Early Identification of Extubation Failure Using Integrated Pulmonary Index and High-Risk Factors

Ramandeep Kaur, David L Vines, Ankeet D Patel, Roberta Lugo-Robles, and Robert A Balk

BACKGROUND: Early detection and prevention of extubation failure offers the potential to improve patient outcome. The primary aim of this study was to compare the predictive ability of the Integrated Pulmonary Index and presence of high-risk factors in determining extubation failure. METHODS: A retrospective cross-sectional study of intubated adult subjects receiving mechanical ventilation for > 24 h was conducted at an academic medical center. The primary outcome was extubation failure, defined as the need for re-intubation or rescue noninvasive ventilation within 48 h after planned extubation. RESULTS: Among 216 subjects, 170 (78.7%) were successfully extubated, and 46 (21.3%) failed extubation. Extubation failure group had higher body mass index (26.21 vs 28.5 kg/m^2, $P = .033$), rapid shallow breathing index during spontaneous breathing trial (43 vs 53.5, $P = .02$), and APACHE II score (11.86 vs 15.73, $P < .001$). Presence of ≥3 high-risk factors (odds ratio 3.11 [95% CI 1.32–7.31], $P = .009$), APACHE II > 12 on extubation day (odds ratio 2.98 [95% CI 1.22–7.27], $P = .02$), and Integrated Pulmonary Index decrease within 1 h after extubation (odds ratio 7.74 [95% CI 3.45–17.38], $P < .001$) were independently associated with extubation failure. The failed extubation group had higher ICU mortality (8.8% vs 19.6%; absolute difference 10.7% [95% CI –1.9% to 23.4%], $P = .040$) and hospital mortality (10% vs 22%; absolute difference 16.1% [95% CI 2.2–30%], $P = .005$) compared to the successful group. CONCLUSIONS: Among subjects receiving mechanical ventilation for > 24 h, decreasing Integrated Pulmonary Index within the first hour postextubation was a predictor of extubation failure and was superior to other weaning variables collected in this retrospective study. The presence of ≥ 3 high-risk factors was also independently associated with extubation failure. Future clinical studies are required to prospectively test the ability of postextubation Integrated Pulmonary Index monitoring to guide additional interventions designed to reduce re-intubation rates and improve patient outcome. *Key words: mechanical ventilation; extubation failure; Integrated Pulmonary Index; extubation outcome.* [Respir Care 2021;66(10):1542–1548. © 2021 Daedalus Enterprises]

Introduction

The decision to discontinue mechanical ventilation is challenging. Both the premature removal of ventilatory support and the delay in discontinuing mechanical ventilation are linked with adverse clinical outcomes.[1] Extubation failure occurs in 10–20% of mechanically ventilated patients and is associated with poor outcomes in terms of length of hospital stay, morbidity, and mortality.[2,3] Extubation failure is defined as the need to re-institute ventilatory support within 24–48 h of planned extubation, and its prevalence is higher among medical and multidisciplinary ICU patients.[4] Extensive literature has been published on the assessment of a patient's ability to breathe with minimal ventilatory support in the form of a spontaneous breathing trial (SBT).[5] However, past evidence reveals that neither respiratory functional parameters nor clinical evaluation during SBT accurately predict subsequent extubation failure.[6,7] Several weaning tools have been evaluated in an attempt to predict extubation failure, but to date these pre-extubation weaning tools are poor predictors of extubation failure in the critical care unit.[8,9]

The need to re-intubate a recently weaned patient is associated with an increased ICU mortality rate of 26–50% as compared to 3–12% among patients who do not need to be re-intubated.[10,11] The reason for high mortality rate among re-intubated patients is attributed to greater severity of illness, clinical deterioration between extubation and re-

intubation, and the adverse effects of prolonged mechanical ventilation.[12,13] To improve outcome in high-risk patients, past researchers have recommended implementing clinical strategies to recognize at-risk patients early and timely re-institute the ventilatory support.[2,3,13] In a concise clinical review, Thille et al[10] summarized a list of potential risk factors associated with extubation failure: age > 65 y, underlying cardiorespiratory disease, pneumonia as a reason for intubation, high rapid shallow breathing index (RSBI), positive fluid balance, prior failed extubations, Glasgow coma scale < 8, moderate or abundant endotracheal secretions, and absent or weak cough. However, currently there is no evidence available detailing whether the presence of 1, 2, or 3 high-risk factors accurately predicts extubation failure.

