ORIGINAL ARTICLE

Proportional-Assist Ventilation for Minimizing the Duration of Mechanical Ventilation

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This article was published on June 13, 2025, at NEJM.org.

N Engl J Med 2025;393:1088-103.
DOI: 10.1056/NEJMoa2505708

ABSTRACT

BACKGROUND

In critically ill patients, acceleration of liberation from mechanical ventilation is important in order to reduce the risk of complications and to improve long-term outcomes. Whether the use of proportional-assist ventilation with load-adjustable gain factors (PAV+) results in a shorter time to successful liberation from mechanical ventilation than pressure-support ventilation (PSV) is unclear.

METHODS

In this international clinical trial, we randomly assigned adult patients who had been receiving mechanical ventilation for at least 24 hours and were able to undergo partial ventilatory support with PSV but were not yet ready for liberation from ventilation to undergo PAV+ (which targeted normal work of breathing) or PSV (which targeted a normal respiratory rate and tidal volume). The primary outcome was the time from randomization to successful liberation from mechanical ventilation.

RESULTS

Across 23 centers in seven countries, 722 patients were enrolled, and 573 underwent randomization and were included in the analysis. The median time to successful liberation from mechanical ventilation was 7.3 days (95% confidence interval [CI], 6.2 to 9.7) in the PAV+ group and 6.8 days (95% CI, 5.4 to 8.8) in the PSV group (P=0.58). The median number of ventilator-free days, the incidence of reintubation and tracheostomy, and the incidence of death by day 90 (29.6% in the PAV+ group and 26.6% in the PSV group), all of which were secondary outcomes, were similar in the two groups. With respect to sedative drugs, the mean (±SD) difference in the midazolam-equivalent dose at day 28 relative to the baseline dose was −1.51±3.28 mg per kilogram of body weight in the PAV+ group and 0.04±0.97 mg per kilogram in the PSV group. Serious adverse events occurred in 31 patients (10.8%) in the PAV+ group and in 28 patients (9.8%) in the PSV group (P=0.79).

CONCLUSIONS

The time to liberation from mechanical ventilation did not differ significantly between the group that underwent PAV+ and the group that underwent PSV. (Funded by the Canadian Institutes of Health Research and others; PROMIZING ClinicalTrials.gov number, NCT02447692.)

Of the 20 million people worldwide who undergo invasive mechanical ventilation each year, up to 35% will have difficult or prolonged weaning from the ventilator or will die during the weaning process.[1-4] Prolonged invasive ventilation is associated with an increased risk of complications, death, and long-term sequelae and an increased cost of care. The duration of ventilation is the main modifiable driver of long-term functional outcomes among survivors.[5,6] To minimize the duration of ventilation and maximize the proportion of patients who are successfully liberated from ventilation, guidelines promote both daily discontinuation of sedation and the use of daily spontaneous breathing trials (SBTs),[7,8] but implementation of these recommendations varies substantially.[2,9] The appropriate mode of ventilation to mitigate the risk of weaning failure is unclear.[10]

Rapid deconditioning of respiratory muscles during controlled ventilation under sedation has been described, and such deconditioning places patients at risk for prolonged weaning.[2,11] Early transition to a partial ventilatory support mode, in which the patient triggers every breath, may help to mitigate this risk. Pressure-support ventilation (PSV) is the most common partial ventilatory support mode used after the first few days of full ventilatory support,[12] but this mode has limitations: breathing may become passive after triggering of breathing has begun, and the patient's respiratory muscle activity cannot be evaluated. If not carefully adjusted, PSV may lead to over-assistance, diaphragmatic atrophy, and patient–ventilator dyssynchrony, all of which are associated with prolonged weaning.[11,13,14] Alternatively, proportional-assist ventilation with load-adjustable gain factors (PAV+) delivers assistance that is proportional to patients' efforts.[15,16] Clinicians can adjust the gain (i.e., the proportional assistance) to maintain a normal patient respiratory workload.[17] Previous studies have shown short-term advantages of PAV+ over PSV, including fewer adverse effects associated with ventilation, a decrease in dyspnea, and improved patient–ventilator synchrony and sleep quality.[18-24]

We hypothesized that PAV+ could improve patient-centered outcomes, potentially by reducing the risk of ventilator-induced diaphragm dysfunction and promoting safe reconditioning of respiratory muscles. The primary objective of the Proportional Assist Ventilation for Minimizing the Duration of Mechanical Ventilation (PROMIZING) trial was to determine whether ventilation with PAV+, instituted early after acute respiratory failure and set to maintain a normal range of breathing workload, would result in a shorter time to successful ventilator liberation than PSV, which was set to maintain a normal tidal volume and breathing frequency.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN AND OVERSIGHT

This trial was an investigator-initiated, multicenter, open-label, randomized, superiority trial. Details regarding the trial design and statistical analyses were described previously,[25,26] and the trial protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The trial was conducted at 23 hospitals in Argentina, Canada, France, Greece, Italy, Saudi Arabia, and Spain and was endorsed by the Canadian Critical Care Trials Group and Réseau Européen de Recherche en Ventilation Artificielle, also known as REVA. The appropriate research ethics board for each center approved the protocol, and all the patients or their substitute decision makers provided written informed consent. A data and safety monitoring committee independently reviewed safety data and adherence to the protocol twice yearly. Further details regarding the trial oversight are provided in the Supplementary Appendix, available at NEJM.org.

PATIENTS

We enrolled critically ill patients 18 years of age or older who had been receiving mechanical ventilation for at least 24 hours and were able to undergo PSV for at least 30 minutes but were not yet ready for liberation from ventilation. We used a staged recruitment process, with assessment of inclusion and exclusion criteria at each step, for enrollment and subsequent randomization of eligible patients. Patients who had severe chronic respiratory diseases or severe neurologic disorders were excluded, as were patients in whom withdrawal of life support was anticipated. Potential participants were screened daily until ventilator settings, blood-gas levels, and the hemodynamic status met enrollment criteria. Enrolled patients who had provided written informed consent had

to be receiving PSV for less than 24 hours or had to undergo a 30-minute PSV trial, followed by a blood-gas analysis.

To avoid the randomization of patients who were ready to breathe spontaneously, a specific successive-step process was used.[27] Patients could undergo randomization if, after successfully completing the PSV trial, they did not meet predefined standard weaning criteria (as described in the Supplementary Appendix), if they had a rapid shallow-breathing index of greater than 100 after 2 minutes without ventilatory support, or if they were unable to pass a 30-minute SBT. Patients were excluded if they had been receiving PSV for more than 24 hours, if they passed the SBT, or if they were considered for extubation within 24 hours. Patients could be randomly assigned with a priori or deferred consent, with consent to continued participation sought at the earliest possible time. Trial recruitment was paused in April 2020 during the coronavirus disease 2019 pandemic and subsequently resumed in accordance with local center policies.

