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6 7 8	3	Short-title: PAV+ for mechanical ventilation in the ICU
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Abstract

Background

- Mechanical ventilation is a cornerstone of the intensive care unit (ICU) and has been vital
- during the coronavirus pandemic, but it adds expense to what is already one of the highest
- cost care settings. As hospitals expand ICU capacity during the pandemic, optimizing
- provision of MV could provide patient and cost benefits, whilst also alleviating pressure on
- hospital capacity. Here, the cost-effectiveness of proportional-assist ventilation with load
- adjustable gain factors (PAV+ mode) versus pressure-support ventilation (PSV), is evaluated.

Methods

- A published Markov model of the care pathway for mechanically ventilated ICU patients was
- adapted to the Canadian public-payer perspective. Outcomes of interest were the cost of care
- in year one, and the cost-effectiveness of PAV+ mode versus PSV after 20 years. Clinical and
- cost model inputs (2017 CAD [\$]) were informed by a structured literature review of
- PubMed. In an update to the published model, comparative effectiveness of PAV+ mode
- versus PSV was determined via pragmatic meta-analysis.

Results

- PAV+ mode was considered likely to be cost-effective compared to PSV, having a cost per
- quality-adjusted life year gained of \$6,575 after 20 years. Over 20 years, higher care costs were driven by increased patient survival, and in cost-effectiveness acceptability analysis,
- 95% of simulations would be cost-effective at a willingness-to-pay threshold of \$14,729.
- Over one year, use of PAV+ mode reduced care costs (\$53,898 versus \$60,271).

Interpretation

Use of PAV+ mode is expected to benefit patient care in the ICU and be a cost-saving or cost-effective alternative to PSV.

Keywords

Critical Care; Respiration, Artificial; Economics, Medical; Health Care Costs; Hospital Costs

Introduction

Mechanical ventilation (MV) is an important component of patient critical care. A report on intensive care unit (ICU) usage in Canada suggests 33% of ICU patients in 2013-14 needed invasive ventilation,¹ and MV is increasingly being used in patients admitted to the ICU.² Awareness of MV has increased in the current global coronavirus disease 2019 (COVID-19) health crisis, where ventilator support has become an essential component of care for patients suffering hypoxia and acute respiratory distress syndrome that often accompanies the disease.³ A review of published studies from around the world found 29%–90% of patients with COVID-19 admitted to ICUs received invasive MV.⁴ With COVID-19 disrupting the availability of critical care resources,⁶ including MV, and straining hospital finances due to cancellation of elective surgeries,⁷ there is increasing need for strategies to optimize use of

- critical care resources. Even pre-COVID-19, Ontario alone saw ~125,000 patients requiring MV in ICUs, accounting for around 570,000 days of ventilation, from 2009–2012.5 Ventilation support can be delivered via a variety of modes, such as those which target a preset volume or constant pressure of inspired air. Constant pressure ventilation, in the form of pressure support ventilation (PSV), is the most common mode of ventilator support used worldwide after the initial acute phase of critical illness.⁵ It works by delivering airflow until a target pressure is reached, and held constant for a duration that is influenced by the patient's respiratory system mechanics. While this method is effective at overcoming the resistive and elastic forces limiting the patient's capacity to sustain the work of breathing independently, clinicians cannot know the work performed by the patient's respiratory muscles. Patient-ventilator interaction can therefore be suboptimal, with risk of promoting diaphragm atrophy or inducing a form of muscle strain injury.^{8,9} Asynchrony between patient breathing and ventilator delivery is also a potential problem of PSV,¹⁰ and it has been associated with increased requirements for tracheostomy,¹¹ longer time on MV,¹² and higher ICU mortality.12,13 To improve the patient-ventilator interaction, adaptive modes of ventilation were developed, whereby the volume or pressure of air is modulated within each breath.¹⁴ One such adaptive mode is proportional-assist ventilation with load-adjustable gain factors (PAV+ mode) in which respiratory system capacity is measured to help offload the respiratory muscle work in a relationship proportional to patient effort. This allows for measurement and control of the level of respiratory muscle work to ensure it remains in an optimal range,^{15–17} and helps improve the coupling of patient and ventilator inspiratory and expiratory times.¹⁸ Multiple studies suggest a clinical benefit of PAV+ mode over PSV,^{18–20} however it is unknown if increasing use of PAV+ mode in Canadian ICUs would result in resource use
- ³⁵ 91 savings and be cost effective. In this study we synthesize available evidence to explore the
- utility and cost-effectiveness of PAV+ mode in the Canadian setting.

93 Methods

- 40 94 Ventilation patient care pathway and model development
- The published Markov cohort cost-utility model²¹ considered patient care from the point of initiating invasive MV (Figure 1). While on MV, patients could be synchronous or asynchronous with the ventilator. Synchronous patients had a higher probability of being stable during a spontaneous breathing trial (SBT) and progressing to extubation (being removed from the ventilator).²² After successful weaning, patients were in the ICU without MV before transfer to the general ward (GW) and subsequent discharge. The model has daily cycles, such that a patient can move between health states (e.g. from asynchronous to synchronous MV, or from ICU to GW) once per day. At any stage of the pathway, patient mortality was possible. Adverse events (AEs) considered during care were tracheostomy, ventilator-associated pneumonia (VAP), other nosocomial infection, and reintubation. The published model contained a single health state for "weaning", depicted by an SBT and extubation occurring as one step.²¹ For the Canadian setting, an additional health state of liberation was included after the SBT to formalize the weaning process and liberation from the ventilator (Figure 1). Patients failing the SBT remain on the ventilator until their next

- SBT, while those passing are assessed for extubation. During the liberation phase, patients
- are extubated and then monitored closely to ascertain whether they can breathe unaided and
- clear secretions sufficiently without the need for an artificial airway (endotracheal tube). The
- outcomes of this state are remaining in the liberation phase (being in the ICU without MV),
- returning to MV in the ICU, or progression to the GW without MV.

Model outputs

- Outcomes of interest in this health-economic model were total costs of care and patient
- quality of life (QoL). Cost-effectiveness was reported as an incremental cost-effectiveness
- ratio (ICER), measured as the cost per quality-adjusted life year (QALY) gained.

Model inputs

- A structured literature review (see Appendix) was conducted to identify relevant data. As
- multiple efficacy data sources for PAV+ mode versus PSV were identified, to best
- summarize PAV+ mode efficacy, a pragmatic meta-analysis was performed to prevent
- introduction of bias from arbitrary selection of a single study (see Appendix). Additional
- inputs for MV that can impact on costs and patient QoL considered were initial one-off cost
- of PAV+ mode, time on MV, time in the ICU, time in hospital, ICU mortality, hospital
- mortality, occurrence of AEs, and outpatient mortality. Cost inputs from the public payer perspective, were sourced from the literature review where available and otherwise identified
- through reports from Canadian authorities and the Canadian Management Information
- Systems Database. All costs are reported in 2017 CAD (\$), with costs from earlier years
- inflated to 2017 using the Canadian consumer price index for healthcare (Statistics Canada,
- Table 326-0021). Half-cycle correction was applied to both costs and OoL.

Time horizon and discounting

- The model considers short-term (1 year) and long-term (20 years) time horizons. The former is to assess the immediate impact of a change in ventilation mode (a patient stay in ICU is often less than one month, and so all relevant clinical outcomes are realized within one year) and the latter to cover the assumed lifespan of a patient, given the base case mean age of 67 years. Costs and QoL utilities (measured using the EuroQoL 5 dimensions survey [EQ-5D]) incurred after the first year are discounted at 1.5% per annum in line with guidelines from the Canadian Agency for Drugs and Technologies in Health.²³ The full list of model parameters
- is provided in Table 1.

Statistical analysis

- The robustness of the base case results was assessed through probabilistic sensitivity analysis (PSA), whereby the model is run repeatedly (2,000 times) and for each iteration, each input parameter is sampled from a distribution around the base case (default) value. The distribution is defined by the uncertainty (standard deviation, interguartile range, or 95% confidence interval) provided in the source publication. The distribution is normal for most inputs but is log-normal for odds ratios. The results of these analyses are presented as median (95% credible interval [CrI]) and as a cost-effectiveness scatter plot. The willingness-to-pay (WTP) threshold was set at \$50,000 per QALY gained, in the suggested \$20,000 to \$100,000 range.²⁴ Scenario analyses were additionally conducted.

