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The Early Phase of the Minute Ventilation Recovery Curve Predicts Extubation Failure Better Than the Minute Ventilation Recovery Time

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The Early Phase of the Minute Ventilation Recovery Curve Predicts Extubation Failure Better Than the Minute Ventilation Recovery Time*

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Study objectives: **To determine, in patients who had successful outcomes in spontaneous breathing trials (SBTs), whether the analysis of the minute ventilation ($\dot{V}$E) recovery time obtained by minute-by-minute sequential monitoring after placing the patient back on mechanical ventilation (MV) may be useful in predicting extubation outcome.**
Design: **Twelve-month prospective observational study.**
Setting: **Medical-surgical ICU of a university hospital.**
Patients: **Ninety-three patients receiving > 48 h of MV.**
Interventions: **Baseline respiratory parameters (*ie*, respiratory rate, tidal volume, and $\dot{V}$E) were measured under pressure support ventilation prior to the SBT. After tolerating the SBT, patients again received MV with their pre-SBT ventilator settings, and respiratory parameters were recorded minute by minute.**
Measurements and results: **Seventy-four patients (80%) were successfully extubated, and 19 patients (20%) were reintubated. Reintubated patients were similar to non-reintubated patients in baseline respiratory parameters and baseline variables, except for age and COPD diagnosis. The recovery time needed to reduce $\dot{V}$E to half the difference between the $\dot{V}$E measured at the end of a successful SBT and basal $\dot{V}$E (RT50%Δ$\dot{V}$E) was lower in patients who had undergone successful extubation than in those who had failed extubation (mean [± SD] time, 2.7 ± 1.2 vs 10.8 ± 8.4 min, respectively; $p < 0.001$). Multiple logistic regression adjusted for age, sex, comorbid status, diagnosis (*ie*, neurocritical vs other), and severity of illness revealed that neurocritical disease (odds ratio [OR], 7.6; $p < 0.02$) and RT50%Δ$\dot{V}$E (OR, 1.7; $p < 0.01$) were independent predictors of extubation outcome. The area under the receiver operating characteristic curve for the predictive model was 0.89 (95% confidence interval, 0.81 to 0.96).**
Conclusion: **Determination of the RT50%Δ$\dot{V}$E at the bedside may be a useful adjunct in the decision to extubate, with better results found in nonneurocritical patients.**

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Key words: extubation; mechanical ventilation; outcome; weaning

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; End-SBT-$\dot{V}$E = minute ventilation measured at the end of a successful spontaneous breathing trial; FIO_2 = fraction of inspired oxygen; GCS = Glasgow coma scale; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; PSV = pressure-support ventilation; ROC = receiver operator characteristic; RR = respiratory rate; RT = recovery time; SBT = spontaneous breathing trial; $\dot{V}$E = minute ventilation; VT = tidal volume; RT50%Δ$\dot{V}$E = recovery time needed to reduce minute ventilation to half the difference between the minute ventilation measured at the end of a successful spontaneous breathing trial and basal minute ventilation

The standard method for deciding to extubate mechanically ventilated patients is to conduct a spontaneous breathing trial (SBT) lasting from 30 to 120 min.[1] Most studies measure ventilatory parameters every 5 to 15 min,[1] but, to date, a minute-by-minute protocol of monitoring ventilatory parameters during the SBT has not been fully validated. When the patient tolerates the SBT, the decision to remove the artificial airway is based on the assessment of airway patency and the capability to protect the airway.