Due to the poor predictive ability of pre-extubation weaning parameters to detect extubation failure,[8,9] postextubation monitoring offers the potential to early identify at risk patients who may benefit from timely application of clinical therapies such as high-flow nasal cannula or noninvasive ventilation. The Integrated Pulmonary Index (IPI) is a proprietary, clinical monitoring algorithm that is available on commercial patient monitoring systems. It combines 4 vital physiological parameters to provide a rapid and real-time assessment of a patient's respiratory status: end-tidal carbon dioxide pressure (P_{ETCO_2}), breathing frequency, heart rate, and S_{pO_2}. IPI is displayed as a single indexed value (range 1–10). In a clinical validation study, Ronen et al[14] reported that an IPI ≤ 4 predicted the need for immediate clinical intervention due to deterioration in patient's respiratory status. The authors noted a good correlation between continuous P_{ETCO_2}, breathing frequency, heart rate, and S_{pO_2} values and expert clinical opinions.[14] However, in a clinical study setting, our preliminary data indicated that a declining IPI trend is a better predictor of extubation failure.[15] Currently there are no published data comparing IPI to other weaning indices or high-risk factors. The primary objective of this study was to compare the predictive ability of IPI within first hour of extubation with high-risk factors as well common weaning indices like RSBI among patients receiving mechanical ventilation for > 24 h.

QUICK LOOK

Current knowledge

Extubation failure is associated with poor clinical outcomes in term of mortality rate, hospital length of stay, and costs. Early identification and timely application of clinical interventions in patients at risk for failing extubation offer the potential to improve patient outcome.

What this paper contributes to our knowledge

In subjects mechanically ventilated for > 24 h, decreasing Integrated Pulmonary Index within the first hour postextubation was a predictor of extubation failure. The presence of ≥ 3 high-risk factors was also independently associated with extubation failure.

Methods

This was a retrospective study of adult subjects who were intubated for > 24 h and received mechanical ventilation in adult ICUs at the Rush University Medical Center from February 2018 through December 2018. The study protocol was approved by the institutional review board (18112803). In this study, we retrospectively reviewed the electronic medical record of subjects who fulfilled inclusion and exclusion criteria. The inclusion criteria were: adult subjects ≥ 18 y old who were endotracheally intubated, received assisted mechanical ventilation for > 24 h, and underwent planned extubation based on medical team approval. Patients were excluded from the study if they were < 18 y old, pregnant, had a tracheostomy tube, had a do-not-resuscitate order, had unplanned or terminal extubation, or were receiving extracorporeal membrane oxygenation at the time of extubation.

Data Collection

Demographic and clinical data were obtained from the subject's electronic medical record. Data included age, gender, ethnicity, reason for intubation, length of mechanical ventilation, number of failed SBTs, and the presence/absence of following high-risk factors: age > 65 y, APACHE II > 12 on extubation day, body mass index > 30 kg/m^2, inadequate secretion management (continuous coarse crackles not resolved after cough/suctioning), difficult or prolonged weaning (failure of > 3 SBTs), heart failure as primary indication

Dr Vines, Dr Kaur, and Mr Patel are affiliated with the Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, Illinois. Dr Lugo-Robles is affiliated with the Henry M. Jackson Foundation for the Advancement of Military Medicine, Department of Preventive Medicine and Biostatistics, Uniformed Services University-USUHS, Bethesda, Maryland. Dr Balk is affiliated with the Division of Pulmonary, Critical Care, and Sleep Medicine, Rush University Medical Center, Chicago, Illinois.