3 150 Ethics approval

⁴ 151 The study is an economic model informed by aggregate data from published literature. The

 $\frac{5}{6}$ 152 study was deemed exempt from ethics commission review (independent assessments by the

¹⁵³ clinical author and the data protection officer of Coreva Scientific) as no human patients are

treated or face risk of harm in the performance of this work.

¹⁰ 155 **Results**

¹² 156 Seven clinical studies comparing PAV+ mode with $PSV^{18-20,22,25-27}$ were identified from

- ¹³ 157 studies known to the clinical author (KJB) and identified in systematic reviews.^{28,29} As these
- 14 157 studies known to the united autor (RSD) and identified in systematic reviews. This systematic reviews^{28,29} did not report on all outcomes required for our model, and no
- 16 159 individual study among those identified in the literature review presented robust clinical data
- 17 160 on the required model inputs, comparative efficacy of PAV+ mode versus PSV was
- ¹⁸ 161 determined via a pragmatic meta-analysis (see Appendix). For dichotomous endpoints, PAV+
- 162 mode was associated with improved, although not always statistically significant, outcomes.
- 21 163 PAV+ mode was associated with a significant reduction in ICU length of stay and time on
- MV (see Appendix). All findings were included as model inputs (Table 1).

24 165 Cost-effectiveness of PAV+ mode versus PSV

Base case cost-effectiveness results are shown in Table 2. Over one year, the cost of care per 166 25 26 patient was \$6,373 less costly with PAV+ mode (\$53,898) compared with PSV (\$60,271). In 167 27 the PSA, there was a 95.8% chance of PAV+ mode being cost saving at one year (Figure 2), 168 28 with the median (95% CrI) saving being \$6,667 (-\$1,208 to \$14,782). Over one year, use of 169 29 PAV+ mode resulted in 0.04 extra QALYs (0.29 vs. 0.25). The increase in QALYs occurred 170 30 31 171 in 100% of simulations in the PSA, and there was a 99.6% likelihood of PAV+ mode being 32 172 cost effective at the WTP threshold of \$50,000 per QALY gained. 33

34 Over 20 years, the cost of care per patient with PAV+ mode (\$144,041) was \$6,065 higher 173 35 174 than with PSV (\$137,976). With PAV+ mode, patients lived on average 1.44 years longer 36 and accumulated an additional 0.92 QALYs. In the base case, the cost per QALY gained at 175 37 20 years was \$6,575 (Table 2). In the PSA, at 20 years there was a 19.9% chance of PAV+ 38 176 39 177 mode being cost saving and all simulations led to increased QALYs. The likelihood of PAV+ 40 178 mode being cost effective at a WTP threshold of \$50,000 was 100% with a 20-year time 41 179 horizon (Figure 2). 42

- ⁴³ ⁴⁴ 180 Varying the WTP threshold influenced whether the use of PAV+ mode versus PSV mode
- 45 181 would be considered cost-effective (**Figure 3**). With a time horizon of 1 year, most PSA 46 182 simulations were dominant. Over a 20-year time horizon, the WTP threshold at which 95
- simulations were dominant. Over a 20-year time horizon, the WTP threshold at which 95% of
 simulations would be considered cost-effective was found to be \$14,729.
- 49 Scenario analyses were performed to understand if certain model parameters were driving the 184 50 results and how PAV+ mode performed in different conditions. The meta-analysis performed 185 51 here determined that PAV+ mode was associated with significantly shorter time on MV and 186 52 187 in hospital, but differences in most AEs did not reach significance. Running the model with 53 54 188 only significant differences included did reduce the cost and QALY benefit of PAV+ mode 55 189 but did not change overall outcomes (Table 3). At 20-years, cost and QALY outcomes for 56 190 PAV+ mode versus PSV were +\$425 and +0.53, respectively, giving an ICER of \$802 per 57 191 QALY gained. A younger or more female patient population had little impact on either 58
- 59 60

- 192 absolute or relative results (**Table 3**). The same was true if PSV had a purchase cost or if the
- ⁴ 193 difference in asynchrony between PAV+ mode and PSV was eliminated. Including costs per day for ICU and GWs from the Canadian Institute for Health Information rather than from
- day for ICU and GWs from the Canadian Institute for Health Information rather than from
 published literature increased the saving with PAV+ mode at one year by 27.7% (Table 3).
- ⁸ 196 The most notable change to the base case came from use of Canadian data instead of meta-
- ⁹ 197 analysis data. In this scenario, PAV+ mode was cost saving at both 1 year (-\$8,268) and 20
- years (-\$5,857), with QoL being equal (1-year) or improved (20-year) with use of PAV+ mode.
- 12 199 13

14200Interpretation

16 201 Clinicians have a medical and fiscal responsibility to choose wisely in spending healthcare 17 dollars, and to optimize patient access to hospital resources and flow through the hospital 202 18 from admission to discharge. This requires discerning which treatments are most likely to be 203 19 clinically effective and most cost-effective for patient-important outcomes. As hospitals look 204 20 to increase ICU capacity during the COVID-19 pandemic, health-economic models provide a 205 21 22 206 means of modelling the economic and clinical impact of a change in intervention before 23 207 committing to implementation. 24

- ²⁵₂₆ 208 This analysis sought to synthesize available data regarding mode of MV (PAV+ mode versus
- 209 PSV) on patient outcomes and corresponding costs from a Canadian perspective. The
- 28 210 pragmatic meta-analysis aimed to provide an objective assessment of the clinical
- ²⁹ 211 effectiveness of the PAV+ mode versus PSV. Significant reductions were observed in
- $\frac{30}{31}$ 212 patient-ventilator asynchrony and in-patient time on MV, time in the ICU, and time in
- $_{32}$ 213 hospital.

33 214 Applying these data to our health-economic model, we found use of PAV+ mode relative to 34 PSV reduced costs to payers in year one, but increased costs over a longer time horizon. The 215 35 cost per QALY gained over the 20-year time horizon was found to be \$6,572. Acceptability 36 216 37 analysis found that PAV+ mode would be cost-effective in 95% of cases if the WTP was 217 38 \$14,729 per QALY gained. From these results, use of PAV+ mode has a high likelihood to be 218 39 considered cost effective in Canada.²⁴ The increased costs observed align with previous 219 40 analyses in the United States and United Kingdom, where higher patient survival with PAV+ 41 220 42 221 mode resulted in higher costs of care (the survival paradox).²¹ Key drivers of cost in the 43 current model were time on MV and in the ICU. The reasons for PAV+ mode resulting in 222 44 223 shorter time on MV and in the ICU in this model can only be surmised and may well be 45 224 multifactorial. For example, the algorithms underlying PAV+ mode may help maintain the 46 47 patient's respiratory muscles allowing for earlier success in SBTs and/or earlier readiness for 225 48 liberation. Alternatively, or additionally, reduced incidence of tracheostomy may play a role 226 49 227 as time to tracheostomy has been previously associated with time on MV and in the ICU.³⁰ 50 228 Results of a large, multi-centre clinical trial [ClinicalTrials.gov Identifier: NCT02447692] are 51 52 pending, but may help to answer these questions definitively. 229 53