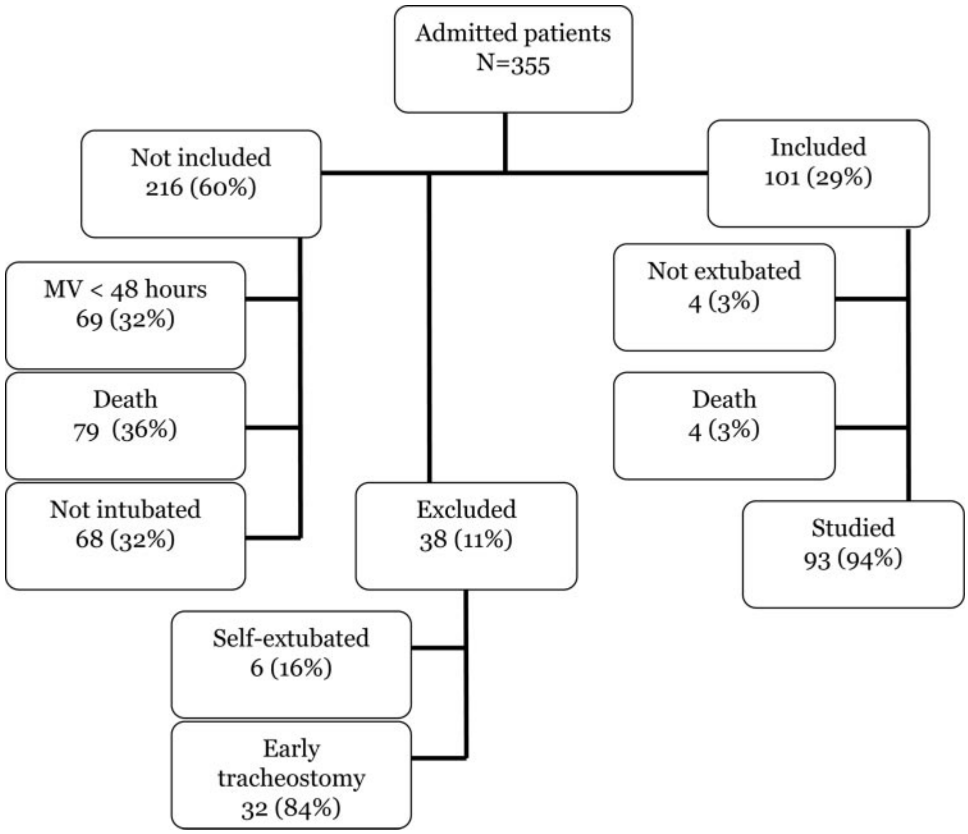

FIGURE 1. Flowchart of the patients.

Nevertheless, even when this standard is correctly implemented, the reintubation rate remains high. The incidence of extubation failure ranges from 2 to 25%, depending mainly on the case mix of patients and the 24-h vs 72-h period used to define extubation failure.[1–4] The importance of this issue is the severe increase (up to sixfold) in mortality observed in patients needing reintubation.[5]

A few options have been suggested to improve extubation success. These include serial measurements of several variables, such as the respiratory rate (RR)/tidal volume (VT) ratio,[6] respiratory effort,[7] oxygen uptake,[8] dead space,[9] and respiratory patterns.[8,10–13] Some of these measurements increase the predictive capacity of the extubation outcome in the studied populations but scarcely translate into the predictive capacity in individual patients.

A 2003 study[14] investigated the behavior of ventilatory variables during reconnection to the ventilator after a successful SBT. The authors found that the longer the time needed to recover basal minute ventilation ($\dot{V}E$), the higher the likelihood of extubation failure, suggesting an occult impairment in the ventilatory reserve.

Clinical observation suggests that $\dot{V}E$ is predominantly recovered in the early phase after reconnecting patients to MV. Our hypothesis was that continuous objective minute-by-minute monitoring of the recovery time (RT) might improve the predictive power of the previously reported method.[14] The objective of the present study was thus to serve as a second validation of this method and to explore whether a deeper analysis of RT could improve performance.

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Table 1—*Patient Characteristics**

Characteristics	Successful Extubation (n = 74)	Failed Extubation (n = 19)	p Value
Age, yr	55 ± 15	62 ± 12	0.03
Male sex	67	63	0.4
APACHE II score	22 ± 8	24 ± 8	0.6
Previous length of MV, d	8.4 ± 6.2	6.7 ± 5.3	0.7
GCS score (motor + ocular components only)	9 ± 1	9 ± 1	0.3
PSV level, cm H_2O	14 ± 2.2	14 ± 2	0.8
PEEP, cm H_2O	5 ± 1	5 ± 1.3	0.9
Comorbidities			
Cardiac failure	12	21	0.5
Hypertension	40	42	1
Diabetes	23	11	0.5
COPD	14	31	0.04
OSAS	7	5	1
Medical diagnosis			
Respiratory	22	21	0.8
Neurological	29	37	0.8
Other	20	16	0.8
Surgical diagnosis			
Thorax/abdomen	27	32	
Neurosurgery	11	16	

*Values are given as the mean ± SD or %. OSAS = obstructive sleep apnea syndrome. Medical and surgical diagnoses may coexist in some patients.

