Original Contributions

Hypercapnia Test As a Predictor of Success in Spontaneous Breathing Trials and Extubation

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BACKGROUND: The ventilatory capacity of the respiratory neuromuscular system can be studied with the hypercapnia test. OBJECTIVE: To determine whether decreased response to the hypercapnia test is associated with failure to pass a spontaneous breathing trial (SBT) or extubation failure. METHODS: We studied 103 intubated patients ready for SBT. We used a hypercapnia test in which we approximately doubled the dead space and thus caused re-inhalation of expired air. We calculated 3 ratios: the ratio of $P_{0.1}$ (airway occlusion pressure 0.1 s after the onset of inspiratory effort) during hypercapnia test to baseline $P_{0.1}$; the ratio of the change in minute volume $[\Delta \dot{V}_E]$ to the change in P_{aCO_2} (we call this ratio the hypercapnic ventilatory response); and the ratio of the change in $P_{0.1}$ $[\Delta P_{0.1}]$ to the change P_{aCO_2} (we call this ratio the hypercapnic-respiratory-drive response). RESULTS: Thirty-six patients failed the SBT, and 11 patients failed extubation. The mean values for the SBT/extubation-success group, the extubation-failure group, and the SBT-failure group, respectively, were: ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$: 4.3 ± 2.7, 3.7 ± 1.3, and 3.0 ± 1.8 ($P = .03$); hypercapnic ventilatory response: 0.60 ± 0.35 L/min/mm Hg, 0.50 ± 0.26 L/min/mm Hg, and 0.31 ± 0.21 L/min/mm Hg ($P < .001$); hypercapnic respiratory-drive response: 0.48 ± 0.24 cm H_2O/mm Hg, 0.42 ± 0.19 cm H_2O/mm Hg, and 0.27 ± 0.15 cm H_2O/mm Hg ($P < .001$). For predicting SBT/extubation success, the sensitivities and specificities, respectively, were: ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$ 0.80 and 0.47; hypercapnic ventilatory response 0.86 and 0.53; hypercapnic respiratory-drive response 0.82 and 0.55. CONCLUSIONS: The SBT/extubation-failure patients had less response to the hypercapnia test than did the SBT/extubation-success patients, and the hypercapnia test was not useful in predicting SBT or extubation success. *Key words: mechanical ventilation, intensive care, ventilator weaning, hypercapnia, spontaneous breathing trial, respiratory function tests, respiratory center.* [Respir Care 2008;53(8):1012–1018. © 2008 Daedalus Enterprises]

Introduction

The use of protocols may facilitate weaning and discontinuing mechanical ventilation.[1,2] However, several clinical trials found that 24–42% of patients who satisfied the classic criteria failed the first weaning attempt.[3-5]

Multiple factors cause weaning/extubation failure, and failure usually means either incomplete resolution of the initial illness that required mechanical ventilation, or new complications, such as worsening of lung mechanics,[6] abnormal respiratory drive,[7] muscular weakness,[8] myocardial ischemia,[9] or ventricular dysfunction.[10] Despite several decades of research, a reliable predictor of success of a spontaneous breathing trial (SBT) and extubation has not been identified.

Frequently, SBT/extubation failure indicates an imbalance between ventilatory demand and work capacity and

endurance. The ventilatory capacity of the respiratory neuromuscular system can be studied with the hypercapnia test by measuring the changes in minute volume ($\dot{V}_E$) and airway occlusion pressure 0.1 s after the beginning of inspiration ($P_{0.1}$) induced by a P_{aCO_2} increase.[11] Montgomery et al[12] found that measuring the $P_{0.1}$ change during the hypercapnia test was useful to identify patients who would succeed extubation. We hypothesized that patients who fail SBT/extubation would have less response to the hypercapnia test than patients who pass an SBT and successfully extubate, so we assessed the hypercapnia test as a predictor of success of SBT and extubation.

Methods

Patients

We prospectively studied patients with acute respiratory failure admitted to 2 medical-surgical intensive care units. They all had required tracheal intubation and mechanical ventilation for more than 72 hours. The patients were clinically stable and their attending physicians considered them ready for SBT. The study was approved by the review boards of both hospitals, and informed consent was obtained from each patient.

All patients underwent a daily screening by the physician in charge. The routine clinical criteria for considering an SBT were: a clear improvement or resolution of the condition that initially necessitated mechanical ventilation, $P_{aO_2} > 60$ mm Hg while receiving a fraction of inspired oxygen (F_{IO_2}) ≤ 0.4, positive end-expiratory pressure ≤ 5 cm H_2O, temperature $< 38°C$, hemoglobin > 8 g/dL, no requirement for vasoactive drugs, and no need for intravenous sedation during the previous 24 hours. The patient had to be awake and able to obey oral commands. Patients with chronic obstructive pulmonary disease or neurologic deficit (eg, head injury, stroke, myasthenia gravis, and Guillain-Barré syndrome) were excluded.