There are two published meta-analyses of PAV+ mode.^{28,29} As in our analysis, these studies converted data reported as a median and (interquartile) range to means and standard deviations for analysis using the methods of Wan et al.³¹ (used by Kataoka et al. ²⁹) or Hozo et al.³²(used by Vijayaraghavan et al.²⁸ via personal communication). Our results are more

aligned to those of Kataoka et al.²⁹ Potential reasons for this may be the consensus use of the methodology presented by Wan et al.³¹ or the greater overlap in included studies. Limitations This study uses a pragmatic meta-analysis to determine the comparative effectiveness of PAV+ mode compared with PSV. As no systematic review was undertaken, there remains the potential that data relevant to the analysis were not captured. All data identified in previous meta-analyses,^{28,29} were included, plus a prospective, observational case-control study.²⁶ The use of a computational model allowed for cost and outcomes data to be extrapolated to 20 years, but no model can fully reproduce clinical practice. Results should be treated as estimates and interpreted with respect to their uncertainty and the readers' clinical judgment. Sensitivity and scenario analyses across a range of clinical parameters suggest that results are robust, but confirmation in a real-world analysis on patients is recommended. Conclusions Based on available evidence to date, PAV+ mode is likely to be cost effective in the Canadian setting. Costs of care in the year of admission to ICU are expected to be reduced, though over a 20-year time period would increase due to longer patient life expectancy. **Data-sharing statement** Data relating to results presented will be made available on reasonable request. Contributions RS and KB contributed substantially to conception and design, acquisition of data, and analysis and interpretation of data. JD contributed substantially to acquisition, analysis, and interpretation of data. RS and JD drafted the manuscript, KB revised it critically for important intellectual content. RS, JD, and KB all gave final approval of the version to be published and agreed to act as guarantor of the work. List of abbreviations AE, adverse event; CAD, Canadian dollar; COVID-19, coronavirus disease 2019; CrI, credible interval; GW, general ward; ICU, intensive care unit; MD, mean difference; MV, mechanical ventilation; OR, odds ratio; PAV+, proportional-assist ventilation with load adjustable gain factors; PSV, pressure support ventilation; OALY, quality-adjusted life year; QoL, quality of life; SBT, spontaneous breathing trial; VAP, ventilator-associated pneumonia; WTP, willingness-to-pay. References Canadian Institute for Health Information. Care in Canadian ICUs.; 2016. 1. https://secure.cihi.ca/free products/ICU Report EN.pdf. Hill AD, Fowler RA, Burns KEA, Rose L, Pinto RL, Scales DC. Long-Term 2. Outcomes and Health Care Utilization after Prolonged Mechanical Ventilation. Ann

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Tables

Table 1Model parameters

Grouping	Parameter	Base case reference	
Dationt och out dom o monking	Age, mean years (SD)	67 (12) ³³	
Patient cohort demographics	Gender, % female (SE)	39.7 (0.13) ²	
	Asynchrony >10% at MV initiation, % (range)	4.2% (0.7, 14.1) 34	
	Time on MV, mean days (95% CI)	8.1 (4.5, 28.3) 35	
Reference efficacy	Time in ICU, mean days (95% CI)	12.6 (7.4, 33.3) 35	
Standard of care (PSV)	Time in hospital, mean days (95% CI)	43.5 (18.6, 68.4) 35	
	Spontaneous breathing trial success, % (95% CI)	77.9 (73.8, 82.1) 22	
	Liberation success, % (95% CI)	85.3 (85.1, 85.6) ³⁶	
	Tracheostomy, % (95% CI)	26 (8.1, 44.0) 33	
	VAP, % (95% CI)	8.8 (5.7, 11.9) ³⁵	
	Nosocomial infection, % (95% CI)	0.85 (0.66, 1.04) 37	
	ICU mortality (95% CI)	25.4 (20.7, 30.1) ³⁵	
AE rates	Hospital mortality (95% CI)	30.3 (25.3, 35.3) ³⁵	
	Post-discharge mortality, % (95% CI)	Year 1: 12.5 (12.4, 12.6) ³⁸ Year 2: 19.3 (19.2, 19.5) ³⁸ Year 3: 27.5 (27.3, 27.7) ³⁸ Year 4+: life tables	
	Total time MV, mean days (95% CI)	-1.53 (-2.24, -0.83)†	
	ICU length of stay, mean days (95% CI)	-1.54 (-2.19, -0.90)†	
	Hospital length of stay, mean days (95% CI)	-1.83 (-2.51, -1.16)†	
	Successful weaning/liberation, OR (95% CI)	1.49 (0.59, 3.79)†	
Comparative effectiveness PAV+ vs. PSV	ICU mortality, OR (95% CI)	0.70 (0.41, 1.20)†	
1111 - 45.154	Hospital mortality, OR (95% CI)	0.70 (0.40, 1.22)†	
	Tracheostomy, OR (95% CI)	0.76 (0.44, 1.31)†	
	Extubation failure/re-intubation, OR (95% CI)	0.52 (0.25, 1.08)†	
	Asynchrony index >= 10 (95% CI)	0.13 (0.07, 0.23)†	
	ICU, \$ per day (95% CI)	2,765 (2,354, 3,690) 39	
	GW, \$ per day (95% CI)	1,019 (717, 1,400) ³⁹	
	MV initiation, \$ per event (95% CI)	139 (125, 153) ⁴⁰	
	MV maintenance, \$ per day (95% CI)	851 (766, 936) ⁴⁰	
Casta	Tracheostomy, \$ per event (95% CI)	4,193 (3,908, 4,477) 41	
Costs	VAP, \$ per day (95% CI)	58 (30, 73) 42,43	
	VAP, additional length of stay (95% CI)	9.5 (8.8, 10.1) ‡	
	Other nosocomial infection, \$ per event (95% CI)	870 (783, 956) 44	
	PSV, \$ purchase cost	0 (assumption)	
	PAV+, \$ one-off purchase cost	27,000 *	

Grouping	Parameter	Base case reference
	Post-discharge, \$ annual cost (95% CI)	13,707 (6,241, 37,631) ²
	Baseline (95% CI)	$0.776 (0.677, 0.899)^{21}$
	Annual disutility (95% CI)	0.003 (0.003, 0.004) ²¹
	MV (95% CI)	$-0.390 (-0.590, 0.090)^{21}$
Health state utility	ICU (95% CI)	$0.402 \ (0.362, \ 0.442)^{21}$
	Hospital (95% CI)	0.520 (0.450, 0.590) ²¹
	Post-discharge to 1 year (95% CI)	0.550 (0.480, 0.610) ²¹

[†]Present study, determined from meta-analysis (see Appendix). ‡Canadian MIS Database, F2010/11 - F2014/15. ***** Personal communication fromMedtronic. Probabilistic model inputs (used for the PSA) were based on input variance, calculated from reported confidence intervals. *AE*, adverse event; CI, confidence interval; GW, general ward; ICU, intensive care unit; MV, mechanical ventilation; OR, odds ratio; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation; SE, standard error; VAP, ventilator-associated pneumonia.

Table 2Base case cost and quality-adjusted life year outcomes

Time horizon	Mode/result	Costs	QALY	ICER
	PAV+	\$53,898	0.29	
1 year	PSV	\$60,271	0.25	
	Difference	-\$6,373	+0.04	Dominant
	PAV+	\$144,041	6.79	
20 years	PSV	\$137,976	5.86	
	Difference	\$6,065	+0.92	\$6,592

Results for the base case analysis with total costs and total QALYs, the difference (PAV+ minus PSV), and the associated ICER. In the 1-year time horizon, where PAV+ was associated with savings for the QALYs gained, the ICER is considered dominant as there is no additional cost associated with a QALY gain.

ICER, incremental cost-effectiveness ratio; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; QALY, quality-adjusted life year.