Materials and Methods

Patients

We studied all patients meeting the inclusion criteria and having no exclusion criteria who had been admitted to the medical-surgical ICU at the University Hospital 12 de Octubre over a 1-year period. The chairman of the institutional review board waived informed consent because this observational study did not change the standard practice in our ICU.

The inclusion criteria were patients who had received mechanical ventilation for > 48 h who fulfilled the following initial weaning criteria: recovery from the precipitating illness; respiratory criteria consisting of a Pa_{O_2}/fraction of inspired oxygen (F_{IO_2}) ratio of > 150 mm Hg at a positive end-expiratory pressure (PEEP) of < 8 cm H_2O, and an arterial pH of > 7.32; and clinical criteria consisting of the absence of myocardial ischemia (determined by ECG), no need for vasoactive drugs or dopamine (≤ 5 μg/kg/min), a heart rate of < 140 beats/min, hemoglobin concentration of > 8 g/dL, temperature of < 38°C, no need for sedative drugs, the presence of respiratory stimulus and spontaneous cough deemed clinically appropriate, and a Glasgow coma scale (GCS) score of ≥ 8 points determined by including only ocular and motor components.

The exclusion criteria were as follows: age < 18 years; tracheotomized patients; self-extubation; and patients with severe neuromuscular pathology (*eg*, amyotrophic lateral sclerosis or Guillain-Barre syndrome). Basal ventilation was defined in the pressure support mode with sufficient inspiratory pressure to allow a basal RR of ≤ 25 breaths/min.

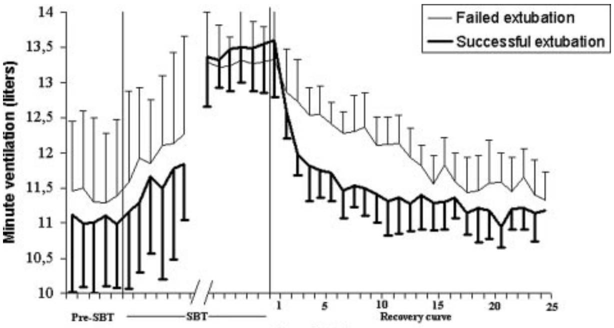

FIGURE 2. Evolution of the $\dot{V}_E$ during the monitoring period.

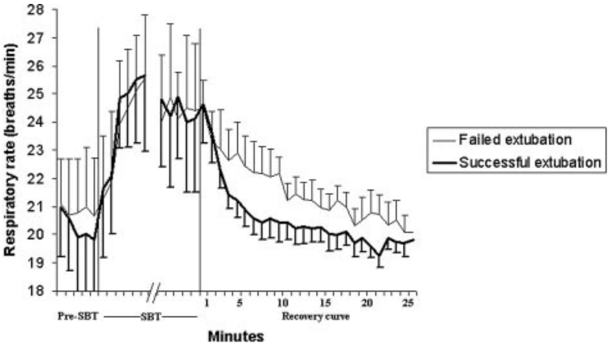

FIGURE 3. Evolution of the RR during the monitoring period.

Weaning Protocol

Tolerance to spontaneous ventilation was tested by means of an SBT of 30 to 120 min using pressure-support ventilation (PSV) of 7 cm H_2O and PEEP of ≤ 4 cm H_2O. During the study, the humidification system was unchanged (Thermovent 1200 hydrophilic heat and moisture exchanger; Sims-Portex; Kent, UK). When patients tolerated the SBT (see criteria later in this section), the patient again began receiving MV with the same PSV as that used in the basal period for 60 min. Then, the attending physician clinically evaluated the capacity to protect the airway and, when adequate, proceeded to extubation. When the SBT was not tolerated, or when the attending physician decided that the airway protection was inadequate, the patient was reconnected to MV for 24 h for rest and to

Table 2—*Univariate Analysis of Ventilatory Variables**

Variables	Successful Extubation (n = 74)	Failed Extubation (n = 19)	p Value
Basal $\dot{V}_E$, L	11.2 ± 3	10.9 ± 2.9	0.7
Basal RR, breaths/min	20 ± 6	19.6 ± 6.2	0.8
Basal V_T, mL	557 ± 263	580 ± 249	0.7
RT of $\dot{V}_E$, min	5.4 ± 5.2	14.5 ± 9.7	0.001
RT of RR, min	9.2 ± 8.8	10.2 ± 9.4	0.8
RT50%Δ$\dot{V}_E$, min	2.7 ± 1.2	10.7 ± 8.4	0.001
RT50%ΔRR, min	4.3 ± 4.5	7.3 ± 8.7	0.8

*Data are presented as the mean ± SD, unless otherwise indicated. RT50%ΔRR = recovery time needed to reduce RR to half the difference between the RR measured at the end of a successful spontaneous breathing trial and basal RR.