Protocol

All the pulmonary function measurements were carried out with the patient in the semirecumbent position, immediately following endotracheal suctioning. We continuously recorded electrocardiogram, heart rate, pulse oximetry, and invasive systemic blood pressure.

Maximum inspiratory pressure (MIP) was measured after 1–2 min of spontaneous breathing. Just before the hypercapnia test we applied 5 min of pressure-support ventilation (PSV) with a pressure of 7 cm H_2O, no positive end-expiratory pressure, and F_{IO_2} of 1.0. Then, $\dot{V}_E$, respiratory rate, and $P_{0.1}$ were recorded from the ventilator (Evita 2 Dura or Evita 4, Dräger, Lübeck, Germany), and an arterial blood sample was drawn. We then began the

hypercapnia test (explained below) while maintaining the patient's breathing with PSV of 7 cm H_2O, and, after at least 4 min and exhaled CO_2 (measured via capnography) had increased by almost 10 mm Hg, we again measured $\dot{V}_E$, respiratory rate, and $P_{0.1}$, and took another arterial blood sample. When the hypercapnia test was finished, the patient was returned to his or her original assisted ventilation mode. The physician in charge, who was unaware of the response to the hypercapnia test, began to apply the weaning protocol 15–30 min after the hypercapnia test.

The SBT was for 2 hours, with a T-piece and the same F_{IO_2} as during mechanical ventilation. The SBT was considered successful if the patient had no signs of distress (respiratory rate > 35 breaths/min, arterial oxygen saturation < 90%, heart rate > 140 beats/min, systolic blood pressure > 180 mm Hg or < 90 mm Hg, agitation, diaphoresis, or anxiety).[3] If the patients showed distress during the SBT, the discontinuation of mechanical ventilation was done with progressive reduction of the pressure-support level. The PSV was titrated to achieve a respiratory rate of 20–30 breaths/min, and progressively reduced by 2–4 cm H_2O at least twice a day if clinically tolerated. When a pressure-support of 5–7 cm H_2O was tolerated with no apparent distress for 2 hours, the patient was extubated. If the patient failed to tolerate a decreased pressure-support level (tachypnea, increased accessory muscle activity, diaphoresis, tachycardia, arrhythmia, hypertension), we reinstituted the previous pressure. The decision to extubate or to reconnect the patient to the ventilator was made by the physician in charge, according to the above criteria. If the SBT was successful, the patient was extubated, and extubation was considered successful if re-intubation was not required within 48 hours of extubation.

Measurements and Procedures

MIP was measured with an external pressure transducer via a unidirectional valve (Hans Rudolph, Kansas City, Missouri) connected to the endotracheal tube. MIP was obtained starting at residual volume by occluding the inspiratory port of the unidirectional valve.[13] After 20–25 s of occluded inspiration, the most negative pressure was recorded for that test. MIP was considered the most negative value of 2 measurements. $P_{0.1}$ values were measured with the ventilator's built-in system,[14,15] and $P_{0.1}$ was calculated as the mean of 5 measurements at each point of the study.[16] Arterial blood gases were measured with a blood gas analyzer (IL-1650, Instrument Laboratory, Izasa, Spain).

Our method for inducing hypercapnia was to cause re-inhalation of expired air[17,18] by inserting a length of corrugated tube between the Y-piece and the endotracheal tube, which increased the dead space by a volume similar to the tidal volume (V_T) obtained with a pressure support

of 7 cm H_2O. After the hypercapnia test the added dead space was removed.

We studied the following derived indexes:

- The ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$, described by Montgomery et al.[12]

- The ratio of $\dot{V}_E$ to $P_{0.1}$, proposed by Scott and Burki[19] for the clinical assessment of ventilatory drive and lung mechanics.

- The ratio of $P_{0.1}$ to MIP, proposed by Fernández et al.[20]

- The ratio of the change in $\dot{V}_E$ ($\Delta\dot{V}_E$) to the change in P_{aCO_2} (ΔP_{aCO_2}). We call this ratio the hypercapnic ventilatory response.

- The ratio of $\Delta P_{0.1}$ to ΔP_{aCO_2}. We call this ratio the hypercapnic-respiratory-drive response.

The changes in $\dot{V}_E$, $P_{0.1}$, and P_{aCO_2} were calculated as the difference between the value at the end of the hypercapnia test and the baseline value.

Data Collection

We recorded age, sex, weight, date of admission and discharge from the intensive care unit and the hospital, and main diagnosis that required initiation of mechanical ventilation. Severity of illness was evaluated with the Simplified Acute Physiology Score II during the patient's first 24 hours in the intensive care unit.

Duration of mechanical ventilation was defined as the number of days between the beginning of mechanical ventilation and the patient's first SBT. Weaning time was defined as the time elapsed between the first SBT and the day of extubation, or, in patients with tracheostomy, withdrawal of mechanical ventilation. Patients were followed until discharged from the hospital.