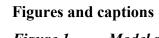
Table 3Scenario analyses

Scenario	1 year		20 years	
	Difference	ICER	Difference	ICER
Base case (default values)	-\$6,373 +0.04	Dominant	\$6,065 0.92	\$6,592
Only significant differences in comparative effectiveness included	-\$6,767 +0.02	Dominant	+\$425 +0.53	\$802
Younger population (50 years)	-\$6,373 +0.04	Dominant	+\$8,281 +1.08	\$7,668
Population 70% female	-\$6,373 +0.04	Dominant	+\$6,345 +0.94	\$6,750
No difference in asynchrony between PAV+ mode and PSV	-\$5,477 +0.03	Dominant	+\$6,319 +0.87	\$7,263
PSV also has a purchase cost (\$27,000)	-\$6,550 +0.04	Dominant	+\$5,888 +0.92	\$6,400

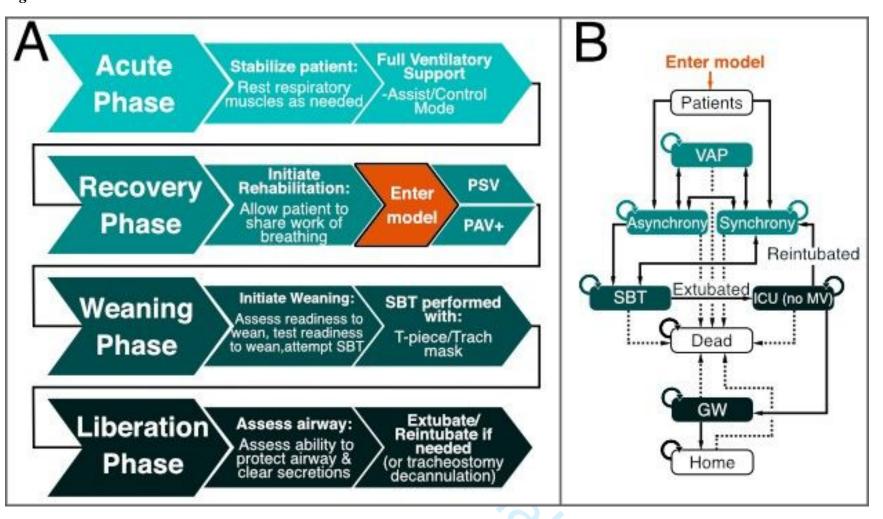
Per day hospital costs taken from CIHI data. ¹ ICU \$3,592; GW \$1,135	-\$8,138 +0.04	Dominant	+\$4,320 +0.92	\$4,696
Canadian efficacy data only ³³	-\$8,268 0.0	Cost saving	-\$5,857 +0.17	Dominant

Results are presented as PAV+ versus standard care PSV with difference in costs over difference in QALYs. The associated ICER is shown; in cases where costs decrease and QALYs increase, the ICER is taken as dominant. Care in Canadian ICU1: Data Tables, Table 13 Average daily cost for stay in ICU and GW by hospital type, 2013–2014. https://www.cihi.ca/sites/default/files/document/icu_datatables_en.xlsx

CIHI, Canadian Institute for Health Information; GW, general ward; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation.

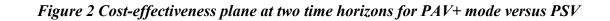


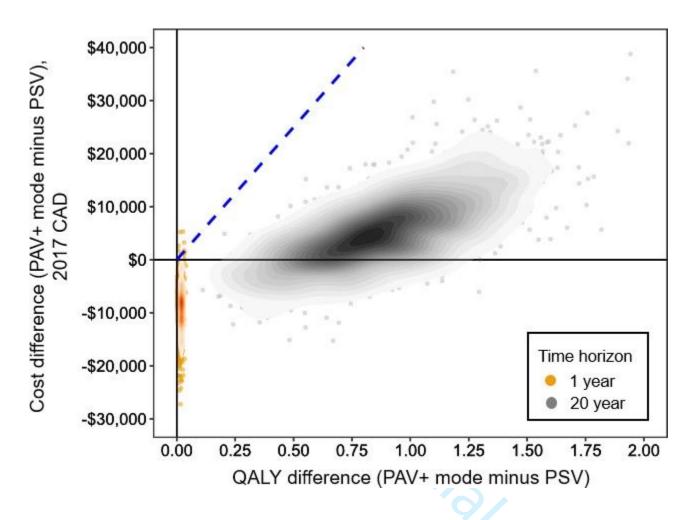




The clinical stages of MV are shown in A. The model beings once the patient is out of the acute phase and enters the Recovery phase. The model is shown in B. Patients on MV are either synchronous or asynchronous with the ventilator. Synchronous patients can become asynchronous and vice versa. Patients on MV are at risk of ventilator-associated pneumonia. From MV, patients undergo a spontaneous breathing trial, which if successful results in liberation (extubation and removal from invasive MV). After successful liberation. the patient is transferred to lower-acuity care (GW) and later discharged home. If there is patient compromise after extubation (extubation failure) the patient will be reintubated and placed back on MV. At any stage patients may die.

GW, general ward; *MV*, mechanical ventilation; *PAV*+, proportional-assist ventilation with adjustable gain parameters; *PSV*, pressure support ventilation; *SBT*, spontaneous breathing trial; *VAP*, ventilator-associated pneumonia.





A sensitivity analysis of 2,000 replicates was performed for cost-effectiveness time horizons of 1 year and 20 years. The blue reference line indicates a willingness-to-pay threshold of \$50,000 per QALY gained. Points underneath this line are considered cost-effective. Simulations in the lower right quadrant (increase in QALY, decrease in cost) are considered dominant. Density of individual probabilistic simulation results for each time horizon is represented by highlighted areas of the cost-effectiveness plane.

CAD, *Canadian dollar*; *PAV*+, *proportional-assist ventilation with adjustable gain parameters*; *PSV*, *pressure support ventilation*; *QALY*, *quality-adjusted life year*.

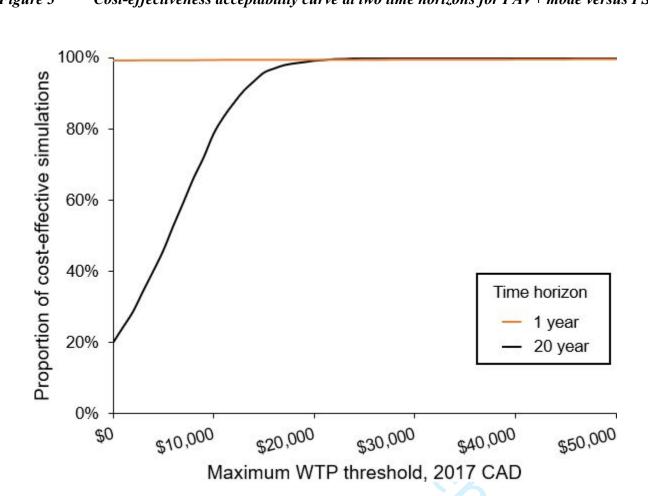


Figure 3 Cost-effectiveness acceptability curve at two time horizons for PAV+ mode versus PSV

The proportion of simulations is shown according to varying thresholds of cost effectiveness. Cases where the result was dominant (a decrease in costs accompanied by an increase in QALY) are counted among the cost-effective scenarios, hence the curves' indicating non-zero proportions of simulations as cost-effective even at a willingness to pay threshold of \$0.

PAV+, proportional-assist ventilation with adjustable gain parameters; CAD, Canadian dollar; PSV, pressure support ventilation; QALY, quality-adjusted life year; WTP, willingness to pay (threshold).

Appendix - The clinical and cost effectiveness of PAV+ mode for mechanical ventilation

Short-title: PAV+ for mechanical ventilation in the ICU

Rhodri Saunders (DPhil)

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Appendix

Identifying relevant literature

The aim of the literature searches was to supplement data identified from the original model publication,¹ by identifying recent literature reporting on efficacy, safety, and costs associated with MV in Canada. In combining data from the previous study with that from the Canadian setting, the aim was to provide a holistic view of data on PAV+ mode. As the focus of the publication is an economic model, the intent of the searches was to obtain a representative assessment of additional data available on outcomes in the Canadian setting, thus they were performed pragmatically rather than systematically.

To inform the model design and data analysis, a structured literature search of PubMed was performed using search terms detailed in **Table 1**. These were supplemented by hand searches of Google Scholar to identify relevant, non-PubMed-indexed clinical studies. The supplementary materials of included studies were also reviewed for relevant data.

