerized protocol in North America is feasible. A computer-driven protocol that also manages children younger than 2 years old would help to decrease the number of PICU admissions screened in a multicentre trial on this topic.

Keywords Computers · Extubation · Children · Mechanical ventilation · Weaning protocols

List of abbreviations

ET_{CO_2}	End tidal partial pressure of CO_2
PEEP	Positive end expiratory pressure
PICU	Pediatric intensive care unit
BW	Body weight
PS	Pressure support
RCT	Randomised clinical trial
RR	Respiratory rate
Vt	Tidal volume
SBT	Spontaneous breathing test

Introduction

There is evidence that clinical decision-making using protocols decreases practice variation between clinicians [1], standardizes patient care [2] and improves patient outcomes [2–6]. This is proven in adult critical care units with the use of written protocols developed to improve the weaning of respiratory support [7–10]. In children, the use of written protocols has not had such an impact: a shorter duration in weaning time was documented in two studies involving one or two centers [11, 12], but no difference was observed in weaning duration when compared with usual physician orders in a multicenter trial [13]. Limited adherence to written protocols was suggested as one of the factors reducing the ability to infer a true benefit associated with these ventilation strategies [14]. To overcome this issue and to reduce individual customization of respiratory support, computer-driven explicit protocols have been developed. Computer-driven explicit protocols function as a set of standardized orders, with detailed explicit instructions based on dynamic patient-specific parameters, available at the point-of-care [15]. A computer-driven explicit protocol can work in a closed-loop and/or open-loop mode. In the former (closed-loop), the computer implements its recommendation without caregiver intervention; in the latter (open-loop), the computer provides advice that can be approved or not by caregivers. In adults, a computer-driven explicit protocol in closed-loop for the weaning of mechanical ventilation reduced weaning duration in the computer-driven group from a median of 5–3 days when compared to written protocols [16]. In children, a prospective single center study demonstrated that the mean duration of mechanical ventilation using Smartcare was 5.1 ± 4.2 days, compared with 6.7 ± 11.5 days in a historical control group, although this was not statistically significant [17].

The objective of this pilot randomized clinical trial (RCT) was to assess the feasibility of conducting a multicenter randomized clinical trial comparing the duration of weaning from mechanical ventilation in those managed by a computer-driven explicit protocol versus usual care, and determine the potential magnitude of the treatment effect.

Materials and methods

Patients

Eligible patients were children between 2 and 18 years with body weight (BW) ≥15 kg admitted to the pediatric intensive care unit (PICU) of Sainte-Justine Hospital for any reason, except cardiac surgery, between September 2007 and June 2009, for whom mechanical ventilation for at least 12 h was expected. Children were included if the Evita XL respirator with SmartCare/PS^{TM} was available and if they fulfilled the following weaning criteria: patient able to breath spontaneously, no vasopressor or inotrope medication [other than digoxin or low-dose dopamine (<5 μg/kg/min)], FiO_2 ≤60 % with oxygen saturation ≥95 %, positive end expiratory pressure (PEEP) ≤8 cmH_2O, plateau pressure ≤25 cmH_2O, endotracheal tube leak ≤20 %. Patients were excluded if: they had severe chronic respiratory insufficiency due to neurological, neuromuscular or lung diseases prior to PICU admission, primary pulmonary hypertension, or cyanotic congenital heart disease. Children expected to be extubated on the day of inclusion, not expected to survive, with a decision to withdraw care or with no parental consent were also excluded. The study protocol was approved by the institutional review board of Sainte-Justine Hospital.

Pilot trial design (for more details see electronic supplement)

After inclusion, a pressure support (PS) test was performed (ventilation in PS mode at a level of ±5 cmH_2O of the pre-inclusion plateau pressure). When the PS test was positive, the patient was ventilated with an Evita XL respirator in PS mode and was allocated randomly to wean via SmartCare/PS^{TM} (SmartCare group) or usual methods.

