Premature, Opportune, and Delayed Weaning in Mechanically Ventilated Patients: A Call for Implementation of Weaning Protocols in Low- and Middle-Income Countries

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Objectives: Weaning protocols establish readiness-to-wean criteria to determine the opportune moment to conduct a spontaneous breathing trial. Weaning protocols have not been widely adopted or evaluated in ICUs in low- and middle-income countries. We sought to compare clinical outcomes between participants whose weaning trials were retrospectively determined to have been premature, opportune, or delayed based on when they met readiness-to-wean criteria.

Design: Prospective, multicenter observational study.

Setting: Five medical ICUs in four public hospitals in Lima, Perú.

Subjects: Adults with acute respiratory failure and at least 24 hours of invasive mechanical ventilation ($n = 1,657$).

Interventions: None.

Measurements and Main Results: We established six readiness-to-wean criteria and retrospectively categorized our sample into three weaning groups: 1) premature: if the weaning trial took place before fulfilling all criteria, 2) opportune: if the weaning trial took place within 24 hours after fulfilling the criteria, and 3) delayed: if the weaning trial took place over 24 hours after fulfilling criteria. We compared 90-day mortality, ventilator-free days, ICU-free days, and hospital-free days between premature, opportune, and delayed weaning groups. In our sample, 761 participants (60.8%) were classified as having a premature weaning trial, 196 underwent opportune weaning (15.7%), and 295 experienced delayed weaning (23.6%). There was no significant difference in 90-day mortality between the groups. Both the premature and delayed weaning groups had poorer clinical outcomes with fewer ventilator-free days (−2.18, $p = 0.008$) and (−3.49, $p < 0.001$), ICU-free days (−2.25, $p = 0.001$) and (−3.72, $p < 0.001$), and hospital-free days (−2.76, $p = 0.044$) and (−4.53, $p = 0.004$), respectively, compared with the opportune weaning group.

Conclusions: Better clinical outcomes occur with opportune weaning compared with premature and delayed weaning. If readiness-to-wean criteria can be applied in resource-limited settings, it may improve ICU outcomes associated with opportune weaning. (*Crit Care Med* 2020; 48:673–679)

Key Words: artificial respiration; clinical protocols; critical care; mortality; weaning

Weaning, defined as the reduction in the level of ventilatory support that can happen either gradually or abruptly, is a fundamental process in the care of mechanically ventilated patients. The majority of patients experience a smooth weaning process leading to liberation from the ventilator; however, 20–30% of patients are considered difficult to wean (1). Currently, there is no way to precisely predict which patients will encounter difficulties in the weaning process until a weaning trial is carried out. Therefore, some weaning trials are attempted too early (premature) and some too late (delayed).

Delayed weaning can prolong mechanical ventilation and it is associated with high rates of morbidity and mortality (2, 3), including diaphragmatic dysfunction (4–6), ventilator-associated pneumonia, and ventilator-associated lung injury (7, 8). Premature weaning can result in reintubation (9) and can

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cause airway loss, compromised gas exchange, and aspiration (10, 11). Therefore, physicians need to balance aggressiveness versus caution when weaning from mechanical ventilation to avoid poor outcomes.

Numerous weaning protocols implementing readiness-to-wean criteria have been developed and provide structured guidance for a more consistent practice in the ICU (12, 13). In a Cochrane review, weaning protocols had overall positive outcomes, leading to a 26% mean reduction in total mechanical ventilation duration, and a 11% mean reduction in ICU length of stay (14). Furthermore, the use of weaning protocols for patients who are mechanically ventilated for greater than 24 hours has been suggested by the most recent guidelines from the American Thoracic Society (15). However, some of the main studies favoring weaning protocols suffered from design limitations that affected their internal validity (16), such as not using the same weaning approach between the control and intervention group (17) or having differences in disease severity at baseline between study groups (18). Other studies have found no difference in the main outcomes including mechanical ventilation duration between protocolized groups and usual care (19–22). Different results from weaning protocols studies can be largely influenced by the control group, considering that usual care practices can vary significantly depending on the context. Finally, most of the studies evaluating the implementation of weaning protocols in clinical practice have been carried out in high-income countries (14, 17, 18, 23, 24).