#	Aim	Search string	Hits
1	Country specific	canada[ad] OR "Canada"[tw] OR "Canadian"[tw] OR "Canadians"[tw] OR "Canada"[Mesh] OR "Alberta"[tw] OR "British Columbia"[tw] OR "Manitoba"[tw] OR "New Brunswick"[tw] OR "Newfoundland and Labrador"[tw] OR "Northwest Territories"[tw] OR "Nova Scotia"[tw] OR "Nunavut"[tw] OR "Ontario"[tw] OR "Prince Edward Island"[tw] OR "Quebec"[tw] OR "Saskatchewan"[tw] OR "Yukon Territory"[tw] OR "Toronto"[tw] OR "Ottawa"[tw] OR "Winnipeg"[tw] OR "Regina"[tw] OR "Edmonton"[tw] OR "Vancouver"[tw] OR "Montreal"[tw] OR "Saint John"[tw] OR "Halifax"[tw] OR "St John's"[tw] OR "Charlottetown"[tw] OR "Alberta"[ad] OR "British Columbia"[ad] OR "Manitoba"[ad] OR "Northwest Territories"[ad] OR "Nova Scotia"[ad] OR "Nunavut"[ad] OR "Ontario"[ad] OR "Prince Edward Island"[ad] OR "Nunavut"[ad] OR "Saskatchewan"[ad] OR "Yukon Territory"[ad] OR "Toronto"[ad] OR "Ottawa"[ad] OR "Yukon Territory"[ad] OR "Toronto"[ad] OR "Ottawa"[ad] OR "Winnipeg"[ad] OR "Regina"[ad] OR "Edmonton"[ad] OR "Vancouver"[ad] OR "Montreal"[ad] OR "Saint John"[ad] OR "Ottawa"[ad] OR "St John's"[ad] OR "Saint John"[ad] OR	216,400
2	All cost studies	 "Costs and Cost Analysis" [Mesh] OR "Cost-Benefit Analysis" [Mesh] OR "Cost of Illness" [Mesh] OR "Health Care Costs" [Mesh] OR "Cost Sharing" [Mesh] OR "Cost Savings" [Mesh] OR "Technology, High-Cost" [Mesh] OR "Cost Control" [Mesh] OR "Cost Allocation" [Mesh] OR "Direct Service Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Employer Health Costs" [Mesh] OR "Drug Costs" [Mesh] OR "Health Expenditures" [Mesh] OR "Health Resources/economics" [Mesh] OR "Economics, Hospital" [Mesh] OR "Economics, Medical" [Mesh] OR "Economics, Pharmaceutical" [Mesh] OR "Economics, Nursing" [Mesh] OR "Managed Care Programs" [Mesh] OR "Economics" [Mesh] OR "Commerce" [Mesh] OR Cost[tw] OR economic [Mesh] OR "Commerce" [Mesh] OR "Length of Stay/statistics and numerical data" [Mesh] OR "Financial Management, Hospital" [Mesh] OR "Hospital Charges/statistics and numerical data" [Mesh] OR "Locst" [Mesh] OR "Locst" [Mesh] OR "Costs" [Mesh] OR "Locst" [Mesh] OR "Costs" [Mesh] OR "Financial Management, Hospital Costs" [Mesh] OR "Adata" [Mesh] OR "Financial Management, Hospital Costs" [Mesh] OR "Economics, Hospital" [Mesh] OR "Locst" [Mesh] OR "Locst" [Mesh] OR "Costs" [Mesh] OR "Locst" [Mesh] OR "Hospital Costs" [Mesh] OR "Economics, Hospital" [Mesh] OR "Hospital Costs" [Mesh] OR "Economics, Hospital" [Mesh] OR "Locst" [Mesh] OR ((USD [tw] OR CAD [tw] OR dollar [tw] OR dollars [tw]) AND (Cost [tw] OR price [tw] or expense [tw] OR burden [tw] OR "pricing" [tw] OR "prices" [tw])) OR (("Cost" [tw] OR spending [tw] OR "economic" [tab] OR "health care" [tiab] or "economics" [tab] OR "Locst" [tab] OR "Locst" [tab] OR "Costs" [tw] OR 	1,013,47

Table 1Structures searched in PubMed to identify relevant cost data

#	Aim	Search string	Hits
		"medical"[tiab] OR treatment[tiab] OR hospital[tiab] OR hospitalization[tw] OR hospitalisation[tw] OR "health service"[tiab]))	
3	Studies since 2012	"2012/01/01"[PDAT]:"2018/05/01"[PDAT]	6,589,304
4	Recent cost studies	#1 AND #2 AND #3	6,942
5	Adverse events (AE) of interest	"Tracheotomy"[Mesh] OR "Tracheotomy"[tw] OR "Tracheostomy"[tw] OR "Pneumonia, Ventilator-Associated"[Mesh] OR VAP[tw] OR "ventilator-associated pneumonia"[tw] OR "Respiration, Artificial/adverse effects"[Mesh] OR "Respiration, Artificial/complications"[Mesh] OR "Respiration, Artificial/conomics"[Mesh] OR "Respiration, Artificial/conomics"[Mesh] OR "Respiration, Artificial/mortality"[Mesh] OR "Respiration, Artificial/statistics and numerical data"[Mesh] OR "Length of Stay/economics"[Mesh] OR synchrony[tw] OR synchronous[tw] OR asynchrony[tw] OR asynchronous[tw] OR ((LOS[tw] OR stay[tw]) AND (ICU[tw] OR "intensive care"[tw])) OR ((mortality[tw] OR death[tw] OR surviving[tw] OR survival[tw]) AND (ICU[tw] OR "intensive care"[tw] or "critically ill"[tw]))	160,942
6	Those reporting on assisted ventilation	"Respiration, Artificial"[Mesh] OR "High-Frequency Ventilation"[Mesh] OR "Interactive Ventilatory Support"[Mesh] OR "mechanical ventilation"[tw] OR "assisted ventilation"[tw] OR "proportional assist"[tw] OR "proportional-assist"[tw] OR PAV[tw] OR "PAV+"[tw] OR NAVA[tw] OR PSV[tw] OR "neurally adjusted"[tw] OR "artificial respiration"[tw] OR "artificial ventilation"[tw]	92,907
7	AEs and assisted ventilation	#5 AND #6	26,126
8	Cost of assisted ventilation	#4 AND #7	36

Literature search results

Regarding clinical effectiveness outcomes, the literature review identified seven clinical studies comparing PAV+ mode with PSV.^{2–8} Of these, four covered the recovery phase of critical care, ^{2,3,5,7} three the weaning phase,^{4,6,8} two were Canadian,^{2,3} and one was not randomized.⁷ A total of 271 patients were managed with PAV+ mode and 253 with PSV. Clinical and safety data of interest from these studies were extracted and used for meta-analysis.

Pragmatic meta-analysis

Methods

No individual study among those identified in the literature review presented robust clinical data on the required model inputs for the Canadian setting. In their absence, a pragmatic meta-analysis of results was conducted. Included studies were reviewed independently by both RS and KJB, with data extraction also performed independently by both authors. Where there was disagreement between included data, this was resolved by discussion. Unless already in the correct form for analysis, extracted data were converted to means and standard deviations according the method of Wan et al.⁹ Data conversion (using R) and meta-analysis (using RevMan v5.3) were performed by JD and outcomes checked by RS and KJB. In the meta-analysis, a random-effects model was used to account for low powered studies and potential differences in clinical practice between countries. Dichotomous outcomes were calculated as odds ratios or as Peto odds ratios for rare outcomes or where numerous groups had zero events.

Results

Data extraction resulted in sufficient data to assess all required endpoints for hospital time: total time on MV, ICU length of stay, and hospital length of stay. Total patient numbers were 524 for time on MV and in the ICU, and 253 for hospital length of stay. For each endpoint, heterogeneity was low (I² \leq 24%) and PAV+ mode was associated with a significant reduction in time in each care setting. Meta-analysis results for these endpoints are shown in Figure 1.

For dichotomous endpoints, six events had three or more studies reporting on the outcome: weaning success, extubation/liberation failure, need for tracheostomy, ICU mortality, hospital mortality, and asynchrony index ≥ 10 . For all outcomes, heterogeneity of reported data was low ($I^2 \leq 16\%$). PAV+ mode was generally associated with improved outcomes, although not statistically significant (**Figure 2**), with the exception of asynchrony index ≥ 10 , where PAV+ mode was significantly associated with decreased odds of asynchrony (OR 0.13, 0.07-0.23). The meta-analysis results represent the base-case inputs for our health-economic analysis and are summarized in **Table 2**.