In the usual care group, physicians were instructed to wean according to their practice. In the SmartCare group, the SmartCare/PS^{TM} option of the Evita XL was switched on after adjusting for BW [17]. In addition, PEEP was adjusted according to the following guidelines: (1) decrease of PEEP level by 1 cmH_2O per 8 h to a minimum of 5 cmH_2O, if FiO_2 ≤50 % with SpO_2 ≥95 %; (2) if FiO_2 ≥60 % to maintain a SpO_2 ≥95 % during 1 h, the attending physician could decide to increase PEEP. If the patient clinical status deteriorated, ventilation was switched back to assist control ventilation. The patient was then retested with PS test daily and SmartCare/PS^{TM} was restarted when the test was positive.

The decision to extubate was made by the attending clinicians in both groups. In the SmartCare group, if the extubation was performed later than 30 min after a ''separation recommendation'', the reason for this delay was collected prospectively. In accordance with current mechanical ventilation practice, no recommendation of separation from the respirator was provided by the SmartCare/PS^{TM} between 8:00 pm and 6:00 am.

The primary endpoint studied was the time from randomization to the first extubation. Secondary endpoints included: (1) weaning failure: resuming mechanical ventilation (non invasive or invasive) within 48 h after extubation or failure to wean within 28 days of

randomization. Causes of failure were documented; (2) total duration of mechanical ventilation. If a patient was reintubated within 48 h after extubation, both mechanical ventilation episodes were considered as the same episode; (3) length of PICU stay; (4) length of hospital stay; (5) Ventilator free days at 28 days.

Power and sample size calculations

This pilot study included 30 patients (15 in each group), which corresponded to 10 % of the sample size that we expect to include in a multicentre randomized clinical trial that we plan to conduct after this pilot study (see electronic supplement).

Data analysis

Analysis was done using the intention to treat principle. Mann–Whitney *U* test was used to assess for statistical significance of the primary end point ($p < 0.05$). Statistical analysis was performed with SPSS software, version 13.0. The probability of remaining on mechanical ventilation was analyzed by the Kaplan–Meier method, and a log-rank test was used to assess differences. Cox proportional hazards modelling was performed to estimate the adjusted effect of selected variables on the primary end point.

Results

During the 21-month trial, a total of 2,178 ventilated patients were screened, of whom a total of 186 patients were eligible and 30 patients were randomized (Fig. 1). The most common reason for noneligibility was age $\leq$2 years; 42 patients were excluded because the experimental ventilator was not available.

The characteristics and primary indication for ventilation of study patients are summarized in Table 1. Both SmartCare and usual care groups were similar.

The median time (25th and 75th quartiles) from randomization to first extubation was 21 h (3–142 h) in SmartCare group and 90 h (4–552 h) in the usual care group ($p = 0.007$). This difference remained statistically significant after adjustment in a Cox model for FiO_2 and PS level at baseline ($p = 0.026$). The results for the secondary outcomes are shown in Table 2. The Kaplan–Meier curves estimating probability of remaining on invasive mechanical ventilation are shown in Fig. 2; the two curves are statistically different ($p = 0.002$). The duration of ICU stay, total duration of mechanical ventilation, hospital length of stay and sedation score were not significantly different between the two groups.

Ventilation management

Ten of the 15 patients in the usual care group and 4 out of 15 patients in the SmartCare group had at least one change of ventilation mode during the study period. The number of changes of ventilation mode per group (median-range) were 2 (0–5) and 0 (0–6), respectively. In SmartCare group, mode changes followed protocol rules: heavy sedation in 3 patients and increase in FiO_2 above 60 % in one patient. When the patients were switched from pressure support to another ventilation mode, the ventilation modes used were either synchronized intermittent mandatory ventilation (SIMV) or pressure assist control.

The written protocol to manage PEEP was followed in the 15 patients of SmartCare group. After inclusion, 8 patients in the SmartCare group and 9 in the usual care group had a PEEP above 5 cmH_2O. PEEP was decreased to 5 cmH_2O in 7.7 $\pm$ 13.9 h in SmartCare group and 10.1 $\pm$ 14.4 h in usual care group ($p = 0.68$). A SBT (PS level $\leq$10 cmH_2O during at least 30 min in PSV mode) prior to extubation was performed in 10/15 patients in the usual care group and 15/15 patients in SmartCare group.