Dr Vines has disclosed relationships with Teleflex Medical, Rice Foundation, and Ohio Medical. The other authors have disclosed no conflicts of interest.

Correspondence: Ramandeep Kaur PhD RRT RRT-ACCS, 1620 W Harrison St, Tower LL1202, Chicago, IL 60612. E-mail: ramandeep_kaur@rush.edu.

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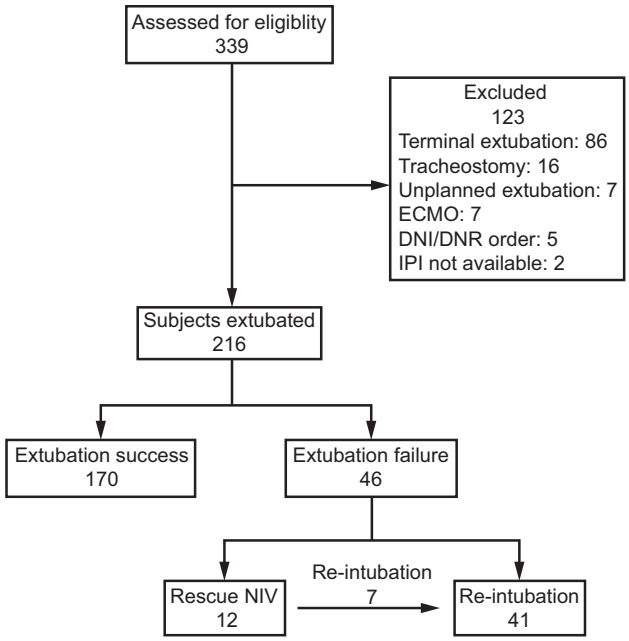

Fig. 1. Flow chart. ECMO = extracorporeal membrane oxygenation; DNI/DNR = do not intubate/do not resuscitate; IPI = Integrated Pulmonary Index; NIV = noninvasive ventilation.

for mechanical ventilation, diagnosis of COPD, prolonged mechanical ventilation (> 7 d on ventilator), and Glasgow coma scale < 8. SBT was performed for 30 min via 100% automatic tube compensation per institution weaning guidelines. RSBI was calculated as the ratio of breathing frequency to exhaled tidal volume within 3–5 min of the start of the SBT and at the end of the SBT (30 min). The modified Integrated Weaning Index (IWI) score was calculated based on the following equation (static compliance × S_{pO_2}/RSBI)[16]. Compliance was recorded when the patient was receiving full ventilatory support. S_{pO_2} and RSBI were obtained at the end of the SBT. IPI, heart rate, breathing frequency, S_{pO_2}, and P_{ETCO_2} at 5 min, 30 min, and 1 h after extubation and the amount of supplemental oxygen and type of oxygen device used after extubation were recorded. The extubation outcome within 48 h postextubation and, if subject was re-intubated, causes for re-intubation and the time from extubation to re-intubation were collected.

Study Outcome

The primary objective was to compare the predictive ability of IPI decrease by 1 from baseline after extubation, and the presence of and number of high-risk factors for re-intubation, in predicting extubation failure. Extubation failure, was defined as either the subject was re-intubated and returned to mechanical ventilation within 48 h after the initial discont inuation from the ventilation, or the subject required rescue noninvasive ventilation within 48 h after the initial discontinuation from ventilation. Successful extubation was defined as freedom from mechanical ventilation 48 h after extubation. Secondary outcomes were ICU and hospital mortality as well as tracheostomy received.

Statistical Analysis

Categorical variables were expressed as frequency (percentage). Continuous variables were presented as mean ± SD or as median and interquartile range (IQR). Differences between groups were determined with the 2-tailed *t* test, Mann-Whitney test, or Kruskal-Wallis test for quantitative variables, and with the chi-square test or Fisher exact test for categorical variables, as appropriate. A multivariate logistic regression model was used. Outcome variable and covariates were assessed using the backward method. The model fit was assessed Hosmer-Lemeshow goodness-of-fit statistic. Coefficient of determination, R^2, was evaluated using the Nagelkerke R^2 and model performance by the classification table. Statistically significant independent variables were maintained in the model. Covariates such as gender, age, and body mass index were also maintained in the model, even if they did not reach statistical significant values. A 2-tailed significance level $\alpha = 0.05$ and 95% CIs were adopted. All analyses were performed using SPSS 26.0 (IBM, Armonk, New York).