Readiness-to-wean criteria are based on simple daily screening of objective variables, suggesting their application is feasible in different settings. However, the moment to initiate a weaning trial is not determined strictly by readiness-to-wean criteria but is strongly influenced by the physician's clinical judgment and experience (25). Overall, there is a lack of research in ventilator protocols in resource-poor settings (26) and, therefore, their feasibility, application, and effects on clinical outcomes in ICUs of low- and middle-income countries (LMICs) have not been widely evaluated.

In this study of five ICUs in Lima, Peru, we compared 90-day mortality, ventilator-free days, ICU-free days, hospital-free days, and need of tracheostomy or reintubation between participants whose weaning trials were retrospectively classified to have occurred in a premature, opportune, or delayed manner determined by when they met readiness-to-wean criteria and when they actually had a weaning trial.

MATERIALS AND METHODS

Study Setting

Adults with acute respiratory failure were screened at five ICUs in four public hospitals in Lima, Peru from December 2010 to October 2013. Eligibility criteria included 1) greater than or equal to 18 years old, 2) at least 24 hours of invasive mechanical ventilation, and 3) enrollment into the study within 48 hours of initiation of mechanical ventilation. We received ethics approval and permission to conduct this study in each of the participating institutions: Hospital Nacional Edgardo Rebagliati Martins, Hospital Nacional Guillermo Almenara Irigoyen, Hospital Nacional Arzobispo Loayza, and Hospital de Emergencias Casimiro Ulloa. Ethics approvals were obtained from the institutional review boards of A.B. PRISMA and ESSALUD Hospital Nacional Edgardo Rebagliati Martins in Lima, Peru, and the Johns Hopkins School of Medicine, in Baltimore, MD. We obtained a waiver of written informed consent to conduct this observational study.

Study Design

This was a prospective, multicenter, longitudinal study. At enrollment, demographic data, chronic disease, and acute physiologic data were obtained for all participants meeting eligibility criteria. We also assessed disease severity using the Sequential Organ Failure Assessment (SOFA), the Simplified Acute Physiology Score (SAPS) II, and the Acute Physiology and Chronic Health Evaluation (APACHE) III scores (27–29). Participants were monitored daily for vital status, clinical and ventilator management, physiologic variables, and the use of sedation during their ICU stay. We followed participants until ICU discharge, death, or for 28 days, which was set as the day of administrative censoring. Participants who were discharged from the ICU were followed for vital status during their hospital stay. All participants were contacted 90 days after enrollment to assess vital status. We also collected information regarding mechanical ventilation duration, ICU length of stay, and the need for tracheostomy and reintubation.

Definitions

We established six criteria for readiness to wean based on the variables described in studies included in a recently published Cochrane systematic review and supported by the American Thoracic Society guidelines (14). These included three cardiovascular variables: systolic blood pressure greater than or equal to 90 mm Hg, heart rate less than or equal to 140 beats/minute, and no vasopressor support; two respiratory variables: F_{IO_2} less than or equal to 50% and positive end-expiratory pressure (PEEP) less than or equal to 5 cm H_2O; and one neurologic variable: either a Glasgow greater than or equal to 9, Ramsay greater than or equal to 3, or a Richmond Agitation-Sedation Scale score between –2 and 1 in that order of priority. We retrospectively identified when participants fulfilled the six criteria and defined this day as the opportune weaning date. Then, we retrospectively classified participants into three weaning groups, according to when they had fulfilled the criteria (opportune weaning date) and when their actual weaning trial had taken place. The groups were premature, if the weaning trial took place before fulfilling all criteria; opportune, if the weaning trial took place within 24 hours after fulfilling the criteria; and delayed, if the weaning trial took place over 24 hours after fulfilling criteria. A weaning trial was defined as the first attempt to discontinue mechanical ventilation support through a spontaneous breathing trial (SBT) with either of the following methods: T-piece, continuous positive airway pressure (CPAP), pressure support ventilation (PSV), or synchronized intermittent mandatory ventilation (SIMV).

Extubation failure was defined as either the need for reintubation within 48 hours of extubation or tracheostomy placement at any time after attempting a weaning trial. We defined ventilator-free days as the difference in days between the last extubation day and day 28 after study enrollment. This was defined as 0 if the participant died before 28 days or if the participant had greater than 28 days of mechanical ventilation. ICU-free days was defined as the number of days between the last day of ICU discharge and day 28 after study enrollment. This was defined as 0 if dead before 28 days or if the participant remained greater than 28 days in the ICU. We defined hospital-free days as the number of days between the last day of hospital discharge and day 60 after study enrollment. This was 0 if dead before 60 days or if the participant had greater than 60 days of length of stay in the hospital.