In the SmartCare group, the children spent 87 % of their time (median) with the SmartCare/PS^{TM} protocol active. A median of 3 interruptions of the computerized protocol (range 0–18) was observed. The main reasons for interruption were technical problems in 37 % (13/35) of cases (failure of CO_2 sensor, spirometer failure, interruption during suctioning) and patient agitation in 40 % (14/35).

Extubation success and failure

Two patients in the SmartCare group and one in the usual care group were reintubated within 48 h after the first extubation. One child in the SmartCare group was reintubated 24 h after the first extubation due to unscheduled surgery. The other child had a 10 h course of noninvasive ventilation and was reintubated due to upper airway obstruction and chronic aspiration pneumonia. After discussion with the parents, this child received palliative care and died after the second extubation. One patient in the usual care group was reintubated due to respiratory failure, in the context of acute chest syndrome. After reintubation, the patient was ventilated for 68 h then extubated successfully.

In 14/15 patients in the SmartCare group, extubation was delayed for more than 30 min (median 6 h (range 0–82 h) after SmartCare/PS^{TM} recommended separation from the respirator. The reasons for this delay were: planned procedure (6 children), extubation deemed impossible by the attending physician because of compromised airways (2 children), unavailability of staff (3 children), extubation postponed until the end of a

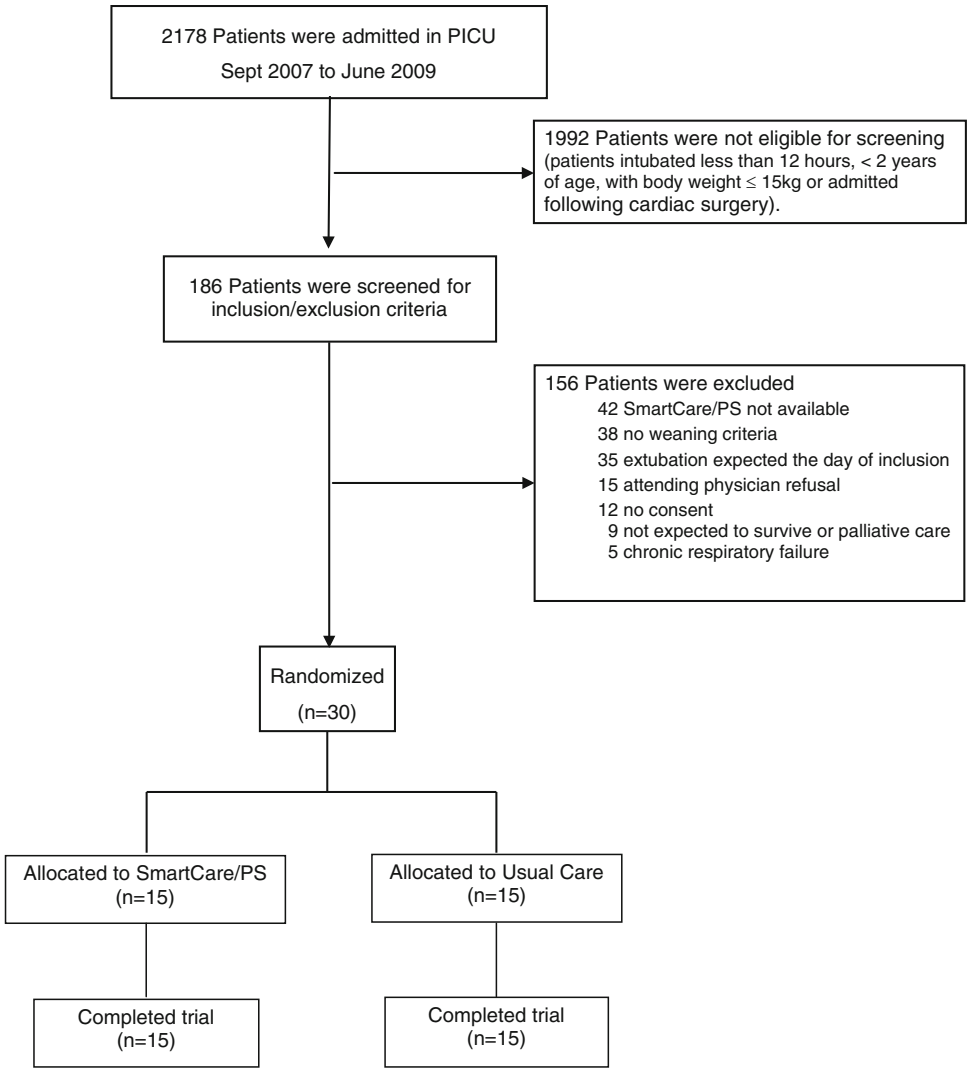

Fig. 1 Flow diagram of study

transfusion (1 child), extubation delayed until parents were at the bedside (1 child), unexplained delay (1 child). One patient who was awaiting a planned procedure had an accidental extubation and was not reintubated.

Discussion

The median duration of weaning from mechanical ventilation decreased significantly in the group treated with the computer-driven protocol group compared to the usual care group [21 h (range 3–142 h) vs 90 h (range 4–552 h), respectively]. There was high compliance in the computerized protocol group, with similar extubation failure rates between the two groups. We also documented that many extubations are delayed in PICUs due to factors that are independent of patient respiratory status.