Results

Subject Characteristics

During the study period, 339 patients were screened for eligibility (Fig. 1); 123 patients were excluded because they were terminally extubated ($n = 86$), had a tracheostomy ($n = 16$), had an unplanned extubation ($n = 7$), were receiving extracorporeal membrane oxygenation ($n = 7$), or had a do-not-intubate/do-not-resuscitate order ($n = 5$), or when an IPI recording was not available ($n = 2$). A total of 216 subjects were included in the data analysis. Of 216 subjects, 170 (78.7%) underwent successful extubation, and 46 (21.3%) failed extubation. Of those who failed extubation, 34 subjects were re-intubated, and 12 received rescue noninvasive ventilation. Of the 12 subjects who received rescue noninvasive ventilation, 7 subjects received re-intubation.

The demographic and clinical characteristics of overall subjects are presented in Table 1. The demographic and clinical characteristics of subjects in the extubation success and failure groups were similar (Table 1), except for a higher body mass index (26.21 vs 28.5 kg/m^2, $P = .033$), higher RSBI at the end of the SBT (43 vs 53.5, $P = .02$), and higher APACHE II score (11.86 vs 15.73, $P < .001$) in the extubation failure group. Extubation failure group had median 3 high risk factors whereas success group had

Table 1. Subject Characteristics

	Overall ($N = 216$)	Extubation Success ($n = 170$)	Extubation Failure ($n = 46$)	P
Age, y	59.2 ± 15.2	58.2 ± 15.9	63.1 ± 11.4	.053
Male	120 (55.5)	93 (54.7)	27 (58.7)	.73
Body mass index, kg/m^2	27 (23–32)	26.2 (22–32)	28.5 (24–36)	.033
Ethnicity				.13
Black	79 (36.6)	68 (40)	11 (23.9)	
White	88 (40.7)	66 (38.8)	22 (47.8)	
Hispanic	24 (11.1)	18 (10.6)	6 (13)	
Asian	6 (2.8)	3 (1.8)	3 (6.5)	
Other	19 (8.7)	15 (8.8)	4 (8.7)	
Reason for mechanical ventilation				.66
Airway protection	88 (40.7)	69 (40.6)	19 (41.3)	
Elective	63 (29.2)	53 (31.2)	10 (21.7)	
Hypoxic respiratory failure	43 (19.9)	35 (20.6)	8 (17.4)	
Hypercapnic respiratory failure	15 (6.9)	7 (4.1)	8 (17.4)	
Cardiac arrest	7 (3.2)	6 (3.5)	1 (2.2)	
Duration of mechanical ventilation, h	62.37 (42–116)	62.10 (42–110)	71.13 (40–123)	.65
APACHE II score	12.69 ± 5.26	11.86 ± 4.95	15.73 ± 5.31	< .001
RSBI at the end of SBT	44 (33–62)	43 (31–58)	53.5 (38–72)	.02
Modified IWI	96.24 (59.4–145)	101 (71.25–151)	67.82 (44.48–13.65)	.004
High-risk factors, no.	2 (1–3)	2 (1–3)	3 (2–3.25)	< .001
High-risk factors for re-intubation				
Age > 65 y	83 (38.4)	61 (35.8)	22 (47.8)	.14
Heart failure as primary indication for mechanical ventilation	15 (6.9)	12 (7)	3 (6.5)	.89
Diagnosis of COPD	19 (8.8)	11 (6.5)	8 (17.4)	.035
APACHE II > 12 on extubation day	104 (48.1)	69 (40.6)	35 (76.1)	< .001
Body mass index > 30 kg/m^2	71 (32.9)	54 (31.8)	17 (37)	.50
Difficult weaning	8 (3.7)	6 (3.5)	2 (4.3)	.67
Inability to clear secretions	10 (4.6)	8 (4.7)	2 (4.3)	.58
Presence of > 2 comorbidities	179 (82.9)	137 (80.6)	42 (91.3)	.08
GCS < 8 on extubation day	11 (5.1)	7 (4.1)	4 (8.7)	.25
P_{aCO_2} > 45 mm Hg pre-extubation	22 (10.2)	15 (8.8)	7 (15.2)	.30
Mechanical ventilation duration > 7 d	31 (14.4)	24 (14.11)	7 (15.2)	.85
IPI 5 min after extubation	8 (7–9)	8 (7–9)	8 (6–9)	.040
IPI 30 min after extubation	8 (7–10)	8 (7–10)	7 (5–8)	< .001
IPI 1 h after extubation	8 (7–10)	8 (7–10)	6 (5–9)	< .001