Figure 1 Meta-analysis results for continuous outcomes

		AV+			PSV			Mean Difference	Mean Difference
Study or Subgroup	Mean [days]						Weight	IV, Random, 95% CI [days]	IV, Random, 95% CI [days]
Aguirre-Bermeo 2014	11.667	9.574	20	11	10.372	20	1.3%	0.67 [-5.52, 6.85]	
Bosma 2016	7.454913	6.762683	27	11.7	12.2	23	1.5%	-4.25 [-9.85, 1.36]	
Botha 2018	8.961	7.286	25	9.25	8.435	24	2.4%	-0.29 [-4.71, 4.13]	
Elganady (failure) 2014	6.33	0.58	3	8.9	0.88	10	30.0%	-2.57 [-3.42, -1.72]	+
Elganady (success) 2014	2.43	0.91	27	3.85	1.23	20	37.3%	-1.42 [-2.06, -0.78]	
Sasikumar 2013	7.333	3.738	13	7.75	2.795	10	6.1%	-0.42 [-3.09, 2.25]	
Teixeira 2015	6.1	4.2	48	6.6	4.4	46	12.5%	-0.50 [-2.24, 1.24]	
Xirouchaki 2008	9.333	7.514	108	10.267	8.124	100	9.0%	-0.93 [-3.07, 1.20]	
Total (95% CI)			271			253	100.0%	-1.53 [-2.24, -0.83]	•
Heterogeneity: Tau ² = 0.24	Chi ² = 9.62, df =	7 (P = 0.21); I ² = 2	7%					-10 -5 0 5 10
Test for overall effect Z = 4	.29 (P < 0.0001)								Favours [PAV+] Favours [PSV]
Study or Subgroup		AV+			PSV			Mean Difference	Mean Difference
Study of Subgroup				Mean [days]	SD [days]	Total	Weight	IV, Random, 95% CI [days]	IV, Random, 95% CI [days]
Aguirre-Bermeo 2014	15	9.574	20	13.333	11.17	20	1.0%	1.67 [-4.78, 8.11]	
Bosma 2016	7.967	4.853	27	16.9	18.411	23	0.7%	-8.93 [-16.68, -1.19]	
Botha 2018	10.933	8.569	25	12.8	10.718	24	1.4%	-1.87 [-7.31, 3.58]	
Elganady (failure) 2014	8.33	0.58	3	10	1.05	10	35.6%	-1.67 [-2.59, -0.75]	+
Elganady (success) 2014	3.7	0.94	27	5.45	1.43	20	50.1%	-1.75 [-2.47, -1.03]	
Sasikumar 2013	10.25	3.945	13	10.917	6.235	10	2.1%	-0.67 [-5.09, 3.75]	
Teixeira 2015	11.5	8.9	48	11.9	7.4	46	3.7%	-0.40 [-3.70, 2.90]	
Xirouchaki 2008	14.667	9.768	108	14.167	10.155	100	5.4%	0.50 [-2.21, 3.21]	
Total (95% CI)			271			253	100.0%	-1.54 [-2.19, -0.90]	•
Heterogeneity: Tau ² = 0.08	Chi ² = 7.61, df =	7 (P = 0.37); I ² = 8	96					-20 -10 0 10
Test for overall effect Z = 4	.70 (P < 0.00001)							-20 -10 0 10 Favours (PAV+) Favours (PSV)
	Р	AV+		1	PSV			Mean Difference	Mean Difference
Study or Subgroup	Mean [days]	SD [days]	Total	Mean [days]	SD [days]	Total	Weight	IV, Random, 95% CI [days]	IV, Random, 95% CI [days]
Bosma 2016	37.733	48.605	27	28.133	21.809	23	0.1%	9.60 [-10.79, 29.99]	
Botha 2018	22	12.814	25	20.767	14.973	24	0.7%	1.23 [-6.58, 9.05]	
Elganady (failure) 2014	9.67	0.58	3	11.5	1.6	10	32.3%	-1.83 [-3.02, -0.64]	
Elganady (success) 2014	4.81	1.24	27	6.65	1.57	20	66.0%	-1.84 [-2.67, -1.01]	-
Teixeira 2015	22.2	15.4	48	27.6	19.8		0.9%	-5.40 [-12.59, 1.79]	
Total (95% CI)			130			123	100.0%	-1.83 [-2.51, -1.16]	•
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 5			l); l* = 0	196					-10 -5 0 5 10

Results for time on MV (A), length of stay in the ICU (B) and length of stay in hospital (C) are shown. CI, confidence interval; IV, inverse variance; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Figure 2 Meta-analysis results for dichotomous outcomes