Biostatistical Methods

Our primary outcomes were 90-day mortality, ventilator-free days, ICU-free days, and hospital-free days. Secondary outcomes were rates of reintubation, tracheostomy, and extubation failure. The primary exposure variable was timing of the initial weaning trial in relation to the day readiness-to-wean criteria were met: premature, opportune, or delayed. Analysis of variance and chi-square tests were used to determine differences in baseline continuous and categorical variables, respectively. The main objective was to determine differences in outcomes between the three weaning groups. Single variable or multivariable linear or logistic regression was used to compare outcomes between the weaning classification groups. For each model, the outcome of interest was regressed onto weaning classification. All multivariable models were adjusted for age, sex, disease severity, and indicator variables for ICU to control for potential confounding. All analyses were conducted in STATA 13 (StataCorp, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

RESULTS

Participant Characteristics

A total of 1,858 participants were screened between December 2010 and October 2013, of which 116 did not meet eligibility criteria. Eighty-five participants were missing either baseline information, daily clinical information, or clinical outcomes, leaving a final sample of 1,657 participants included in the analysis (**Fig. 1**).

We summarized baseline characteristics of study participants in **Table 1**. Average age was 59.9 years (SD = 18.8) and 54% were men. The proportion of participants with premature, opportune, and delayed weaning varied between the different ICUs enrolled ($p = 0.01$). At admission, the premature group had a higher respiratory rate, use of vasopressors, FIO_2, and PEEP requirements. Additionally, the premature group also had the worst disease severity given by the highest values for the SOFA, SAPS II, and APACHE III scores. The delayed group had a higher proportion of chronic kidney disease.

Categorization of Weaning Groups

Of the full sample, 1,252 participants (75.6%) had a weaning trial at some point during the first 28 days in the ICU and were therefore classified into our three main study groups: premature (761, 60.8%), opportune (196, 15.7%), and delayed weaning (295, 23.6%). Overall, participants had their initial weaning trial a median of three days after intubation (**Fig. 2**). Four-hundred five participants (24.4%) were not categorized because they did not have a weaning trial. Of those who were not categorized, the majority died before any weaning attempt was made (89.4%), while others were extubated without an initial weaning trial, were transferred to another hospital, or were never weaned during the study time.

Differences in Main Outcomes by Weaning Group

Overall 90-day mortality was 49.1%. There was no significant difference in 90-day mortality among groups (**Table 2**). Mean ventilator-free days, ICU-free days, and hospital-free days for

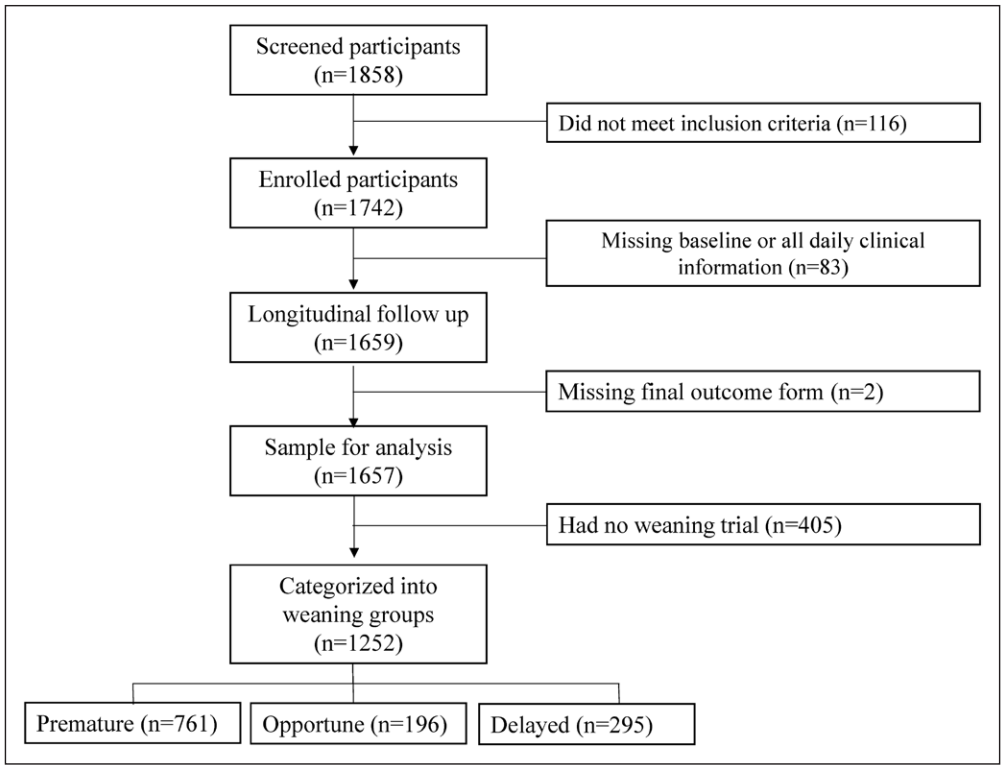

Figure 1. Flow diagram of study population.