No randomized clinical trial has reported a significant decrease in weaning duration when using a computer-driven protocol in children. In this pilot study, we observed a median difference of more than 2 days between the two groups. The effect of a computerized protocol on duration of weaning from mechanical ventilation may be due to several factors including: (1) better compliance to a protocol that is designed to decrease ventilatory support on a continuous mode according to the patient's respiratory condition; (2) consistent orders that inhibit variations in interpretation among caregivers and result in a more efficient application of the protocol; (3) reduction of time lags between assessment of patient status and order writing, and between order and execution; (4) earlier training of respiratory muscles that increases muscles strength; (5) more efficient training since respiratory support is reloaded if too much dyspnea is observed in order to avoid fatigue.

Table 1 Characteristics of patients at baseline

	SmartCare $n = 15$	Usual care $n = 15$	p value
Age (months)	119 ± 53	116 ± 57	0.92
Weight (kg)	35 ± 20	34 ± 25	0.76
Severity of illness scores			
PIM 2	5.7 ± 5.3	8.6 ± 18.4	0.31
PELOD	9.1 ± 10.4	11.3 ± 13.1	0.84
PaO_2/FiO_2 (mmHg)	336 ± 71	288 ± 98	0.28
Male gender, *n*	11	7	0.14
Chronic condition, *n*			0.71
Respiratory system	5	5	1.00
Cardiovascular system	1	3	0.60
Neurologic system	4	3	1.00
Oncologic disorder	1	2	1.00
Immunosuppressive non oncologic disorder	2	2	1.00
Indication for ventilation, *n*			
Pulmonary failure	8	8	1.00
Heart failure	2	6	0.21
Coma	3	3	1.00
Postoperative	6	4	0.43
Trauma	3	1	0.60
Sepsis	0	2	0.48
Other	2	0	0.48
Ventilation duration before randomization (h)	157 ± 189	141 ± 104	0.89
PS test at inclusion			
PS level (cmH_2O)	12 ± 3	14 ± 4	0.05
PEEP (cmH_2O)	6 ± 1	6 ± 1	0.90
FiO_2	0.3 ± 0.1	0.4 ± 0.1	0.06
Sedation status the day of randomization			
Sedation score [11]	48 ± 66	31 ± 37	0.37
Comfort score [25]	15 ± 4	14 ± 1	0.48

Values are means (SD) unless stated otherwise

PIM 2 pediatric index of mortality 2 score [26], *PELOD* pediatric logistic organ dysfunction score [27], *PEEP* positive end-expiratory pressure, *PS* pressure support

The use of a computer-driven protocol was associated with high compliance (87 %). Compliance with the protocol in the SmartCare group was higher than compliance usually observed with use of a written protocol (40–66 %) [13, 17].