RANDOMIZATION AND INTERVENTIONS

Participating sites underwent a "run-in" training phase with at least one patient undergoing each mode (PSV or PAV+) before being granted permission to randomly assign patients in the trial; details are provided in the protocol. These patients were not included in the analysis.

A centralized Web-based, concealed, computer-generated randomization sequence was used to randomly assign patients in a 1:1 ratio to undergo PAV+ or PSV with variable and undisclosed blocks and with stratification according to center. The clinicians and research assistants were aware of the intervention assignments, but the trial statistician was unaware of these assignments.

For patients who had been randomly assigned to undergo PAV+, ventilators that offered this mode were used (Puritan Bennett 840 or 980 ventilators, Medtronic); any ventilator could be used for patients who had been assigned to undergo PSV. Strict algorithms for adjusting PAV+ and PSV were provided to trial personnel; details are provided in the protocol. In brief, the support (gain) provided by PAV+ was adjusted to keep the peak respiratory muscle pressure generated by the patient in a normal target range (5 to 10 cm of water).[17] PSV was adjusted to keep the respiratory rate at 12 to 35 breaths per minute and the tidal volume at 5 to 10 ml per kilogram of predicted body weight. Airway occlusion pressure ($P_{0.1}$) was recorded but was not used to adjust the ventilation support. In both trial groups, the algorithms for adjustment provided adaptations for hypoventilation, hyperventilation, and respiratory distress, with criteria to switch to assist–control mode if the maximum settings were reached or if clinical instability occurred.

The weaning process, whereby patients were assessed once daily for criteria to initiate SBTs, was performed the same way in the two groups. SBTs were performed without ventilator support through a T-piece (or equivalent instrument); patients received supplemental oxygen, with a fraction of inspired oxygen of 0.40.[28] After a patient passed an SBT, extubation was to occur within 2 hours after meeting all extubation criteria. An indication for tracheostomy was at the discretion of the treating physician. To promote and monitor adherence to the protocol, clinical staff completed a daily case-report form to record ventilator settings, a checklist that prompted assessment for the performance of SBTs and extubation, and a survey question that assessed whether the clinical staff considered the ventilator strategy to be easy to use (referred to as user acceptance).

At each intensive care unit (ICU), nonrespiratory care interventions were at the discretion of the clinical team; guidelines were provided for sedation, nutrition, and early mobilization. Daily doses of opioids, sedatives, and antipsychotic medications were recorded, and scores for sedation or agitation and delirium were collected if they were available in the medical record.

Patients remained in the trial group to which they were assigned until successful liberation from ventilation, live discharge from the ICU, death, or 90 days after randomization, whichever came first. The vital status at 90 days was recorded.

OUTCOMES

The primary outcome was the time from randomization to successful liberation from mechanical ventilation, which was defined as the time of extubation or final separation from the ventilator, provided that the patient remained alive and free from invasive ventilation for 7 days.[2,3,28] Secondary ventilatory outcomes were the time

from randomization to live discharge from the ICU and from the hospital; death in the ICU, in the hospital, and by day 90; ventilator-free days; weaning progress (the time from randomization to the first SBT, to the first successful SBT, and to the first extubation or disconnection from the ventilator), the level of weaning difficulty (short, difficult, or prolonged),[2,3,10] and weaning complications; tolerance of the assigned ventilator mode (as measured by the use of the assist–control mode after randomization); and user acceptance of the assigned ventilator mode. In consultation with patient and family advisors, we devised an ordinal outcome that combined patient disposition and ventilation status at 90 days. Secondary concurrent-intervention outcomes included the change from baseline in the daily total doses of sedatives and opioids, indication for antipsychotic medication, and daily assessments of sedation or agitation and delirium. Safety outcomes were the incidence and severity of serious adverse events. Further details regarding the outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

As prespecified in the protocol, we used aggregate, blinded data from the first 120 patients who were enrolled in the trial to reestimate our sample size; the median time to successful liberation from ventilation in this cohort was 6.8 days. We then calculated the sample size that would be needed to provide the trial with 80% power, at a two-sided alpha level of 0.05, to detect a difference between the trial groups of 1 or 2 days with respect to the primary outcome on the basis of varying hazard ratios (see the Supplementary Appendix). We anticipated the enrollment of 1 patient per center per month and a maximum loss to follow-up of 5%[17,19]; on the basis of these assumptions, the randomization of a minimum of 558 patients during our planned enrollment period was considered to be feasible and would allow for the detection of a between-group difference in the median duration of ventilation of 1.78 days (7.70 days in the PSV group vs. 5.92 day in the PAV+ group, with a hazard ratio of 1.30).

The statistical analysis was performed in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines and the protocol and statistical analysis plan on an intention-to-treat basis.[25,26] The intention-to-treat population included all the patients who had undergone randomization and started the trial intervention. We also performed a per-protocol analysis, which included only the patients who had undergone randomization and remained in the trial until successful liberation from ventilation (see the statistical analysis plan). No interim analyses were performed. Data were examined for completeness; a minimal number of values were missing with respect to individual variables (≤2.6%), and data were missing for a minimal number of variables (<5%). Aside from one patient who had missing data as a result of withdrawal of consent, missing data were assumed to be missing completely at random owing to not being recorded in the patient's medical record.

The time from randomization to successful liberation from mechanical ventilation (the primary outcome) was summarized with the use of cumulative incidence curves, with death treated as a competing risk, and the groups were compared with Gray's test. The main analysis of the primary outcome was performed with the use of a multistate generalization of the Cox proportional-hazards model, which modeled the association between the trial intervention and all transitions in the model simultaneously. The effect of the intervention is expressed as a hazard ratio with a 95% confidence interval. Data from patients with missing outcomes were censored at the last contact. A cause-specific Cox model in which death that occurred before successful liberation from ventilation was treated as a censoring event was fit for comparison. The primary outcome was modified early in the trial, when a blinded aggregate analysis for sample-size verification showed that our original outcome of ventilator-free days at day 21 eclipsed the outcome of many patients who were still receiving ventilation at 21 days (see the protocol amendment for details).

Subgroup analyses of the primary outcome were performed on the basis of prespecified hypotheses, and a sensitivity analysis was performed in which successful liberation from ventilation was defined as at least 48 hours without reinstitution of ventilation. An additonal analysis of the primary outcome was performed with adjustment for prespecified covariates and clinically important baseline prognostic variables.