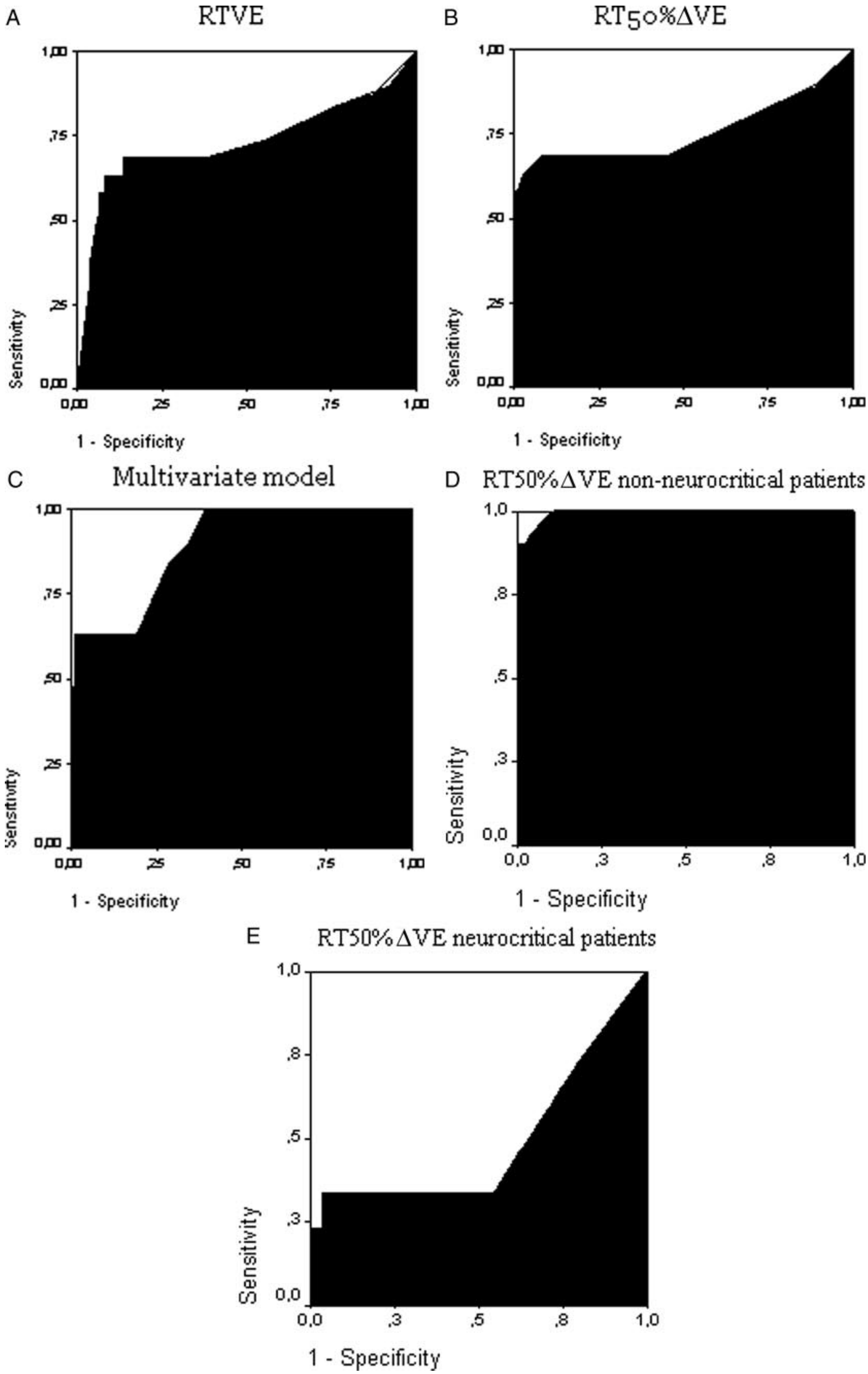

FIGURE 4. Area under the ROC curve for the RT of V̇E, RT50%ΔV̇E for neurocritical vs nonneurocritical patients separately, and the multivariate model.