Consistent orders and reduction of time lags are also optimized with a computer-driven protocol. The main benefit of a computer-driven protocol is the ability to implement changes mandated by the protocol's rules quickly, regardless of organization of care and caregiver workload. If the rules aim to decrease respiratory support, this decrease results in a shortening of the weaning time which can probably explain the difference observed between the two groups. In addition to this benefit, a computer-driven protocol also reduces time lags between assessment of patient status and order writing, and between order and execution. The present standard of care for respiratory support in North America involves changes in ventilator settings by respiratory therapists at variable intervals, as ordered by the attending physician or according to a written protocol. There are important variations in the management of respiratory support in PICUs across the world [18]. The lack of respiratory therapists in some countries results in respiratory support being managed by nurses or attending physicians alone. This can modify the impact of a protocol and even a computerized protocol on the duration of weaning across ICUs. For example, Rose et al. [19] conducted an RCT that compared SmartCare/PS^{TM} to usual care in an Australian adult ICU. In this ICU, nurses were in charge of respiratory support using a 1:1 nurse-to-patient ratio maintained over all shifts. This practice probably attenuated the impact of a computer-driven protocol on weaning duration and may explain, at least partially, why these authors did not observe any difference in weaning duration between the two groups.

Another effect of a computer-driven protocol on weaning time is constant training of respiratory muscles by a frequent decrease of mechanical respiratory support, increasing muscle workload but allowing for a boost of pressure support level in case of dyspnea. Several studies in adults have emphasized the impact of mechanical ventilation on diaphragm atrophy [20, 21]. To increase the strength of respiratory muscles, they must be trained. In a previous study we observed that SmartCare/PS^{TM} resulted in modification of pressure support level of 1.5 per hour. This acts as a form of respiratory muscle training with a constant adaptation of the respiratory support to respiratory muscle strength. Further research to demonstrate such an effect is needed.

The decrease in weaning time in SmartCare group was associated with similar rates of re-intubation and noninvasive ventilation as the usual care group. In our study, weaning failure rate was similar to that of other pediatric studies [13, 22]. It was also similar to that of two studies on SmartCare/PS^{TM} in adults [16, 19]. However, a study with a higher number of patients is needed as our study was not powered to allow us to make conclusions about this issue.

In this study, despite a recommendation of separation from the ventilator after a successful SBT, extubation was delayed in 14/15 patients with a median delay of 6 h. This was also observed by Lellouche et al. [16] who reported that only 42 % of the patients were extubated on the same day of the recommendation. Some of the reasons to delay extubation, including planned procedures within 24 h or no staff available, are organisational and can be addressed by quality improvement processes.

This study has several limitations. The results cannot be generalized to all children admitted to PICU as we included only a small proportion of eligible children. Two-thirds of children ventilated in PICUs are younger than 2 years of age [23]; all these patients were excluded from our RCT. This age limitation was due to the tidal volume monitoring by SmartCare/PS^{TM}, which requires a reliable monitoring of tidal volume measurements and the absence of air leak. The implementation of an air leak

Table 2 Outcomes and complications

	SmartCare $n = 15$	Usual care $n = 15$	p value
Primary outcome			
Duration of weaning[a] (h)	36 ± 36	142 ± 150	0.007
Duration of weaning, median (range) (h)	21 (3–142)	90 (4–552)	
Secondary outcomes			
Duration of ventilation to first extubation (h)	193 ± 189	283 ± 205	0.17
Total duration of ventilation (h)	200 ± 186	288 ± 206	0.20
Ventilator free days at 28 days (days)	24.5 ± 7.0	21.9 ± 6.2	0.29
Length of ICU stay (days)[b]	9 ± 5	17 ± 14	0.11
Length of hospital stay (days)	27 ± 18	29 ± 21	0.68
Sedation score from inclusion to first extubation[c]	382 ± 1,256	498 ± 1,146	0.79
Complications, *n*			
Reintubation within 48 h after 1st extubation	2	1	
Any reintubation	2	1	
Self extubation	1	0	
NIV after first extubation[d]	2	2	
Mechanical ventilation duration after inclusion >14 days	0	2	
Mechanical ventilation duration after inclusion >28 days	0	0	