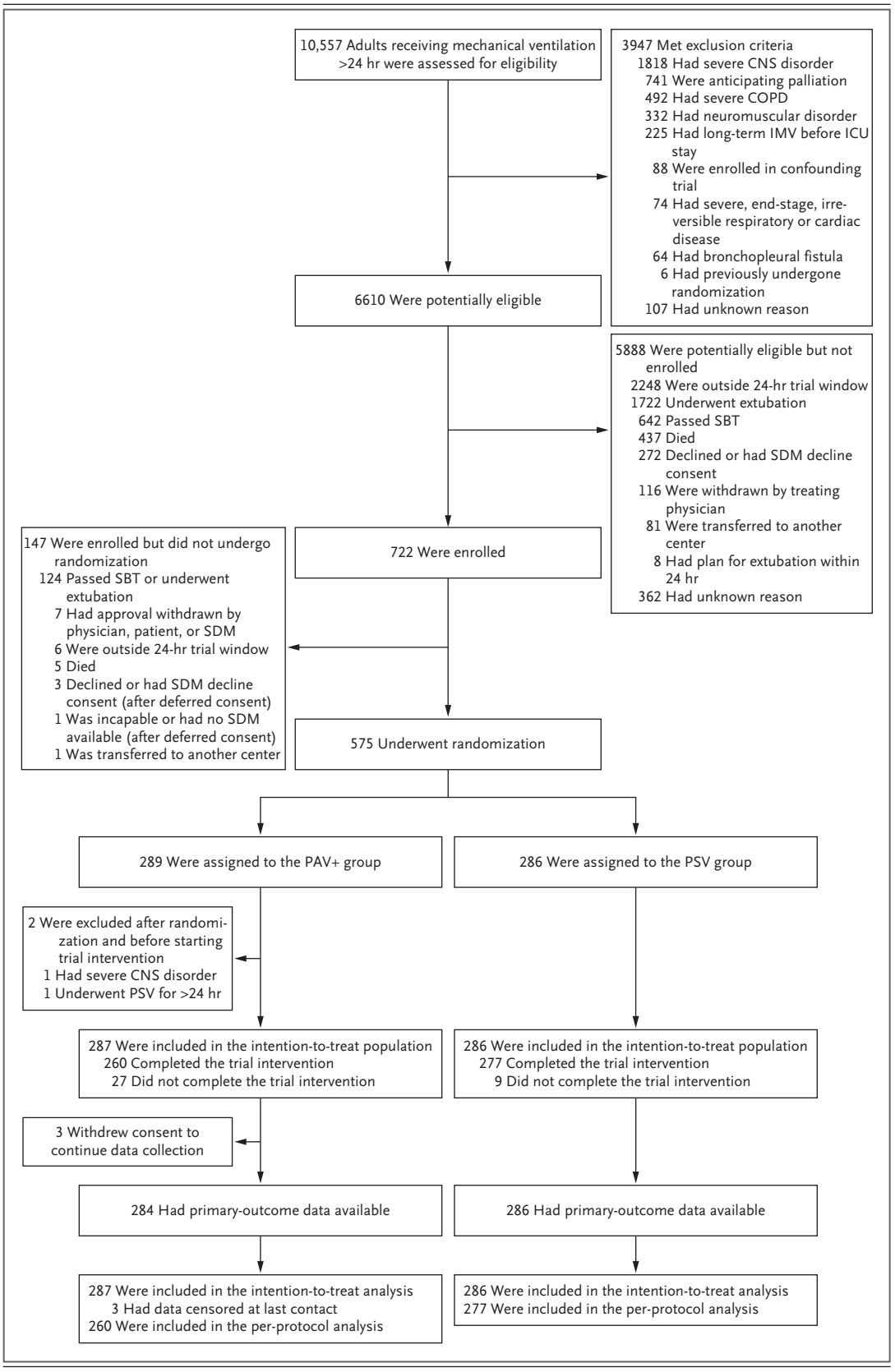


Figure 1 (facing page). Eligibility, Enrollment, Randomization, and Follow-up.

All 573 patients who started the trial intervention were included in the intention-to-treat analysis. Primary-outcome data were available for 570 patients (99.5%), and the vital status at day 90 was available for 572 patients (99.8%); 3 patients (0.5%) withdrew consent to continue data collection, and their data were censored at the last contact for the intention-to-treat analysis of the primary outcome. For the per-protocol analysis, patients were excluded if they did not complete the trial intervention through day 90. Of the patients assigned to receive proportional-assist ventilation with load-adjustable gain factors (PAV+), 27 patients stopped the trial intervention early for the following reasons: 10 were transferred to another intensive care unit (ICU), 4 had mode violations for more than 48 hours, 3 withdrew consent to continue the trial intervention, 3 were discovered to have a diagnosis of exclusion after they had undergone randomization, 1 transferred to a long-term ventilator ward, and 6 stopped the trial intervention before day 90 for other reasons. Of the patients assigned to receive pressure-support ventilation (PSV), 9 patients stopped the trial intervention early for the following reasons: 5 transferred to another ICU, 3 transferred to a long-term ventilator ward, and 1 withdrew consent to continue the trial intervention. CNS denotes central nervous system, COPD chronic obstructive pulmonary disease, IMV invasive mechanical ventilation, SBT spontaneous breathing trial, and SDM substitute decision maker.

For the secondary time-to-event outcomes, cumulative incidence curves were constructed to provide estimates of the outcome, which accounted for death, with the intervention effects expressed as hazard ratios with 95% confidence intervals from Cox models. The time to death was analyzed with the use of Kaplan–Meier curves and a log-rank test, with the intervention effect expressed as a hazard ratio with a 95% confidence interval. The difference between the trial groups in the median number of ventilator-free days is expressed with a 95% confidence interval obtained by bootstrap methods. The percentage of patients with short, difficult, or prolonged weaning[2,3,10] was summarized according to trial group. Daily sedative drug doses (converted to midazolam equivalents)[29] and opioids (converted to morphine equivalents)[30-32] relative to baseline doses were compared between the groups. The incidence of serious adverse events in each group was compared with the use of a chi-square test. All estimates are reported with 95% confidence intervals. The widths of the intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

RESULTS

PATIENTS AND INTERVENTIONS

Patients were enrolled between September 19, 2016, and June 15, 2023 (Table S1 in the Supplementary Appendix). Of 10,557 adult patients who had been receiving mechanical ventilation for at least 24 hours, 722 were enrolled in the trial, and 573 underwent randomization and were included in the intention-to-treat analysis. The most common reason for exclusion from the trial after enrollment was passing an SBT (Fig. 1).[33]

The characteristics of the patients at baseline were generally similar in the two groups (Table 1). A majority of the patients (465 [81.2%]) did not have premorbid frailty,[34] but many (380 [66.3%]) had a moderate-to-high burden of coexisting conditions.[35] Almost half the patients (272 [47.5%]) had a respiratory cause for ICU admission; most were primarily bacterial or viral pneumonia (137 patients) or acute respiratory distress syndrome (64 patients). At the time of enrollment, most of the patients had received opioid and sedative infusions. The trial cohort was representative of populations undergoing mechanical ventilation in high-income and high-to-middle-income countries (Table S2).