Α	Study or Subgroup	PAV+ Events		PSV Events		Weight	Odds Ratio (Non-event) M-H, Random, 95% 0			(Non-event) om, 95% Cl	
, ,	Aquirre-Bermeo 2014	17	20	15	20		0.53 [0.11, 2.60				
	Bosma 2016	23	20	21	23		1.83 [0.30, 11.02				-
								-			
	Botha 2018 Coollaumor 2012	23 12	25	19 9	24		0.33 [0.06, 1.90	-			_
	Sasikumar 2013	12	13	9	10	10.3%	0.75 [0.04, 13.68	9	-		
	Total (95% CI)		85		77	100.0%	0.67 [0.26, 1.70	1			
		75	05			100.070	0.07 [0.20, 1.70	1			
	Total events	75		64	0.500						
	Heterogeneity: Tau ² = I				= 0.59)	¢1*=0%		0.02	0.1	1 1	0 9
	Test for overall effect: 2	2 = 0.84 (P =	= 0.40)						Favours [PAV+]	Favours [PSV]	1
В	Study of Subgroup	PAV-		PSV		Moight	Odds Ratio		Odds R		
D	Study or Subgroup						M-H, Random, 95% Cl		M-H, Randon	n, 95% CI	
	Aguirre-Bermeo 2014	3	20	5	20		0.53 [0.11, 2.60]				
	Bosma 2016	3	27	5	23		0.45 [0.09, 2.13]			_	
	Botha 2018	1	24	2	24	8.9%	0.48 [0.04, 5.66]				
	Sasikumar 2013	0	13	2	10	5.5%	0.13 [0.01, 2.95]	•			
	Teixeira 2015	6	48	8	46	41.5%	0.68 [0.22, 2.13]			_	
	Total (95% CI)		132		123	100.0%	0.52 [0.25, 1.08]				
	Total events	13		22							
	Heterogeneity: Tau ² = I				= 0.91)	; I² = 0%		0.01	0.1 1	10	100
	Test for overall effect: 2	Z = 1.74 (P =	= 0.08)					0.01	Favours [PAV+] F		100
									i arcaio [i /iti -] i	aroaro (r o r)	
		PAV	r.	PSV	,		Odds Ratio		Odds R	atio	
С	Study or Subgroup					Weight	M-H, Random, 95% Cl		M-H, Randon		
	Aguirre-Bermeo 2014	2	20	3	20	8.1%	0.63 [0.09, 4.24]				
	Bosma 2016	4	27	6	23		0.49 [0.12, 2.02]			_	
	Botha 2018	5	24	7	24	16.8%	0.64 [0.17, 2.39]				
	Sasikumar 2013	1	13	1	10	3.5%	0.75 [0.04, 13.68]				
	Teixeira 2015	4	48	6	46	16.5%					
							0.61 [0.16, 2.30]				
	Xirouchaki 2008	13	108	11	100	40.4%	1.11 [0.47, 2.60]		T		
	T-4-1/05% CD		240		223	100.0%	0.76 [0.44, 1.31]				
	Total (95% CI)	20	240	24			0110[0111]				
	Total events	29 0.00: Chił –		34 df = 5 (P -			0.10 [0.14, 10 1]				
		0.00; Chi² = Z = 0.97 (P =	1.32, i = 0.33)	df = 5 (P =	= 0.93)			0.01	0.1 1 Favours [PAV+] F		100
D	Total events Heterogeneity: Tau ² = I	0.00; Chi² = I = 0.97 (P =	1.32, i = 0.33) PAV+	df = 5 (P =	= 0.93) PSV	; I² = 0%	Peto Odds Ratio eight Peto, Fixed, 95% (Favours (PAV+) F		100
D	Total events Heterogeneity: Tau ² = Test for overall effect. 2 <u>Study or Subgroup</u> Bosma 2016	0.00; Chi ^z = Z = 0.97 (P = <u>Eve</u>	1.32, 1 = 0.33) PAV+ ents 1 0	df=5(P= <u>Fotal Ev</u> 27	= 0.93) PSV ents 5	; *= 0% <u>Total We</u> 23 (Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5]	<u>cı</u> 9] —	Favours (PAV+) F	avours [PSV] dds Ratio	100
D	Total events Heterogeneity: Tau ² = 1 Test for overall effect. 2 Study or Subgroup	0.00; Chi ^z = Z = 0.97 (P = <u>Eve</u>	1.32, 1 = 0.33) PAV+ ents 1 0 0	df=5(P= <u>fotal Ev</u>	= 0.93) PSV ents 5 8	() [#] =0% <u>Total We</u> 23 () 30 1	Peto Odds Ratio eight Peto, Fixed, 95% (<u>cı</u> 9] —	Favours (PAV+) F	avours [PSV] dds Ratio	100
D	Total events Heterogeneity: Tau ² = Test for overall effect. 2 <u>Study or Subgroup</u> Bosma 2016	0.00; Chi ^z = Z = 0.97 (P = <u>Eve</u>	1.32, 1 = 0.33) PAV+ ents 1 0	df=5(P= <u>Fotal Ev</u> 27	= 0.93) PSV ents 5	() [#] =0% <u>Total We</u> 23 () 30 1()	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5]	<u>cı</u> 9] — 5] -	Favours (PAV+) F	avours [PSV] dds Ratio	100
D	Total events Heterogeneity: Tau ² = Test for overall effect: 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008	0.00; Chi ^z = Z = 0.97 (P = <u>Eve</u>	1.32, 1 = 0.33) PAV+ ents 1 0 0	df = 5 (P = <u>Fotal Ev</u> 27 30 108	= 0.93) PSV ents 5 8	; *= 0% <u>Total We</u> 23 (30 1) 100 7)	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2	<u>ci</u> 9] — 5] - 7]	Favours (PAV+) F	avours [PSV] dds Ratio	100
D	Total events Heterogeneity: Tau ² = Test for overall effect 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI)	0.00; Chi ^z = Z = 0.97 (P = <u>Eve</u>	1.32, (= 0.33) PAV+ ents 1 0 0 6	df = 5 (P = <u>fotal Ev</u> 27 30	= 0.93) PSV ents 5 8 39	() [#] =0% <u>Total We</u> 23 () 30 1()	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2	<u>ci</u> 9] — 5] - 7]	Favours (PAV+) F	avours [PSV] dds Ratio	100
D	Total events Heterogeneity: Tau ² = Test for overall effect 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events	0.00; Chi ^z = Z = 0.97 (P = Eve 2014	1.32, = 0.33) PAV+ ents 1 0 6	df = 5 (P = <u>Fotal Evo</u> 27 30 108 165	= 0.93) PSV ents 5 8 39 52	; *= 0% <u>Total We</u> 23 (30 1) 100 7)	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2	<u>ci</u> 9] — 5] - 7]	Favours (PAV+) F	avours [PSV] dds Ratio	100
D	Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² =	0.00; Chi ² = Z = 0.97 (P = Eve 2014 0.27, df = 2	1.32,1 = 0.33) PAV+ ents 1 0 0 6 2 (P = 0	df = 5 (P = <u>fotal Eve</u> 27 30 108 165 1.88); P =	= 0.93) PSV ents 5 8 39 52	; *= 0% <u>Total We</u> 23 (30 1) 100 7)	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2	<u>ci</u> 9] — 5] - 7]	Favours (PAV+) F Peto O Peto, Fix	avours [PSV] dds Ratio	
D	Total events Heterogeneity: Tau ² = Test for overall effect 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events	0.00; Chi ² = Z = 0.97 (P = Eve 2014 0.27, df = 2	1.32,1 = 0.33) PAV+ ents 1 0 0 6 2 (P = 0	df = 5 (P = <u>fotal Eve</u> 27 30 108 165 1.88); P =	= 0.93) PSV ents 5 8 39 52	; *= 0% <u>Total We</u> 23 (30 1) 100 7)	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto O Peto, Fix	avours (PSV) dds Ratio ed, 95% Cl 1 10	1
D	Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² =	0.00; Chi ² = Z = 0.97 (P = Eve 2014 0.27, df = 2	1.32,1 = 0.33) PAV+ ents 1 0 0 6 2 (P = 0	df = 5 (P = <u>fotal Eve</u> 27 30 108 165 1.88); P =	= 0.93) PSV ents 5 8 39 52	; *= 0% <u>Total We</u> 23 (30 1) 100 7)	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto O Peto, Fix	avours (PSV) dds Ratio ed, 95% Cl 1 10	1
	Total events Heterogeneity: Tau ² = Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect.	0.00; Chi≇ = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV +	1.32, 1 = 0.33) PAV+ ents 1 0 0 6 2 (P = 0 2 < 0.00	df = 5 (P = <u>fotal Eve</u> 27 30 108 165 1.88); I ² = 1001) PSV	= 0.93) PSV ents 5 8 39 52 0%	; ²= 0% <u>Total We</u> 23 (30 1) 100 7) 153 10	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 Odds Ratio 0	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
D	Total events Heterogeneity: Tau ² = Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV4 Events	1.32, 1 = 0.33) PAV+ ents 1 0 0 6 2 (P = 0 2 (P = 0 2 < 0.00	df = 5 (P = <u>fotal</u> <u>Even</u> 27 30 108 165 0.88); ² = 0001) PSV <u>Events</u>	■ 0.93) PSV ents 5 8 39 52 0% Total	; ² = 0% <u>Total We</u> 23 9 30 14 100 7; 153 10 <u>Weight</u>	Peto Odds Ratio eight Peto, Fixed, 95% 3.7% 0.09 (0.01, 0.5 5.0% 0.10 (0.02, 0.4 5.3% 0.14 (0.07, 0.2 0.0% 0.13 (0.07, 0.2) Odds Ratio M-H, Random, 95% Cl	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Ou Peto, Fix O.1 Favours (PAV+)	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Study or Subgroup Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Aguirre-Bermeo 2014	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV+ Events 5	1.32, 1 = 0.33) PAV+ 0 6 (P = 0 (P = 0 (P = 0 + Total 20	df = 5 (P = <u>fotal Even</u> 27 30 108 165 0.88); I ² = 0001) PSV <u>Events</u> 4	e 0.93) PSV ents 5 8 39 52 0% Total 20	; ² = 0% 23 (30 1/ 100 7; 153 10 <u>Weight</u> 13.3%	Peto Odds Ratio eight Peto, Fixed, 95% (3.7% 0.09 (0.01, 0.5 5.0% 0.10 (0.02, 0.4 5.3% 0.14 (0.07, 0.2 0.0% 0.13 (0.07, 0.2 Odds Ratio M-H, Random, 95% CI 1.33 (0.30, 5.93) 0.30, 5.93)	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Aguire-Bermeo 2014 Bosma 2016	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV4 <u>Events</u> 4	1.32, = 0.33) PAV+ ents 1 0 6 6 ((P = 0 6 (< 0.00 ► Total 20 27	df = 5 (P = <u>fotal Eve</u> 27 30 108 165 0.88); I [≠] = 0001) <u>PSV</u> <u>Events</u> 4 3	E 0.93)	; ² = 0 % Total We 23 9 30 19 100 79 153 10 Weight 13.3% 11.3%	Peto Odds Ratio eight Peto, Fixed, 95% (1) 7% 0.09 [0.01, 0.5] 5.0% 0.10 [0.02, 0.4] 5.3% 0.14 [0.07, 0.2] 0.0% 0.13 [0.07, 0.2] 0.0% 0.13 [0.07, 0.2] 0.0% 1.33 [0.30, 5.93] 1.16 [0.23, 5.81]	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Aguirre-Bermeo 2014 Bosma 2016 Botha 2018	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV+ Events 5 4 1	1.32, (= 0.33) PAV+ ents 1 0 6 6 ((P = 0 6 (< 0.00 ► Total 20 27 25	df = 5 (P = Total Events 27 30 108 165 0.88); I ² = 0001) PSV <u>Events</u> 4 3 6	ents 5 8 39 52 0% Total 20 23 24	() P = 0% Total We 23 (30 1) 100 7; 153 10 Weight 13.3% 6.1%	Peto Odds Ratio eight Peto, Fixed, 95% 9.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.13 [0.0, 5.03] 1.31 [0.30, 5.93] 1.16 [0.23, 5.81] 0.13 [0.21, 1.13]	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Aguirre-Bermeo 2014 Botha 2018 Sasikumar 2013	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV+ Events 5 4 1 0	1.32, (= 0.33) PAV+ ents 1 0 6 (P=0 6 (P=0 6 (P=0 € • Total 20 27 25 13	df = 5 (P = <u>fotal</u> Eve 27 30 108 165 0.88); I [≢] = 0001) PSV <u>Events</u> 4 3 6 1	 PSV PSV ents 5 8 39 52 0% Total 23 24 10 	; F = 0% Total Wa 23 (30 14 100 7; 153 10 Weight 13.3% 11.3% 6.1% 2.7%	Peto Odds Ratio eight Peto, Fixed, 95% 3.7% 0.09 (0.01, 0.5 5.0% 0.10 (0.02, 0.4 5.3% 0.14 (0.07, 0.2 0.0% 0.13 (0.07, 0.2) 0.0% 0.13 (0.07, 0.2) 0.04 Ratio M-H, Random, 95% CI 1.33 (0.30, 5.93) 1.16 (0.23, 5.81) 0.13 (0.01, 1.13) 0.23 (0.01, 6.40]	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Aguirre-Bermeo 2014 Bosma 2016 Botha 2018 Sasikumar 2013 Teixeira 2015	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV4 Events 5 4 1 0 0 0	1.32, = 0.33) PAV+ ents 1 0 0 6 (P = 0 (P = 0 (P = 0 27 20 27 13 48	df = 5 (P = <u>fotal</u> <u>Eve</u> 27 30 108 165 0.88); I [≠] = 0001) PSV <u>Events</u> 4 3 6 1 1	 PSV ents 5 8 39 52 0% Total 20 23 24 10 46 	; * = 0% 23 9 30 1; 100 7; 153 10 Weightt 13.3% 11.3% 6.1% 2.7% 2.8%	Peto Odds Ratio eight Peto, Fixed, 95% / 3.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
_	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Aguirre-Bermeo 2014 Botha 2018 Sasikumar 2013	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV+ Events 5 4 1 0	1.32, (= 0.33) PAV+ ents 1 0 6 (P=0 6 (P=0 6 (P=0 € • Total 20 27 25 13	df = 5 (P = <u>fotal</u> Eve 27 30 108 165 0.88); I [≢] = 0001) PSV <u>Events</u> 4 3 6 1	 PSV PSV ents 5 8 39 52 0% Total 23 24 10 	; * = 0% 23 9 30 1; 100 7; 153 10 Weightt 13.3% 11.3% 6.1% 2.7% 2.8%	Peto Odds Ratio eight Peto, Fixed, 95% 3.7% 0.09 (0.01, 0.5 5.0% 0.10 (0.02, 0.4 5.3% 0.14 (0.07, 0.2 0.0% 0.13 (0.07, 0.2) 0.0% 0.13 (0.07, 0.2) 0.04 Ratio M-H, Random, 95% CI 1.33 (0.30, 5.93) 1.16 (0.23, 5.81) 0.13 (0.01, 1.13) 0.23 (0.01, 6.40]	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect Study or Subgroup Aguirre-Bermeo 2014 Bosma 2016 Botha 2018 Sasikumar 2013 Teixeira 2015 Xirouchaki 2008	0.00; Chi² = Z = 0.97 (P = Eve 2014 0.27, df = 2 Z = 7.02 (P PAV4 Events 5 4 1 0 0 0	1.32, = 0.33) PAV+ ents 1 0 0 6 (P = 0 (P = 0 (P = 0 27 20 27 13 48	df = 5 (P = <u>fotal</u> <u>Eve</u> 27 30 108 165 0.88); I [≠] = 0001) PSV <u>Events</u> 4 3 6 1 1	e 0.93) PSV ents 5 8 39 52 0% Total 20 23 24 10 46 100	; * = 0% 23 9 30 1; 100 7; 153 10 Weightt 13.3% 11.3% 6.1% 2.7% 2.8%	Peto Odds Ratio eight Peto, Fixed, 95%, 3.7% 0.09 (0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.30, 5.93] 1.16 [0.23, 5.81] 0.13 [0.01, 1.13] 0.23 [0.01, 6.40] 0.31 [0.01, 7.87] 0.71 [0.36, 1.41]	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
	Total events Heterogeneity: Tau ² = 1 Test for overall effect 2 Bosma 2016 Elganady (success) 2 Xirouchaki 2008 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Aguirre-Bermeo 2014 Bosma 2016 Botha 2018 Sasikumar 2013 Teixeira 2015 Xirouchaki 2008 Total (95% CI)	0.00; Chi² = Z = 0.97 (P = 2014 0.27, df = 2 Z = 7.02 (P PAV-4 Events 5 4 1 0 0 19	1.32, (= 0.33) PAV+ ents 1 0 0 6 2 (P = C 20 27 25 13 48 108	df = 5 (P = fotal Eve 27 30 108 165 0.88); I [≢] = 0001) PSV Events 4 3 6 1 1 23	e 0.93) PSV ents 5 8 39 52 0% Total 20 23 24 10 46 100	(P = 0% Total W 23 (30 14 100 7; 153 10 Weight 13.3% 11.3% 6.1% 2.8% 63.8%	Peto Odds Ratio eight Peto, Fixed, 95% / 3.7% 0.09 [0.01, 0.5 5.0% 0.10 [0.02, 0.4 5.3% 0.14 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.0% 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2 0.13 [0.07, 0.2	cı 9) — 5) ~ 7] 3]	Favours (PAV+) F Peto Or Peto, Fix 0.1 Favours (PAV+) Odds R	avours (PSV) dds Ratio ed, 95% Cl 1 1 Favours (PSV) atio	1
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Results for weaning success (A), extubation/liberation failure (B), need for tracheostomy (C), asynchrony index ≥ 10 (D), ICU mortality (E) and overall hospital mortality (F) are shown. All are presented as odds ratios with random-effects models, except for odds of asynchrony index ≥ 10 , calculated as Peto odds ratios since 2 of 3 PAV+ had zero events.