Data are presented as mean ± SD, *n* (%), or median (interquartile range).
APACHE II = Acute Physiology and Chronic Health Evaluation II
RSBI = rapid shallow breathing index
SBT = spontaneous breathing trial
IWI = integrated weaning index
GCS = Glasgow coma scale
IPI = Integrated Pulmonary Index

median 2 high risk factors ($P < .001$). Among the high-risk factors for re-intubation, the incidence of having a COPD diagnosis (6.5% vs 17.4%, $P = .035$) and an APACHE II > 12 on extubation day (40.6% vs 76.1%, $P < .001$) were higher in the extubation failure group. Modified IWI was significantly different between the success group and the failure group ($P = .004$). The median IPI values were significantly different between the extubation success and failure group at 5 min ($P = .040$), 30 min ($P < .001$) and 1 h ($P < .001$) after extubation.

Study Outcomes

The prevalence of postextubation IPI decrease by 1 from baseline was higher in the extubation failure group than in the success group (17.6% vs 58.6%, absolute difference 41% [95% CI 25.2–56.9], $P < .001$; Table 2). Before extubation, prevalence of having ≥ 1 high-risk factor was similar in both the groups (90% vs 95.7%, absolute difference 5.1% [95% CI –2.4 to 12.6], $P = .38$). However, the prevalence of having 2 high-risk factors (60% vs 80%, absolute

Table 2. Study Outcome

	Extubation Success ($n = 170$)	Extubation Failure ($n = 46$)	Absolute Difference (95% CI)	P^*
Presence of IPI decrease of 1 from baseline within 1 h after extubation	30 (17.6)	27 (58.6)	41 (25.2–56.9)	< .001
Presence of ≥ 1 high-risk factor	154 (90)	44 (95.7)	5.1 (–2.4 to 12.6)	.37
Presence of ≥ 2 high-risk factors	102 (60)	37 (80)	20.4 (6.5–34.4)	.01
Presence of ≥ 3 high-risk factors	47 (28)	29 (63)	35.4 (19.5–51.3)	< .001
Received tracheostomy	0 (0)	18 (39.1)	39.1 (24.5–53.8)	< .001
ICU mortality	15 (8.8)	9 (19.6)	10.7 (–1.9 to 23.4)	.040
Hospital mortality	17 (10)	12 (22)	16.1 (2.2–30)	.005

Extubation data are presented as *n* (%); absolute difference data are presented as percent difference.
IPI = Integrated Pulmonary Index
* Chi-square test or Fisher exact test.