Measurements of respiratory variables obtained before and after randomization are provided in Table S3. After randomization, the mean (±SD) initial inspiratory pressure support in the PSV group was 10.8±3.0 cm of water, and in the PAV+ group, the mean gain (i.e., proportional assistance) was 65.0±10.1%; these findings led to similar tidal volumes and respiratory rates in the two groups (Fig. S1). In the PAV+ group, the peak respiratory muscle pressure remained in the normal target range on 1334 of 1662 trial days (80.3%), was greater than 10 cm of water on 212 trial days (12.8%), and was less than 5 cm of water on 116 trial days (7.0%) (Fig. S2). The mean airway occlusion pressure across the two groups was 2.4±3.6 cm of water with a similar distribution in the groups (Fig. S3). Major protocol deviations were infrequent; the use of nonprotocolized modes occurred on 169 of 6795 trial days (2.5%). Details regarding the adherence to the trial protocol and the reasons for nonadherence are provided in Table S4.

PRIMARY OUTCOME

The median time from randomization to successful liberation from mechanical ventilation was 7.3

days (95% confidence interval [CI], 6.2 to 9.7) in the PAV+ group and 6.8 days (95% CI, 5.4 to 8.8) in the PSV group (P=0.58 by Gray's test) (Table 2 and Fig. 2). In the multistate model, the hazard ratio for transitioning from ventilation to liberation from ventilation in the ICU was 0.96 (95% CI, 0.80 to 1.15) in the PAV+ group relative to the PSV group, with no state transition showing a significant hazard ratio of the intervention effect with PAV+ (Fig. S4).

The results of the subgroup analysis of the primary outcome (Fig. 3A) and those of the analysis that evaluated for an intervention effect according to trial center (Fig. S5) appeared to be

Table 1. Characteristics of the Patients at Baseline.*

Variable	Overall (N=573)	PAV+ (N=287)	PSV (N=286)
At the time of ICU admission			
Age — yr	62.1±14.5	62.3±13.8	62.0±15.2
Female sex — no. (%)	211 (36.8)	102 (35.5)	109 (38.1)
Body-mass index†	29.3±7.8	28.8±7.6	29.8±7.9
Median Clinical Frailty Scale score (IQR)‡	3 (2–4)	3 (2–4)	3 (2–4)
Median Charlson Comorbidity Index score (IQR)§	3 (2–6)	4 (2–6)	3 (2–6)
APACHE III score on ICU admission¶	80.26±26.6	81.9±27.2	78.4±25.8
APACHE III diagnosis — no. (%)			
Nonoperative	476 (83.1)	236 (82.2)	240 (83.9)
Operative	96 (16.8)	50 (17.4)	46 (16.1)
Category of diagnostic cause of admission — no. (%)			
Respiratory condition	272 (47.5)	135 (47.0)	137 (47.9)
Cardiovascular condition	91 (15.9)	49 (17.1)	42 (14.7)
Sepsis	69 (12.0)	29 (10.1)	40 (14.0)
Gastrointestinal condition	64 (11.2)	31 (10.8)	33 (11.5)
Neurologic condition	22 (3.8)	14 (4.9)	8 (2.8)
Other condition	54 (9.4)	28 (9.8)	26 (9.1)
From ICU admission to enrollment			
Use of glucocorticoids — no. (%)	278 (48.5)	126 (43.9)	152 (53.1)
Use of neuromuscular blockers — no. (%)	217 (37.9)	100 (34.8)	117 (40.9)
Use of opioid continuous infusion — no. (%)	483 (84.3)	241 (84.0)	242 (84.6)
Use of benzodiazepine continuous infusion — no. (%)	277 (48.3)	135 (47.0)	142 (49.7)
At time of enrollment or randomization			
No. of days in hospital, from hospital admission to randomization	10.8±11.4	10.1±9.4	11.5±13.0
No. of days in ICU, from ICU admission to randomization	7.1±5.6	6.8±5.1	7.5±6.1
Median no. of days of IMV receipt, at time of randomization (IQR)	4.9 (3.1–8.9)	4.8 (3.2–8.4)	5.0 (3.0–9.5)
Mode of IMV at time of enrollment — no. (%)			
PSV	505 (88.1)	253 (88.2)	252 (88.1)
Assist–control	60 (10.5)	31 (10.8)	29 (10.1)
PAV+	7 (1.2)	3 (1.0)	4 (1.4)
Median cumulative fluid balance (IQR) — liters	3.40 (1.44–7.78)	3.12 (1.41–7.42)	3.84 (1.48–8.31)
SOFA score — no. (%)‖	5.9 (3.1)	5.8 (3.2)	5.9 (2.9)
Use of vasopressors — no. (%)	275 (48.0)	132 (46.0)	143 (50.0)
Use of renal replacement therapy — no. (%)	84 (14.7)	37 (12.9)	47 (16.4)

Table 1. (Continued.)

Variable	Overall (N = 573)	PAV+ (N = 287)	PSV (N = 286)
Patient status in successive-step process for randomization — no. (%)**			
Patient did not meet weaning criteria	279 (48.7)	140 (48.8)	139 (48.6)
Patient did not pass CPAP trial for assessment of RSBI	219 (38.2)	109 (38.0)	110 (38.5)
Patient did not pass SBT	74 (12.9)	37 (12.9)	37 (12.9)

* Plus–minus values are means ±SD. The percentages may not total 100 because of rounding. All baseline data were missing for 1 patient in the PAV+ group (1 of 287 patients [0.3%]) owing to withdrawal of consent. One additional patient in the PAV+ group (total of 2 of 287 patients [0.7%]) had missing frailty results at baseline; and 15 additional patients (2.6%) had missing results for cumulative fluid balance at baseline, including 7 patients (2.4%) in the PAV+ group and 8 patients (2.8%) in the PSV group. Data are complete for all the other variables. CPAP denotes continuous positive airway pressure, ICU intensive care unit, IMV invasive mechanical ventilation, IQR interquartile range, PAV+ proportional-assist ventilation with load-adjustable gain factors, PSV pressure-support ventilation, RSBI rapid shallow-breathing index, and SBT spontaneous breathing trial.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores range from 1 to 9 (although patients with a score of 9 were not eligible for participation), with higher scores indicating worse frailty; scores higher than 4 are classified as frail.

§ Scores range from 0 to 37, with higher scores indicating a higher burden of coexisting conditions; scores of 3 or higher are classified as a moderate-to-high burden of coexisting conditions. Scores were derived with the use of a calculator at https://www.mdcalc.com/charlson-comorbidity-index-cci.

¶ The Acute Physiology and Chronic Health Evaluation (APACHE) III is a scoring system used in critically ill patients. Scores were calculated on the day of ICU admission. Scores range from 0 to 299, with higher scores indicating a higher severity of illness and a greater likelihood of death in the hospital. Missing values in any of the component scores were assumed to be a normal value of 0.