TABLE 1. Baseline Characteristics of Study Participants

Characteristics	All Participants ($n = 1,252$)	Premature (60.8%, $n = 761$)	Opportune (15.7%, $n = 196$)	Delayed (23.6%, $n = 295$)	p
Demographics					
Age, yr, mean (SD)	59.9 (18.8)	59.3 (18.5)	59.8 (19.6)	61.2 (18.8)	0.33
Male, % (*n*)	54.2 (679)	56.2 (428)	45.9 (90)	54.6 (161)	0.04
Body mass index, kg/m^2, mean (SD)	26.6 (4.9)	26.9 (5.1)	26.4 (4.7)	26.2 (4.6)	0.09
Comorbidities, % (*n*)					
Myocardial infarction	6.4 (80)	7.1 (54)	5.6 (11)	5.1 (15)	0.44
Stroke	9.6 (120)	9.2 (70)	9.7 (19)	10.5 (31)	0.80
Chronic obstructive pulmonary disease	1.8 (23)	1.8 (14)	2.0 (4)	1.7 (5)	0.96
Diabetes	15.4 (193)	16.6 (126)	16.3 (32)	11.9 (35)	0.16
Chronic kidney disease	15.2 (190)	13.0 (99)	17.9 (35)	19.1 (56)	0.03
ICU, % (*n*)					< 0.01
Casimiro Ulloa	21.5 (269)	23.8 (181)	20.9 (41)	15.9 (47)	
Reba gliati 3	38.8 (486)	38.4 (292)	35.7 (70)	42.0 (124)	
Almenara	15.7 (196)	14.3 (109)	19.4 (38)	16.6 (49)	
Loayza	16.6 (208)	18.0 (137)	19.4 (38)	11.2 (33)	
Reba gliati 7	7.4 (93)	5.5 (42)	4.6 (9)	14.2 (42)	
Clinical variables					
Heart rate, beats/min, mean (SD)	86.2 (20.7)	87.0 (21.3)	85.6 (19.0)	84.5 (20.2)	0.20
Respiratory rate, breaths/min, mean (SD)	18.3 (4.1)	18.5 (4.1)	18.0 (4.3)	17.9 (4.0)	0.05
Systolic blood pressure, mm Hg, mean (SD)	121.0 (21.1)	120.0 (20.6)	122.9 (22.0)	122.5 (21.7)	0.08
Use of vasopressors, % (*n*)	57.4 (718)	65.2 (496)	50.5 (99)	41.7 (123)	< 0.01
Acute respiratory distress syndrome, % (*n*)	14.9 (186)	16.2 (123)	13.3 (26)	12.6 (37)	0.27
APACHE II score	23.3 (7.7)	23.5 (7.8)	22.0 (6.5)	23.5 (8.0)	0.04
APACHE III score	79.6 (27.0)	80.6 (27.6)	75.1 (22.7)	79.8 (27.8)	0.04
Sequential Organ Failure Assessment score	9.2 (3.4)	9.6 (3.4)	8.5 (3.3)	8.5 (3.4)	< 0.01
Simplified Acute Physiology Score II	52.9 (15.3)	53.7 (15.6)	50.6 (15.6)	52.2 (15.4)	0.02
Ventilator variables, mean (SD)					
F_{IO_2}, %	41.4 (14.9)	42.3 (14.6)	40.8 (15.8)	39.3 (14.8)	0.01
Positive end-expiratory pressure, cm H_2O	7.4 (3.6)	7.7 (3.7)	6.9 (3.3)	6.6 (3.2)	< 0.01

APACHE = Acute Physiology and Chronic Health Evaluation.

all study participants were 10.1, 7.3, and 11.1 days, respectively. After adjusting for sex, age, hospital, and disease severity at baseline, both the premature and the delayed weaning groups had poorer clinical outcomes (fewer ventilator-free days, ICU-free days, and hospital-free days) compared with the opportune weaning group (Table 2).