Table 3—*Factors Significantly Associated With Extubation Failure on Multivariate Analysis*

Variables	Coefficient	OR (95% CI)	p Value
Diagnosis (neurocritical patients vs others)	0.551	7.7(1.46–40.13)	0.02
RT50%ΔV̇E, min	2.037	1.7(1.28–2.43)	0.001
Constant	−4.834		0.001

correct the reversible factors of weaning failure. After this period, the process was repeated. If three consecutive disconnections failed, the patient was withdrawn from the study. Ventilatory parameters were measured during every SBT in all patients, but monitoring was stopped if the SBT was not tolerated.

Tolerance to an SBT was defined as follows: by gasometric criteria (PaO_2, > 60 mm Hg; arterial pH, > 7.32; and $PaCO_2$ increase, < 10 mm Hg); by clinical criteria (pulse oximetric saturation, > 85%; heart rate, < 140 beats/min; increase in heart rate, < 20%; increase in RR, < 50% up to a maximum RR of 30 breaths/min; no neurologic deterioration; and no sweating or signs of increased respiratory work). Extubation failure was defined as the need for reintubation within 48 h after extubation. The following reintubation criteria were decided on by the attending staff: respiratory or cardiac arrest; apnea episodes; bradycardia of ≤ 50 beats/min; decrease in consciousness; gasping or other movements compatible with agonic respiratory pattern; agitation impossible to control with sedatives; use of accessory muscles and paradoxical thoracoabdominal movements; massive aspiration or inability to cope with respiratory secretions; hemodynamic instability; and pulse oximetric saturation of < 85% and/or PaO_2 of < 60 mm Hg despite the use of a high-flow mask. Reintubated patients were not included in the study in secondary attempts at extubation.

Definition of Respiratory Parameters

The basal V̇E was defined as the smallest V̇E occurring at rest in the 6 h prior to the patient undergoing the SBT and at least 15 min after the occurrence of factors that may falsely elevate V̇E, such as secretion suctioning, exposure to stressing factors such as family presence, medical intervention, position changes, or nursing care. The basal RR and VT were those corresponding to the basal V̇E.

V̇E measured at the end of a successful SBT was recorded as End-SBT-V̇E. Following reconnection to the ventilator, the RT of V̇E was defined as the time taken to reduce V̇E from End-SBT-V̇E to basal V̇E. The RT50%ΔV̇E was defined as the RT needed to reduce V̇E to half the difference between End-SBT-V̇E and basal V̇E. As previously described,[14] in case the patient did not recover basal values after 25 min, the measurement was cancelled out, and the RT of the V̇E recorded was 25 min. Similar definitions were used for the RR.

Table 4—*Power for an RT50%ΔVE of > 7 min To Diagnose Extubation Failure in the Global Population and for Each Subgroup of Patients**

Variables	Sensitivity	Specificity	PPV	NPV
Global	47	99	100	88
Subgroups study				
Nonneurocritical patients	90	100	100	98
Neurocritical patients	22	96	67	77

*Values are given as %. PPV = positive predictive value; NPV = negative predictive value.