‖ The Sequential Organ Failure Assessment (SOFA) score was calculated on the day before randomization. Scores range from 0 to 24, with higher scores indicating more severe organ failure. Missing values in any of the component scores were assumed to be a normal value of 0.

** A staged recruitment process for enrollment and subsequent randomization was used, with assessment of inclusion and exclusion criteria or performance of tests (or both) at each step. Additional details are provided in the Supplementary Appendix.

generally consistent with the overall findings. The sensitivity analysis of the time to liberation from ventilation (Fig. S6) and the per-protocol analysis showed results that were similar to those of the main analysis.

DEATHS AND VENTILATION

Secondary outcomes are shown in Table 2, Table S5, and Figure 2. The incidence of death in the ICU, in the hospital, and by day 90 appeared to be similar in the two groups. The odds ratio for a better weaning category in the PAV+ group relative to the PSV group was 1.1 (95% CI, 0.81 to 1.50) (Fig. 3B). The percentage of patients in whom reintubation or reconnection to the ventilator was indicated was 22.2% (53 of 239 patients) in the PAV+ group and 23.3% (57 of 245 patients) in the PSV group. Overall, 110 patients underwent tracheostomy after randomization, including 58 patients (20.9%) in the PAV+ group and 52 patients (19.2%) in the PSV group. The percentage of patients who underwent noninvasive ventilation was similar in the two groups, and noninvasive ventilation was most often initiated preemptively to prevent extubation failure. The odds ratio for a higher-ranked status of a combination of patient disposition and liberation from ventilation at 90 days in the PAV+ group relative to the PSV group was 0.81 (95% CI, 0.58 to 1.14).

CONCURRENT INTERVENTIONS

With respect to sedative medications, the mean difference in the midazolam-equivalent dose at day 28 relative to the baseline dose was –1.51±3.28 mg per kilogram of body weight in the PAV+ group and 0.04±0.97 mg per kilogram in the PSV group (absolute difference, –1.55; 95% CI, –4.92 to 1.81). Opioid medications, which were converted to morphine equivalents, were weaned at similar rates over time in the two groups (Table S5B and Fig. S7). A total of 130 patients (45.3%) in the PAV+ group and 133 patients (46.5%) in the PSV group received an antipsychotic medication at least once. Patients were categorized as "alert and calm" or as being under "light sedation" on 5783 of 8403 daily assessments (68.8%) (Fig. S8A). Patients who were categorized as being under "deep sedation" could not undergo a delirium assessment. Patients who were assessed for delirium had a positive test on 324 of 1394 trial days (23.2%) in the PAV+ group and on 384

Table 2. Primary and Secondary Outcomes.

Outcome	PAV+ (N=287)	PSV (N=286)	Hazard Ratio or Relative Risk (95% CI)*	P Value	Absolute Difference (95% CI)†
Median time to event (95% CI) — days‡					
Successful liberation from ventilation: primary outcome	7.3 (6.2 to 9.7)	6.8 (5.4 to 8.8)	0.96 (0.80 to 1.15)	0.58	0.5 (–3.0 to 3.5)
Live ICU discharge	13.0 (10.7 to 15.2)	12.2 (9.9 to 14.1)	0.97 (0.80 to 1.17)	—	0.8 (–2.9 to 4.2)
Live hospital discharge	30.2 (27.0 to 35.5)	29.1 (25.4 to 37.9)	0.91 (0.75 to 1.12)	—	1.1 (–7.3 to 8.0)
Median no. of ventilator-free days (IQR)§					
At day 14	6.7 (0.0 to 10.9)	7.1 (0.0 to 11.3)	—	—	0.4 (–2.9 to 1.5)
At day 21	13.1 (0.0 to 17.9)	13.8 (0.0 to 18.2)	—	—	0.7 (–2.9 to 2.4)
At day 28	19.9 (0.0 to 24.8)	20.5 (0.1 to 25.2)	—	—	0.6 (–3.0 to 2.9)
Death — no./total no. (%)					
In the ICU	55/287 (19.2)	53/286 (18.5)	1.03 (0.74 to 1.46)	—	0.6 (–5.8 to 7.0)
In the hospital	78/287 (27.2)	73/286 (25.5)	1.06 (0.81 to 1.40)	—	1.7 (–5.6 to 8.9)
By day 21	42/287 (14.6)	44/286 (15.4)	0.95 (0.64 to 1.41)	—	–0.8 (–6.6 to 5.1)
By day 28	58/287 (20.2)	54/286 (18.9)	1.07 (0.77 to 1.50)	—	1.3 (–5.2 to 7.8)
By day 90	85/287 (29.6)	76/286 (26.6)	1.13 (0.83 to 1.54)	—	3.0 (–4.3 to 10.4)
Weaning progress: median time to event (95% CI) — days					
First SBT	2.7 (2.1 to 3.3)	2.2 (1.9 to 2.7)	0.91 (0.77 to 1.09)	—	0.5 (–0.4 to 1.2)
First successful SBT	4.1 (3.7 to 5.8)	4.1 (3.2 to 5.4)	0.96 (0.80 to 1.15)	—	0.0 (–1.3 to 1.9)
First extubation or disconnection from ventilator	5.2 (4.2 to 6.4)	4.2 (3.3 to 5.4)	0.88 (0.74 to 1.05)	—	1.0 (–0.7 to 2.3)
Level of weaning difficulty — no./total no. (%)¶					
Short weaning	99/260 (38.1)	95/269 (35.3)	—	—	2.8 (–5.5 to 11.0)
Difficult weaning	77/260 (29.6)	83/269 (30.9)	—	—	–1.2 (–9.1 to 6.6)
Prolonged weaning	49/260 (18.8)	52/269 (19.3)	—	—	–0.5 (–7.2 to 6.2)
Unable to wean and still receiving ventilation at day 90	2/260 (0.8)	4/269 (1.5)	—	—	–0.7 (–2.5 to 1.1)
Died before successful liberation	33/260 (12.7)	35/269 (13.0)	—	—	–0.3 (–6.0 to 5.4)
Weaning complications — no./total no. (%)					
Noninvasive ventilation initiated after extubation	71/231 (30.7)	69/240 (28.8)	1.10 (0.74 to 1.63)	—	2.0 (–6.3 to 10.2)
Tracheostomy performed after randomization‖	58/277 (20.9)	52/271 (19.2)	1.12 (0.73 to 1.70)	—	1.8 (–5.0 to 8.5)
Ventilation continued >7 days after randomization**	146/278 (52.5)	129/275 (46.9)	1.25 (0.90 to 1.75)	—	5.7 (–2.7 to 13.9)
Ventilation continued >21 days after intubation††	80/259 (30.9)	84/256 (32.8)	0.92 (0.63 to 1.33)	—	–1.9 (–10.0 to 6.1)
Reintubation performed <7 days after planned extubation‡‡	53/239 (22.2)	57/245 (23.3)	0.93 (0.61 to 1.44)	—	–1.1 (–8.6 to 6.4)
Ordinal outcome: status of combination of patient disposition and liberation from ventilation at 90 days — no./total no. (%)§§					

Table 2. (Continued.)