Reintubation, Tracheostomy, and Extubation Failure

Of the sample population, 834 participants (50.3%) had a first extubation a median of 6 days after initiation of mechanical ventilation. We summarized median and interquartile range for the number of days from initiation of mechanical ventilation to first weaning and first extubation attempts in **Table 3**. The opportune group initiated weaning trials sooner than the premature group. Of the participants who were extubated, 160 (19.1%) were re-intubated at least once and 14 (1.7%) were re-intubated more than once. Three-hundred participants (18.1%) received a tracheostomy after initiating mechanical ventilation at a median of 15 days (Fig. 2). After adjusting for sex, age, hospital, and disease severity at baseline, the premature and delayed

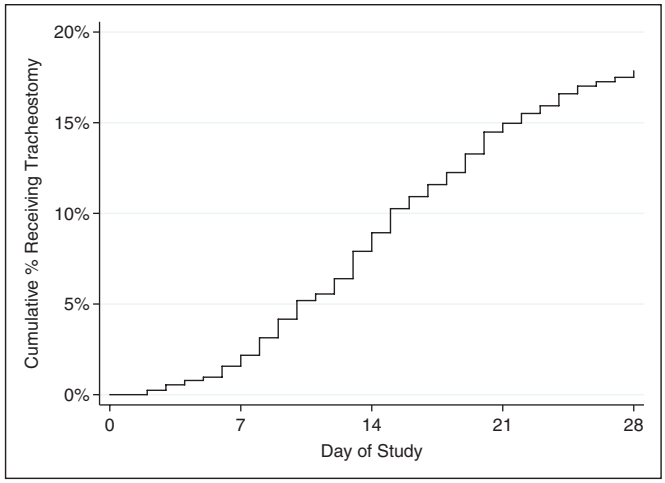

Figure 2. Cumulative percentage of participants receiving tracheostomy.

groups had greater odds of extubation failure, but this did not achieve statistical significance (premature odds ratio [OR], 1.29; 95% CI, 0.86–1.93 and delayed OR, 1.53; 95% CI, 0.97–2.40).

DISCUSSION

Our study of 1,657 participants based in Peru is the largest and one of few multicenter, prospective, observational studies analyzing mechanical ventilation practices, including weaning, in LMICs (30–33). Our data suggest that if readiness-to-wean criteria used in weaning protocols are applied, participants may achieve better clinical outcomes. These findings highlight the potential for the implementation of well-established weaning protocols in ICUs of LMICs. Previous studies have reported no association between the use of weaning protocols and ICU or in-hospital mortality (14, 18, 21, 24, 34). Likewise, we did not find a significant difference in 90-day mortality between weaning groups.

In this study, we found the opportune group achieved better clinical outcomes compared with the premature and delayed weaning groups. Our results show the opportune group had significantly more ventilator-free days, ICU-free days, and hospital-free days when adjusted for disease severity at baseline, and these results are comparable with findings in high-income countries. A meta-analysis by Blackwood et al (23) that included 11 studies (10 conducted in high-income countries) found that the use of weaning protocols led to a 25% reduction (95% CI, 9–39%) in the mean duration of mechanical ventilation and a 10% reduction (95% CI, 2–19%) in the ICU length of stay. In an updated version of the analysis including six new trials (three from high-income countries and three from LMICs), the results were similar, showing a 26% reduction (95% CI, 13–37%) in the mean duration of mechanical ventilation and an 11% reduction (95% CI, 3–19%) in ICU length of stay (14). Nonetheless, both of these analyses were limited by small sample size and heterogeneity among studies. Based on those findings,

TABLE 2. Unadjusted and Adjusted Clinical and Mortality Outcomes for Premature and Delayed Weaning Groups Compared With Opportune Weaning

	Premature vs Opportune		Delayed vs Opportune	
Outcomes	Unadjusted	Adjusted	Unadjusted	Adjusted
Ventilator-free days, mean difference (*p*)	−2.47 ($p = 0.003$)	−2.17 ($p = 0.009$)	−3.84 ($p < 0.001$)	−3.54 ($p < 0.001$)
ICU-free days, mean difference (*p*)	−2.60 ($p < 0.001$)	−2.23 ($p = 0.002$)	−4.14 ($p < 0.001$)	−3.67 ($p < 0.001$)
Hospital-free days, mean difference (*p*)	−3.46 ($p = 0.014$)	−2.76 ($p = 0.044$)	−5.77 ($p < 0.001$)	−4.41 ($p = 0.006$)
90-d mortality, mean difference (*p*)	1.17 ($p = 0.37$)	1.06 ($p = 0.76$)	1.27 ($p = 0.22$)	1.12 ($p = 0.58$)

Linear and logistic regression models were adjusted by age, sex, disease severity, and ICU.