Table 3. Multivariate Analysis of the Extubation Failure Predictors

	Odds Ratio (95% CI)	*P*
IPI decrease of 1 from baseline within 1 h after extubation	7.74 (3.45–17.38)	< .001
Presence of ≥ 3 high-risk factors	3.11 (1.32–7.31)	.009
APACHE II score > 12 on extubation day	2.98 (1.22–7.27)	.02
Age	1.01 (0.98–1.04)	.37
Gender	1.27 (0.55–2.91)	.57
Body mass index	1.02 (0.98–1.07)	.26
Diagnosis of COPD	3.03 (0.86–1.66)	.08
RSBI at the end of SBT	1.0 (0.99–1.01)	.36
Presence of ≥ 2 high-risk factors	0.51 (0.15–1.82)	.30
APACHE II	1.04 (0.94–1.15)	.41
Modified IWI before extubation	1.0 (0.99–1.0)	.38

Variable(s) entered on step 1: Gender, age, body mass index, diagnosis of COPD, APACHE II score > 12 points on extubation day, IPI decrease by 1 from baseline after extubation, RSBI at the end of SBT, 2 high-risk factors, 3 high-risk factors, APACHE II, modified IWI before extubation.
IPI = Integrated Pulmonary Index
APACHE II = Acute Physiology and Chronic Health Evaluation II
RSBI = rapid shallow breathing index
SBT = spontaneous breathing trial
IWI = integrated weaning index

difference 20.4% [95% CI 6.5–34.4], $P = .01$) or 3 high-risk factors (28% vs 63%, absolute difference 35.4% [95% CI 19.5–51.3], $P < .001$) was significantly higher in the extubation failure group. The prevalence of receiving a tracheostomy was higher among the failure group than in the success group (0% vs 39.1%, absolute difference 39.1% [95% CI 24.5–53.8], $P < .001$). Subjects with failed extubation had 2 times higher ICU and hospital mortality as compared to those that were successfully extubated (Table 2). Among 34 subjects who required re-intubation, median time to re-intubation was 14 h (IQR 3–32), and among those who failed initial rescue noninvasive ventilation, median time to re-intubate was 96 h (IQR 84–120). The most common cause for re-intubation was acute respiratory failure followed by airway issues (eg, stridor, need for airway protection).

Multivariate Analysis

Multivariate logistic regression showed that IPI decrease by 1 from baseline within 1 h after extubation (odds ratio 7.74 [95% CI 3.45–17.38], $P < .001$), presence of ≥ 3 high-risk factors (odds ratio 3.11 [95% CI 1.32–7.31], $P = .009$), and APACHE II score > 12 on extubation day (odds ratio 2.98 [95% CI 1.22–7.27], $P = .02$) were independently associated with extubation failure (Table 3).

Discussion

In this study, we tested the ability of a decreasing IPI within 1 h after planned extubation along with the presence of high-risk factors to predict extubation failure. The study results demonstrated that a decreasing IPI within 1 h after extubation was significantly associated with extubation

failure. Subjects with a postextubation decrease in IPI were 7.7 times more likely to fail extubation. Another important study finding revealed that having ≥ 3 high-risk factors was also independently associated with extubation failure. Among all the high-risk factors analyzed for extubation failure, only APACHE II score > 12 on extubation day was predictive of failing extubation by itself. Even though modified IWI recorded before SBT was significantly different between the 2 groups, it did not independently predict the extubation failure.

The precise prediction of extubation failure is challenging but is extremely important, and a reliable tool will allow for application of early intervention in these high-risk patients to prevent the re-intubation and increased morbidity and mortality associated with failed extubation and re-intubation. Timely provision of therapies such as high-flow oxygen therapy, airway clearance, bronchodilator therapy, and others may avoid extubation failure and its associated adverse events. In an attempt to reduce the duration of mechanical ventilation to prevent associated complications, aggressive weaning approaches can lead to increased rates of unsuccessful discontinuation from the ventilator.[17] However, unlike the weaning phase, extubation remains neglected. The majority of the available scientific evidence explores the role of physiological variables, indices, and parameters before extubation occurs, which has limited ability to predict the extubation outcome.[9] Patients who fail planned extubation infrequently show signs of respiratory distress during the weaning process, explaining the low predictive value of RSBI in detecting extubation failure.[18] Most often, these patients gradually develop signs of respiratory distress after extubation, which can go unnoticed by bedside clinicians until it reaches an alarming level. This delay in allocating appropriate clinical therapies postextubation in a timely manner likely plays a major role in the adverse outcomes of re-intubation. Therefore, to prevent delay in detecting postextubation respiratory failure, careful and close postextubation monitoring may be an essential step in identifying high-risk patients.[19] IPI is a simple, concise, and easy-to-use algorithm readily available in some clinical monitoring systems and allows patients to be continuously monitored remotely. Our results indicate the clinical advantage of IPI in identifying postextubation subjects who are at greatest risk of extubation failure in comparison to other commonly used pre-extubation parameters such as RSBI and modified IWI.