Outcome	PAV+ (N=287)	PSV (N=286)	Hazard Ratio or Relative Risk (95% CI)*	P Value	Absolute Difference (95% CI)†
Died	85/284 (29.9)	76/286 (26.6)	—	—	3.4 (–4.0 to 10.7)
Still receiving ventilation at any location	2/284 (0.7)	4/286 (1.4)	—	—	–0.7 (–2.4 to 1.0)
Not receiving ventilation but in hospital or ICU	21/284 (7.4)	14/286 (4.9)	—	—	2.5 (–1.4 to 6.4)
Discharged from hospital and no longer receiving ventilation	176/284 (62.0)	192/286 (67.1)	—	—	–5.2 (–13.0 to 2.7)
Concurrent-intervention outcome: delirium — no. of trial days/total no. of trial days (%)¶¶					
Too sedated to assess for delirium	872/2266 (38.5)	782/2235 (35.0)	—	—	3.5 (0.7 to 6.3)
Positive test for delirium	324/1394 (23.2)	384/1453 (26.4)	—	—	–3.2 (-6.4 to 0)
Use of assist–control mode					
Use of assist–control mode at least once — no./total no. (%)	169/287 (58.9)	142/286 (49.7)	1.2 (1.0 to 1.4)	—	9.2 (1.1 to 17.4)
Median duration of assist–control use (IQR) — days	0.44 (0.00 to 3.31)	0.00 (0.00 to 1.66)	—	—	0.44 (0.03 to 0.67)
Safety — no./total no. (%)‖					
Serious adverse event	31/287 (10.8)	28/286 (9.8)	—	0.79	1.0 (–4.0 to 6.0)
Nonsevere self-extubation	14/287 (4.9)	7/286 (2.4)	—	0.19	2.4 (–0.6 to 5.5)

* Hazard ratios are provided for time-to-event outcomes, and relative risks for binary outcomes. Unadjusted hazard ratios or relative risks and 95% confidence intervals are shown. Fully adjusted models were adjusted for duration of mechanical ventilation before randomization, prerandomization level of weaning difficulty, failed extubation before randomization, Clinical Frailty Scale score, cumulative fluid balance, prerandomization sedation or agitation category, coronavirus disease 2019 status, SOFA score at baseline (the day before randomization), and APACHE III score (data not shown).

† The absolute differences between the percentages are shown in percentage points. Confidence intervals for the absolute differences between medians were calculated with the use of 5000 bootstrap samples. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

‡ The primary outcome was the time from randomization to successful liberation from mechanical ventilation, which was defined as the time of extubation or final separation from the ventilator, provided that the patient remained alive and free from invasive ventilation for 7 days. Primary-outcome data were unavailable for 3 patients who withdrew consent; the data for these patients were censored at the time of last observation for time-to-event outcomes.

§ Ventilator-free days were defined as the number of days that patients were alive and free from invasive ventilation after successful liberation from ventilation. Patients who died before liberation from ventilation had zero ventilator-free days.

¶ Short weaning was defined as successful liberation from ventilation less than 1 day after the first SBT or extubation or disconnection from the ventilator. Difficult weaning was defined as successful liberation at least 1 day, but less than 7 days, after the first SBT or extubation or disconnection from the ventilator. Prolonged weaning was defined as successful liberation 7 or more days after the first SBT or extubation or disconnection from the ventilator. This analysis excluded patients who were lost to follow-up for reasons other than death (withdrawal of consent in 3 patients), as well as those who died before liberation from ventilation without any SBT attempt (41 patients). The level of weaning difficulty is an ordinal outcome.

‖ This analysis included only patients who had not undergone tracheostomy before randomization.

** This analysis included only patients who survived and remained in the trial beyond day 7.

†† This analysis included only patients who survived and remained in the trial beyond day 21.

‡‡ This analysis included only patients who had had at least one extubation and were alive for a minimum of 7 days after extubation. Therefore, patients who died within 7 days after extubation were excluded.

§§ This analysis excludes 3 patients in the PAV+ group whose data were missing owing to withdrawal of consent for ongoing data collection.

¶¶ Data on daily assessment for delirium were obtained from the medical record, if available. The denominator in each group is the number of trial days that data on delirium assessment were available. Patients assessed for delirium could be classified as "too sedated to assess for delirium," "delirious," or "not delirious." The analysis for a positive test for delirium excluded patients who had been classified as "too sedated to assess for delirium."

‖‖ Safety outcomes were compared with the use of chi-square tests.