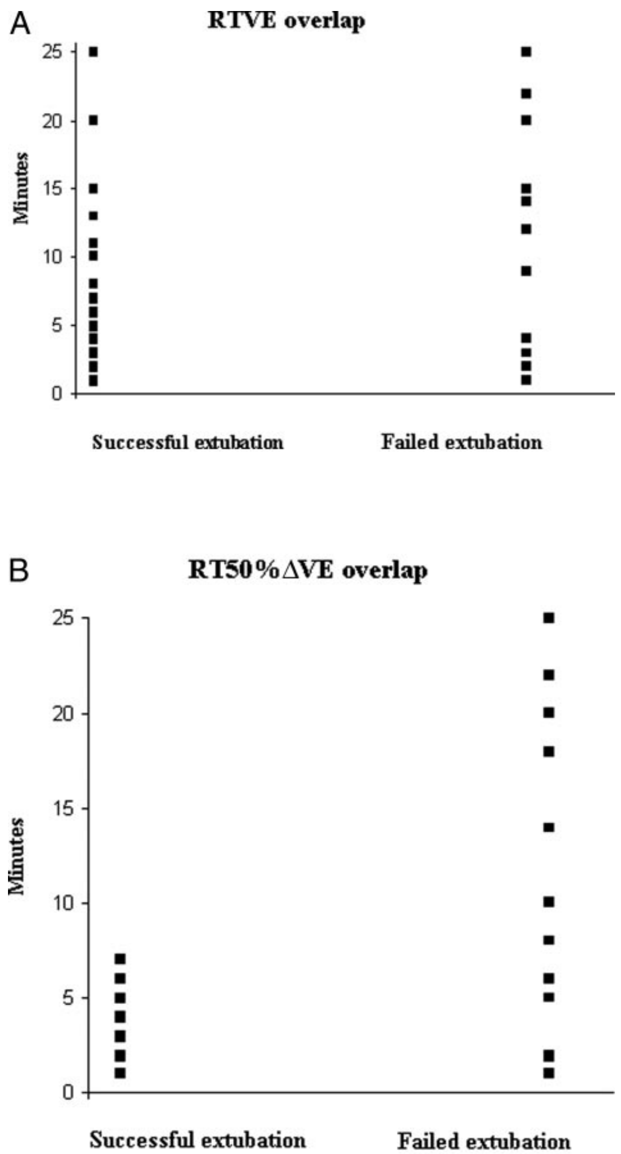

FIGURE 5. Overlap of variables RT of V̇E and RT50%ΔV̇E between patients who had successful extubations and those who failed extubations.

Data Collection

Six hours before starting SBT, a monitor (model 1260; Siemens Elema AB; Berlin, Germany) that allowed minute-by-minute recordings of V̇E, RR, and VT was connected to the ventilator (Servo 300 and 900C; Siemens Elema AB). We also recorded age, sex, APACHE (acute physiology and chronic health evaluation) II scores at ICU admission, serum albumin levels, caloric requirements, primary diagnosis (*ie*, medical or surgical), secondary diagnosis (*ie*, respiratory, neurologic, cardiac, or other), comorbid status, specific medications used, need for reintubation up to 48 h after extubation, time to reintubation, duration of MV use, and length of ICU stay.

Statistical Analysis

Continuous normal variables were described as the mean and SDs and median and 25th to 75th percentiles for nonnormally distributed variables. Continuous variables were compared by Student *t* tests, but for samples of < 30 individuals Kruskal-Wallis and Mann-Whitney *U* tests were used. Categoric data were compared using the χ^2 test with Yates correction or the two-tailed Fisher exact test. The statistical model was designed to predict failed extubation.

Multiple variable models were tested by forward stepwise logistic regression of those variables that were found to be significant in the univariate analysis ($p < 0.05$) or that could act as confounding factors, and the results were expressed as the odds ratio.

We calculated the receiver operating characteristic (ROC) curves for the variables with significant predictive capacity and the combined predictive model, resulting in the multiple regression analysis. Threshold values with clinical relevance were analyzed.

Results

The flowchart of the study is presented in Figure 1. During the study year, 355 patients were admitted to the ICU and 93 met the inclusion criteria. Seventy-four patients (80%) were successfully extubated, whereas 19 patients (20%) needed reintubation.

The clinical characteristics of both groups are presented in Table 1. The median time to reintubation was 10 h (25th to 75th percentiles, 4.2 to 21.2 h). The causes of reintubation were as follows: inability to clear respiratory secretions (22%); increased work of breathing (16%); hypoxia (16%); agitation (5%); hemodynamic instability (5%); neurologic impairment (31% [22% with associated hypercapnia]); and apnea or cardiac arrest (5%). Figures 2 and 3 show the evolution of ventilatory parameters after MV was reinstituted after a successful SBT.

Univariate analysis is presented in Table 2. Of the studied respiratory variables, only the RT of $\dot{V}$E and RT50%$\Delta\dot{V}$E were significantly different between reintubated and non-reintubated patients. The areas under the ROC curve for these variables were 0.73 (95% confidence interval [CI], 0.56 to 0.89) and 0.75 (95% CI, 0.59 to 0.92), respectively, as shown in Figure 4.

The predictive model of extubation failure was tested by multivariate analysis with the following exploratory variables: age; comorbid status; duration of MV before extubation; neurologic vs nonneurologic diseases; and RT50%$\Delta\dot{V}$E. The final model excluded seven variables, and selected only neurologic diseases and RT50%$\Delta\dot{V}$E as independent factors for extubation failure (Table 3). The area under the ROC curve for the probability of this model was 0.89 (95% CI, 0.82 to 0.97) and was a better predictor than the RT of $\dot{V}$E or RT50%$\Delta\dot{V}$E alone (Fig 4).