Other clinical trials have used high-risk factors to identify a population with high rates of extubation failure. In a multicenter randomized clinical trial, Nava et al[20] used the presence of ≥ 1 high-risk factors to demonstrate that noninvasive ventilation is more effective than standard medical therapy in preventing extubation failure in a high-risk population. Similarly, Hernández et al[21] assigned therapy (noninvasive ventilation vs high-flow oxygen therapy) based on the presence of ≥ 1 high-risk factor to test if either of these therapies is noninferior in preventing postextubation respiratory failure and re-intubation in subjects at high risk of re-intubation. However, there is no established evidence available proving if, in fact, the presence of ≥ 1 high-risk factor is predictive of extubation failure. Therefore, in this study, we retrospectively investigated all of the common high-risk factors for re-intubation to test their role in predicting extubation failure. Our results indicated that the presence of ≥ 1 high-risk factor is not predictive of extubation failure. Instead, having ≥ 3 high-risk factors is independently associated with extubation failure. Therefore, to reduce needless application of clinical therapies to patients who are not at high risk for re-intubation and decrease medical cost, future researchers should utilize ≥ 3 high-risk factors to define the high-risk population.

Few studies have demonstrated the predictive role of APACHE II score on day of ICU admission in assessing extubation and patient outcome.[22-26] However, Epstein et al[27] reported the utility of APACHE II score on weaning day as a significant predictor of extubation failure. As a result, APACHE II score > 12 on the day of extubation is regarded as one of the high-risk factors for extubation failure in some clinical studies.[21,28] Our results demonstrate that APACHE II scores recorded on the day of extubation was significantly different among those who succeeded versus failed the extubation outcome (11.86 vs 15.73, $P < .001$), but the APACHE II score was not independently associated with extubation failure. However, an APACHE II score > 12 on extubation day was predictive of extubation failure. Therefore, including APACHE II score > 12 on extubation day into routine extubation decisions on the day of extubation may prove beneficial in identifying patients who are at risk for extubation failure.

The study has some limitations. First, this is a single-center study, which may have different weaning/extubation practices as compared to other medical centers. Second, we intentionally included a heterogeneous population regardless of the reason for intubation to test the ability of predictors to identify high-risk subjects among all patient populations. Third, we included common high-risk factors based on the past randomized clinical trials, concise reviews, etc., which may have led to missing some other high-risk factors and may have affected the predictive ability of the chosen clinical predictors. Fourth, we did not define our population based on the weaning ability (ie, simple, difficult); therefore, our findings may not be generalized to patients with difficult weaning. Fifth, we compared the variables from 2 different time points: weaning and high-risk variables during the pre-extubation phase, and IPI monitoring postextubation. Due to the lack of strong pre-extubation predictors, we believe using postextubation monitoring to early identify high-risk population will be beneficial in the timely allocation of clinical therapies to avoid extubation failure. Lastly, this study is retrospective in nature and therefore helpful in generating hypotheses to

further evaluate the benefits of IPI monitoring in the post-extubation management of critically ill patients.

Conclusions

Our results indicate that a decreasing IPI score within 1 h after extubation is a predictor of extubation failure and superior to other weaning variables. The presence of ≥ 3 high-risk factors is also associated with extubation failure. Future prospective clinical studies are needed to evaluate the clinical utility of using postextubation IPI monitoring to identify patients at high risk of extubation failure and to determine if timely allocation of rescue therapies can successfully reduce re-intubation rates and improve patient outcomes.

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