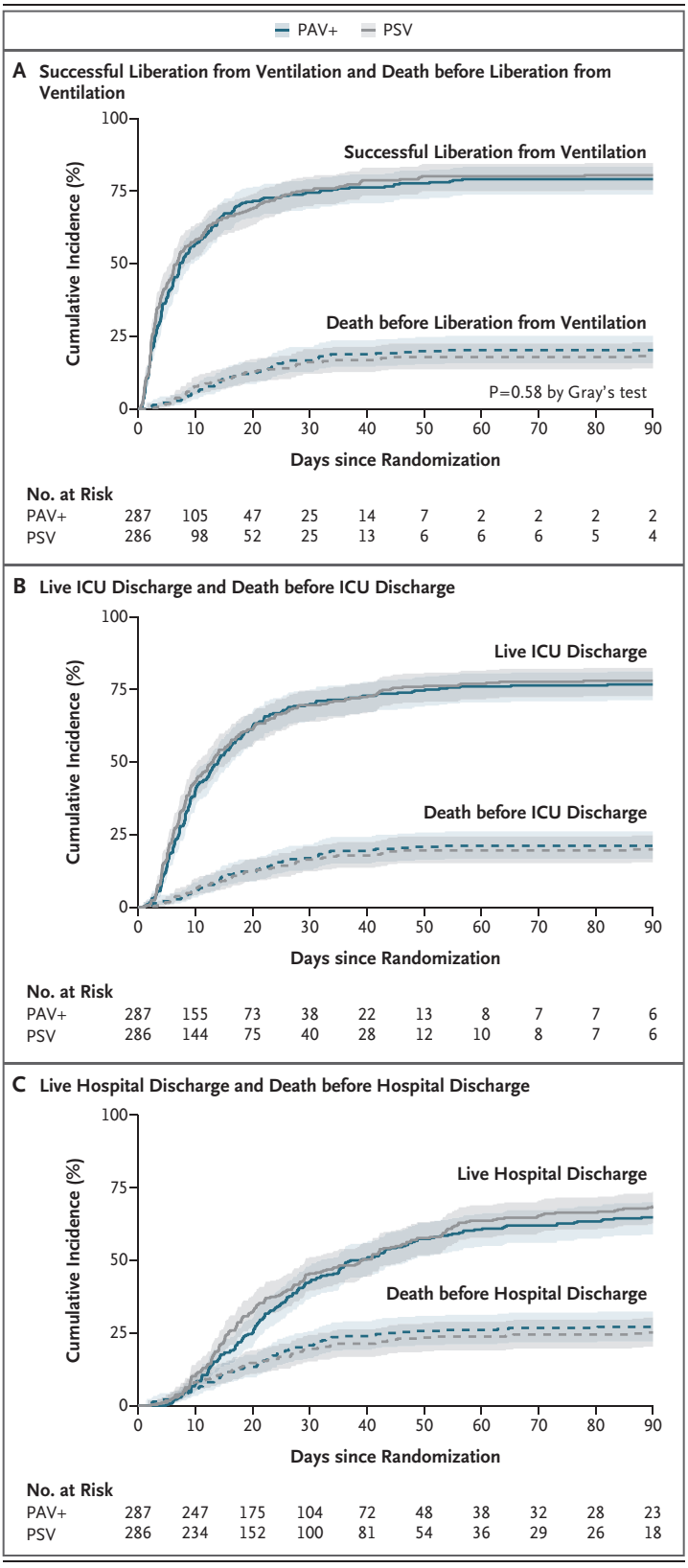


Figure 2. Cumulative Incidence Curves for Successful Liberation from Invasive Mechanical Ventilation, Live ICU Discharge, and Live Hospital Discharge, with Death as a Competing Risk.

Panel A shows the cumulative probability of successful liberation from ventilation and of death before successful liberation. The time of successful liberation was defined as the time of extubation or final disconnection from the ventilator, provided that the patient remained alive and free from invasive ventilation for 7 days. Patients were followed until successful liberation, death, or 90 days after randomization, whichever came first. Panel B shows the cumulative probability of live ICU discharge and of death before live ICU discharge. The time of live ICU discharge was defined as the time that the patient left the ICU after liberation from the ventilator, provided that the patient remained alive and ventilator-free for 7 days and did not return to the ICU for 48 hours. Transfers between ICUs while the patient was still undergoing mechanical ventilation were not considered to be live ICU discharges. Panel C shows the cumulative probability of live hospital discharge and of death before live hospital discharge. The time of live hospital discharge was defined as the time that the patient was discharged from the hospital to a home, long-term care facility, or rehabilitation center. Transfers between hospitals for receipt of ongoing acute care were not considered to be live hospital discharges. The shaded areas indicate 95% confidence intervals.

of 1453 patient-days (26.4%) in the PSV group (Fig. S8B).

USE OF ASSIST–CONTROL MODE AND EASE OF USE

Assist–control mode was used at least once in 169 patients (58.9%) in the PAV+ group and in 142 (49.7%) in the PSV group (relative risk, 1.2; 95% CI, 1.0 to 1.3) (Fig. S9). Clinicians indicated that the PAV+ ventilation strategy was easy to use on 75.7% of trial days and that the PSV strategy was easy to use on 92.0% of trial days (Fig. S10).

SAFETY OUTCOMES

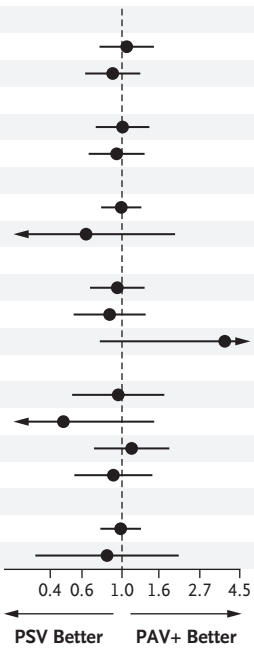
Serious adverse events occurred in 31 patients (10.8%) in the PAV+ group and in 28 (9.8%) in the PSV group (P=0.79). There were also no significant differences between the two groups in either the severity of serious adverse events or the relatedness of serious adverse events to the trial intervention; 3 of the 88 serious adverse events that occurred (3.4%) were considered by the investigator to be probably or definitely related to the trial intervention (Table S6).

DISCUSSION

Although meta-analyses suggest that PAV+ results in a shorter duration of mechanical ventilation and a shorter ICU length of stay than PSV,[36-39] this multicenter trial showed that PAV+ did not lead to a shorter time to successful liberation from ventilation than PSV when each method was introduced at the point at which patients started to be able to undergo partial ventilatory support. Other ventilation-related outcomes and the incidence of death were similar in the two groups.

A Subgroup Analysis of the Primary Outcome

Subgroup	PSV	PAV+	Hazard Ratio (95% CI)
	no. of events/no. of patients		
Duration of mechanical ventilation before randomization			
≤5 days	111/143	119/148	1.06 (0.76–1.48)
>5 days	119/143	106/138	0.89 (0.63–1.25)
Weaning status before randomization			
Did not pass SBT or CPAP trial for assessment of RSBI	120/147	120/146	1.01 (0.72–1.40)
Did not meet weaning criteria	110/139	104/140	0.93 (0.66–1.32)
Unsuccessful extubation before randomization			
No	218/272	216/276	0.99 (0.78–1.26)
Yes	12/14	9/11	0.63 (0.21–1.94)
Frailty at baseline			
None	140/165	142/172	0.94 (0.67–1.32)
Mild	85/111	75/103	0.85 (0.55–1.34)
Severe	5/10	8/10	3.71 (0.76–18.09)
Sedation level at randomization			
Alert and calm	54/65	53/61	0.95 (0.54–1.69)
Restless or agitated	14/14	17/21	0.47 (0.15–1.49)
Light sedation	84/111	82/103	1.13 (0.71–1.81)
Moderate to deep sedation	78/96	73/102	0.90 (0.55–1.45)
Covid-19 status			
Not present	213/265	211/268	0.98 (0.77–1.26)
Present	17/21	14/19	0.83 (0.33–2.04)



B Weaning from Mechanical Ventilator

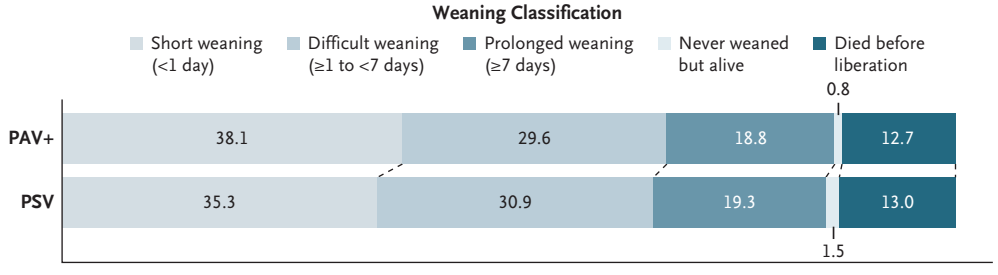


Figure 3. Subgroup Analysis of the Primary Outcome and Weaning Classification.