For clinical decision making, the highest positive predictive value for reducing the reintubation rate without denying extubation to any patient who will tolerate it was found at an RT50%$\Delta\dot{V}$E of ≥ 7 min (Table 4). In other words, all nine nonneurocritical patients and two of three neurocritical patients with an RT50%$\Delta\dot{V}$E of ≥ 7 min were reintubated. Only eight patients with an RT50%$\Delta\dot{V}$E of < 7 min were reintubated; seven of them (85%) were admitted to the ICU with a neurocritical disease. The areas under the ROC curves for nonneurocritical and neurocritical patients are represented separately (Fig 4) as follows: nonneurocritical patients, 0.994 (95% CI, 0.979 to 1.009); and neurocritical patients, 0.486 (95% CI, 0.227 to 0.745).

Discussion

The most important result from this study is that the determination of the RT50%$\Delta\dot{V}$E during reconnection to the ventilator after tolerating a standard SBT may detect patients with very little likelihood for successful extubation, and improves the performance of the previously described RT of $\dot{V}$E.

It is important to emphasize certain peculiarities of the studied population. Neurologic diseases were highly prevalent as this was a subgroup of critically ill patients with specific weaning differences.[15] The impairment in consciousness in our population of patients was somehow higher than those in previous studies[16] because we extubated patients with a mean GCS score (motor and ocular components only) of 9 ± 1 points. This may account for the fact that 31% of reintubations were due to problems in managing respiratory secretions or to the deterioration of consciousness in the absence of hypercapnia. Early tracheotomy was substantial in our population (9%) but was within the reported incidence that reaches a maximum of 34% in some studies in neurocritical patients.[16]

Our proportion of COPD patients (16%) was lower than that in historical series with proportions up to 40%,[17] but somehow was higher than that in contemporary studies.[18] COPD was a nonsignificant factor in the multivariate analysis and did not affect the predictive value of RT.

Limitations of the Study

Some methodological issues in our study deserve mention. The PSV mode has several caveats in defining basal parameters. The target for PSV titration in most weaning trials is RR,[19,20] so any change in ventilatory demands modifies ventilatory pattern mostly by changing RR.

Other ventilatory modes such as proportional assisted ventilation or automatic tube compensation may allow a more physiologic calculation of basal parameters, but their complexity and limited clinical use restrict their wide applicability at the bedside.[21–23] Recently, Seymour et al[24] compared different methods of basal $\dot{V}_E$ measurement and concluded that measurement is not influenced by the method used. This study also reflects the fact that $\dot{V}_E$ is a much more stable parameter than has been previously suggested.[25]

There are several relevant differences between our study and the original study by Martinez et al.[14] In terms of patient selection, Martinez et al[14] included every patient who had undergone MV, and up to 20% of their population were postsurgical patients who had received MV for a very short period. Because difficult weaning is often low in these patients,[26–28] we only included patients receiving prolonged MV (*ie*, for > 48 h). Moreover, in the study by Martinez et al[14] the Pa_{O_2}/F_{IO_2} ratio required for weaning (Pa_{O_2}/F_{IO_2} ratio, > 200) was higher and somehow restrictive, and could delay extubation in some ready-to-wean patients.[29] Our higher basal $\dot{V}_E$ also reinforces the idea of a sicker population during the weaning period.

In terms of studied variables, our RT50%$\Delta\dot{V}_E$ variable has a minimal overlap between extubation successes and failures compared with use of the RT of $\dot{V}_E$ described by Martinez et al[14] (Fig 5); it therefore allows a better predictive model for extubation failure to be built. A basic limitation in the creation of a predictive model for extubation is that it would be desirable to have 100% specificity to avoid any delay in the extubation of patients already prepared for it. The predictive power of RT50%$\Delta\dot{V}_E$ was maximized after excluding neurocritical patients as this group mainly need reintubation because of an inability to adequately manage the airway due to neurologic derangement (Fig 4). The clinical value of this model needs further prospective validation in a wide variety of settings and different populations.

In conclusion, in patients who tolerate a standard SBT, the analysis of the time needed to recover basal $\dot{V}_E$ after reconnection to the ventilator helps to predict extubation failure. Because the differences are maximal in the first minutes after reconnection, the prediction is optimized by evaluating the RT50%$\Delta\dot{V}_E$, yielding a better predictive power in patients without neurologic diseases.

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