 CI, confidence interval; M-H, Mantel-Haenszel; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Outcome	PAV+		PSV		
Continuous	Mean (SD)	Ν	Mean (SD)	Ν	MD
Total time MV (days)	5.33 (0.96)	271	6.87 (1.08)	253	-1.53 [-2.24, - 0.83]
ICU length of stay (days)	6.61 (0.83)	271	8.16 (1.05)	253	-1.54 [-2.19, - 0.90]
Hospital length of stay (days)	6.69 (0.86)	130	8.53 (1.18)	123	-1.83 [-2.51, - 1.16]
Dichotomous	Events	Total	Events	Total	OR
Successful weaning/liberation	75	85	64	77	1.49 [0.59, 3.79]
ICU mortality	29	241	38	223	0.70 [0.41, 1.20]
Hospital mortality	42	208	51	193	0.70 [0.40, 1.22]
Tracheostomy	29	240	34	223	0.76 [0.44, 1.31]
Extubation failure/re-	13	132	22	123	0.52 [0.25, 1.08]
intubation					

Table 2 Meta-analysis summary results

Summary of inputs, after conversion to means and standard deviations where necessary, and results from the pragmatic meta-analysis. Results (MD or OR) are shown with 95% CIs. Mean (SD) values are weighted means, where the weight for each study is taken from the RevMan 5.3 output. ICU, intensive care unit; MD, mean difference (PAV+ mode – PSV); MV, mechanical ventilation; OR, odds ratio (PAV+ mode relative to PSV); PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

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