Panel A shows a forest plot of the hazard ratio for successful liberation from mechanical ventilation in prespecified subgroups. A positive coronavirus disease 2019 (Covid-19) status indicates a positive test for severe acute respiratory syndrome coronavirus 2. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Panel B shows the percentage of patients classified as having short, difficult, or prolonged weaning from the mechanical ventilator; as never having been weaned; or as having died after the first SBT or the first extubation attempt. Patients who died before having a first SBT or a first extubation attempt (41 patients) or who had missing outcome data owing to withdrawal of consent (3 patients) were excluded from this analysis. Of the remaining 529 patients, 36.7% were classified as having short weaning, 30.2% as having difficult weaning, and 19.1% as having prolonged weaning; 1.1% of the patients were alive but still receiving invasive ventilation at day 90; and 12.9% died while still receiving mechanical ventilation. CPAP denotes continuous positive airway pressure, and RSBI rapid shallow-breathing index.

The unique breath-delivery and closed-loop measurements of respiratory-system compliance and resistance with the use of PAV+ afford diaphragm- and lung-protective ventilation[40] and offer several advantages over PSV.[18-24] To test our hypothesis that these physiological benefits would translate into improved clinical outcomes, we designed a randomized trial that strictly controlled for variables known to influence weaning outcomes. The trial used a rigorous approach to determine the earliest possible initiation of the weaning and liberation process and mandated daily assessments for SBT readiness. The international WEAN SAFE trial showed that delays in initiating SBTs were associated with subsequent weaning failure.[2] Our enrollment strategy was designed to identify patients who were capable of transitioning to partial ventilatory support but also to ensure that patients needed ongoing mechanical ventilation. We recently showed that this strategy resulted in 25% of the patients being enrolled but not undergoing randomization because they passed an SBT and rapidly and safely underwent extubation, despite being expected to need ventilation for at least 24 more hours.[33] After randomization, SBTs were mandated on the basis of the same criteria and technique in both trial groups. Prompt extubation was recommended when patients passed SBTs, and this process was accomplished with excellent adherence to the protocol.

In addition to instituting best-evidence practices for weaning, the PSV and PAV+ strategies were treated similarly in the protocol so that a difference in outcome would be attributable to the mode rather than to variability in the approach for setting the ventilator. Our PAV+ algorithm mandated the maintenance of respiratory effort within a normal range. By specifying a target range for respiratory rate and tidal volumes, the PSV strategy may have exacted a more consistently controlled delivery of pressure support than that which occurs with usual care. An index of respiratory drive ($P_{0.1}$) was in the normal range in a similar percentage of patients in the two groups, which suggests that the respiratory effort was similar with both interventions. The weaning outcome may be more dependent on a systematic approach than on the ventilation mode itself when the settings are carefully controlled.

The findings of the PROMIZING trial contrast with those of other clinical trials of proportional modes of ventilation that show favorable results. A randomized clinical trial that was performed at a highly experienced center showed less need for alarm interventions and significantly fewer switches to assist–control mode with PAV+ than with PSV in the first 48 hours of assisted ventilation.[23,41] In our trial, clinicians switched to assist–control mode more often with PAV+ than with PSV and reported more ease of use with PSV than with PAV+. These results may reflect a lack of familiarity with PAV+ in some participating centers. A randomized clinical trial in which neurally adjusted ventilatory assist (NAVA) — another proportional mode of ventilation — was evaluated showed a shorter time to ventilator liberation in the NAVA group than in a control group in which the choice of mode (assist–control, pressure-regulated volume control, or PSV) was at the clinician's discretion.[42] Possible explanations for our findings include the lack of a "usual care" group, the possibility that the clinicians may not have been sufficiently familiarized with PAV+, and the possibility that the mode itself does not affect weaning time.

Two hypothesis-generating findings regarding the use of concurrent interventions may merit formal testing. The trajectory of weaning sedatives over time may be more rapid with PAV+ than with PSV. The administration of sedative medications was not specified in the trial protocol; only recommendations were provided. Similarly, the results suggest a slightly lower number of trial days of delirium with PAV+ than with PSV, although this finding is limited by missing data. The reduction of both sedation and delirium is an important clinical goal. Future research should explore the relationship between sedation, delirium, and neurocognitive outcomes with PAV+.

The PROMIZING trial is among the largest trials to date in which PAV+ was compared with PSV, and the trial is further strengthened by thorough data collection and a high level of follow-up through day 90. The trial sites were primarily academic centers with expertise in mechanical ventilation, which may limit the generalizability of our findings. Furthermore, the control group in our trial was not usual care, which may include the use of assist–control mode until SBTs

are started; whether our algorithms for PAV+ and PSV would perform better or worse than usual care is unknown. At the time of randomization, the patients had been receiving ventilation for approximately 5 days; the effect of earlier introduction of PAV+ is not known. As in many critical-care trials, the inclusion of a heterogeneous population of critically ill patients may have obscured a positive result in some subgroups of patients. We tested one method of setting PAV+ gain on one brand of ventilator. PAV+ will be available in the future on other ventilators with potentially different ways of setting the gain. Whether other features will enhance PAV delivery and clinical outcomes would require further study.

In this trial, the time to liberation from mechanical ventilation did not differ significantly between the PAV+ and PSV ventilation algorithms, whereby the settings were carefully adjusted and the liberation process was strictly controlled.

Supported by a project grant (PJT-162086) and an industry-partnered collaborative research grant (IPR-136755) from the Canadian Institutes of Health Research, with Covidien, a Medtronic company, as the industry partner (ISR 2014-10481), and by the University of Western Ontario Department of Medicine Program of Experimental Medicine. Laurent Brochard is supported by the Keenan Chair in Critical Care and Respiratory Failure.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial and their families; the members of the data and safety monitoring committee for their contributions during the 7-year enrollment period; Dr. B. Taylor Thompson (Boston); Dr. Maureen Meade (Hamilton, ON, Canada); Dr. Jean-Daniel Chiche (Lausanne, Switzerland); Dr. Charles (Charlie) Keown-Stoneman (senior research biostatistician at the Applied Health Research Centre [AHRC], Toronto, ON, Canada) for insightful discussions on statistics throughout the analysis; all the research personnel at the AHRC who helped us with trial management during the 11-year trial; and all our collaborators.

This work is dedicated to the memory of our collaborator, mentor, and friend, Dr. Jordi Mancebo Cortés, as well as his collaborator, Dr. Juan Carlos Suárez Montero, whose help and dedication in successfully conducting the PROMIZING trial have been essential.

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