Values are means (SD) unless stated otherwise
ICU intensive care unit, *NIV* non invasive ventilation
[a] Time from inclusion to first extubation
[b] 1 death in SmartCare group removed from analysis
[c] Sedation score corresponds to the amount of sedation during the weaning phase. It was calculated using a score for which 1 point was given for the amount of each drug that would be equivalent to 1 h of sedation in a nontolerant subject [13]
[d] One patient and NIV followed by reintubation within 48 h after the first extubation

alarm, the improvement of tidal volume monitoring and the use of cuffed tubes should allow application of this computerized protocol in younger children but this cannot be done until the upgraded device is approved. Delays in screening and obtaining parental consent might also have selected children who were ventilated for a longer period of time than the usual population of children who meet inclusion criteria. This may have contributed to the greater than expected effect of SmartCare/PS^{TM} on duration of weaning. Moreover, the small number of participants may have had an impact on the distribution of the severity of the patients across the two groups. We did not observe any significant difference in PIM 2 and PELOD scores between the two groups but there was a slight difference in PS level and FiO_2 at inclusion (Table 1). Even after adjustment of weaning duration for initial PS level and FiO_2, the difference between the two groups remained statistically significant. The absence of

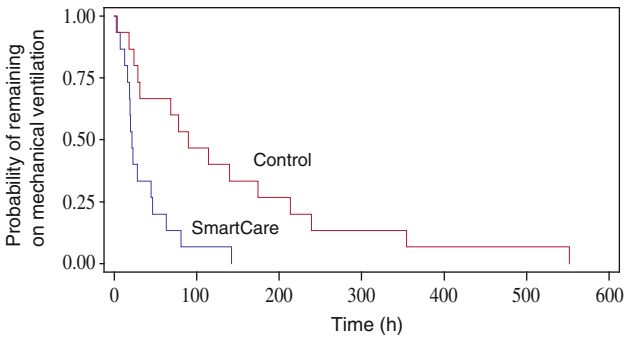

Fig. 2 Kaplan–Meier estimated probability of remaining on invasive mechanical ventilation. The difference between the two curves is statistically significant (log-rank test $p = 0.002$)

blinding might have affected the decision-making process in the usual care group. The median duration of ventilation before inclusion was similar to other studies [13, 22] but the mean duration of weaning in the usual care group was longer to the duration reported by Randolph et al. [13] in the "no protocol" group (142 vs 77 h, respectively). In a multicentre study, with a mean weaning duration of 77 h in the control group, the number of patients that should be included to observe the same decrease of weaning duration to 36 h by a computerized protocol is 160 patients. This corresponds to the screening of around 12,000 PICU admissions. The choice of provision of usual care, rather than a formal protocol, could have increased the risk of bias in decision making by caregivers for patients allocated to the usual care group. This choice was made in order to more closely approach current clinical practice [24]. This does mean that it is not possible to ascertain which element applied to the SmartCare group is responsible for the improvement in weaning duration: the computerized protocol itself or the protocolized follow-up on the recommendation of separation from the ventilator that prompted extubation. The PEEP protocol did not seem to have a significant impact on primary outcome as time from inclusion to PEEP 5 cmH_2O was similar in the two groups.

Conclusions

In this pilot study, we have shown that a pediatric randomized trial on the weaning from mechanical ventilation with a computerized protocol in North America is feasible. According to our study, the mean duration of weaning can be decreased to 1.5 days in the computerized protocol group. To confirm this result, a multicentre trial is needed with the screening of several thousands of PICU admissions. The development of a computerized protocol that also manages the weaning of children younger than 2 years old would help to reduce the number of PICU admissions screened.

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Conflicts of interest Dräger Medical provided one ventilator (Evita XL) equipped with the explicit computerized protocol software: SmartCare/PS™. Dräger Medical was not involved in the design of the study; in the collection, analysis, or interpretation of the data; in the preparation of the manuscript, or in the decision to submit the manuscript for publication.

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