TABLE 3. Median and Interquartile Range of the Number of Days From Initiation of Mechanical Ventilation to First Weaning and Extubation Attempts, Stratified by Weaning Group

Characteristics	All Participants (*n* = 1,252)	Opportune (*n* = 196)	Premature (*n* = 761)	Delayed (*n* = 295)	*p*
Number of days until initial weaning trial, median (IQR)	3 (1–6)	2 (0–4)	3 (1–6)	5 (2–9)	< 0.001
Number of days until first extubation, median (IQR)	6 (3–10)	4 (3–8)	6 (3–10)	5 (8–12)	< 0.001

IQR = interquartile range.

the latest American Thoracic Society/American College of Chest Physicians guidelines on mechanical ventilation suggest using ventilator liberation protocols for patients who are on mechanical ventilation for greater than 24 hours (15). However, studies that provide similar evidence in LMICs are scarce (35–37). Inappropriate weaning results in poorer clinical outcomes, but weaning is a complex clinical intervention influenced by inter-related and inter-dependent components associated with the context (38). Therefore, it is important to study different contexts such as LMICs to identify more targeted practices that could improve clinical outcomes.

So far, results have been inconclusive regarding the effects of the use of weaning protocols on rates of re-intubation, tracheostomy, extubation failure, or success (14, 17, 24, 39). We did not find a significant difference between weaning groups regarding odds for extubation failure. However, an important limitation exists when comparing these outcomes due to differing definitions of extubation failure and success across studies. The fact that the opportune group initiated weaning trials sooner than the premature group, may be secondary to the premature group having worse disease severity at baseline, which could lead to weaning trials being premature even though they were initiated at a later date.

A strength of our study is that, to our knowledge, this is one of the largest and one of very few prospective cohort studies evaluating mechanical ventilation practices in multiple ICUs in LMICs (30–33). It provides valuable information regarding management of mechanically ventilated patients in resource-limited settings. Previous studies in Latin America that evaluated mechanical ventilation and weaning protocols in adults have not included greater than 30–200 participants (35–37).

Our study has some limitations. Because it was an observational study carried out for 3 years, physicians may have inadvertently changed their behaviors during the study period. Specifically, residents, attending physicians, and the staff involved in the study may have changed their behavior and practices over time or as a result of the study. Another limitation was that weaning trials in this study were carried out using a variety of methods including T-piece, CPAP, PSV, or SIMV. This is important because studies comparing the different modalities have shown differences in certain outcomes. For example, when comparing PSV with T-tube: one recent meta-analysis of 31 trials found that PSV patients were more likely to be successfully extubated (40), whereas another meta-analysis showed that PSV reduced work of breathing, effort, and rapid shallow breathing (41). Nonetheless, another systematic review concluded that SBT technique did not influence weaning success, ICU mortality, or reintubation rate (42). Other studies have found that SIMV is the least effective method to wean difficult patients (43, 44). Overall, individual studies have shown mixed results regarding the ideal SBT and evidence has been of low quality (42).

CONCLUSIONS

Better clinical outcomes occur with opportune weaning compared with premature and delayed weaning. These findings highlight the potential for implementing readiness-to-wean criteria as a simple, low-cost intervention that could lead to improvements in ICU outcomes in LMICs. Future studies are required to evaluate the actual impact of implementation of weaning protocols not only in clinical outcomes but also in lowering costs, which would be of great value in resource-limited settings.

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Dr. Diaz-Soto and Mr. Morgan analyzed and interpreted the data, and drafted the article. Dr. Davalos collected, analyzed, and interpreted the data, and drafted the article. Drs. Herrera, Roldan, Paz, Jaymez, Chirinos, Portugal, and Quispe collected the data and drafted the article. Dr. Denney helped with the study design, collected the data, and drafted the article. Dr. Brower helped with the study design, interpreted the data, and drafted the article. Dr. Checkley designed and supervised the study, obtained funding, analyzed and interpreted the data, and drafted the article.

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Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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