Statistical Analysis

Categorical data are expressed as numbers and percentages. Continuous variables are expressed as mean ± standard deviation or as median and interquartile range. Differences between groups were compared with 1-way analysis of variance or Kruskal-Wallis test for continuous data, and chi-square test was used for categorical data. Receiver-operating-characteristic-curve analysis was performed to assess the ability of the various ratios/indexes to discriminate between patients who succeeded SBT/extubation from those who failed. Threshold values were selected according to the minimum sum of false-positive and false-negative test results. A result was deemed true-positive when the test predicted successful SBT/extubation and successful SBT/extubation actually occurred. A false-positive result was when the test predicted successful SBT/

extubation but SBT/extubation failed. A true-negative result was when the test predicted SBT/extubation failure and the patient failed SBT/extubation. A false-negative was when the test predicted SBT/extubation failure but SBT/extubation was successful. The accuracy of the indexes in predicting SBT/extubation outcome was analyzed for sensitivity and specificity. Statistical analysis was performed with statistics software (SPSS 11.0, SPSS, Chicago, Illinois).

Results

We enrolled 103 patients: 61 men, 42 women, mean ± SD age 62 ± 14 y. Thirty-six patients failed the SBT. Eleven failed extubation (Table 1). The reasons for extubation failure included 5 cases of hypoxemia and hypoventilation, 2 cases of septic shock, 2 cases of pulmonary edema, 1 case of stridor, and 1 case of pulmonary hemorrhage. The patients who failed SBT/extubation were slightly older that those who succeeded. There was no significant difference between the groups in days of mechanical ventilation before the first SBT. The mean weaning time for patients who failed the first SBT was 14 ± 16 d (median 8 d, interquartile range 4–26 d). The mortality rate among SBT/extubation-failure patients was 17% (8 patients).

There was a statistically significant differences in baseline P_{aCO_2} between the success and failure groups (Table 2). The SBT/extubation-failure patients had lower $\dot{V}_E$ at the end of hypercapnia test, lower ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$, lower hypercapnic ventilatory response, lower hypercapnic-respiratory-drive response, higher P_{aCO_2}, and higher respiratory acidosis than did the SBT/extubation-success patients (see Table 2 and Fig. 1). Patients who failed extubation (ie, were reintubated) had no significant differences from the successfully extubated patients in the respiratory measurements we obtained, at baseline or during the hypercapnia test (see Table 2).

The values for the area-under-the-receiver-operating-characteristic curve (to discriminate success/failure) were: ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$ 0.66 ± 0.05 (95% CI 0.55–0.75), hypercapnic ventilatory response 0.72 ± 0.05 (95% CI 0.63–0.81), and hypercapnic-respiratory-drive response 0.73 ± 0.05 (95% CI 0.63–0.81). The threshold values for each index with the fewest false classifications were: ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$ ≥ 2.52, hypercapnic ventilatory response ≥ 0.31 L/min/mm Hg, and hypercapnic-respiratory-drive response ≥ 0.27 cm H_2O/mm Hg.

Table 3 shows the sensitivities and specificities of the indexes.

At baseline the ratio of respiratory rate to V_T was 62.9 ± 31.1 in the SBT/extubation-success group, and 83.7 ± 38.5 in the SBT/extubation-failure group ($P = .003$), and at the end of the hypercapnia test it was 56.2 ± 22.5

Table 1.   Characteristics of Subjects, Relative to Success/Failure in Spontaneous Breathing Trial and Extubation

	Failed SBT (n = 36)	Failed Extubation (n = 11)	Succeeded SBT and Extubation (n = 56)	P
Age (mean ± SD y)	64 ± 13	69 ± 10	59 ± 15	.09
Female (n, %)	16 (44.4)	4 (36.4)	22 (39.3)	.84
Weight (mean ± SD kg)	73 ± 17	82 ± 25	75 ± 17	.31
Height (mean ± SD cm)	161 ± 10	165 ± 8	166 ± 9	.07
SAPS II score (mean ± SD)	41 ± 11	39 ± 9	40 ± 15	.92
Cause of ARF (n, %)				.87
Pneumonia	13 (36.1)	4 (36.4)	24 (42.9)	
Other sepsis	13 (36.1)	2 (18.2)	16 (28.6)	
Postoperative ARF	4 (11.1)	2 (18.2)	5 (8.9)	
Miscellaneous	6 (16.7)	3 (27.3)	11 (19.6)	
Duration of mechanical ventilation				.94
Mean ± SD d	11 ± 8	10 ± 5	12 ± 9	
Median and IQR d	10 (5–16)	11 (5–14)	9 (6–15)	

SBT = spontaneous breathing trial
SAPS = Simplified Acute Physiology Score II
ARF = acute respiratory failure
IQR = interquartile range

Table 2.   Results, Relative to Success/Failure in Spontaneous Breathing Trial and Extubation

	Failed SBT (n = 36)	Failed Extubation (n = 11)	Succeeded SBT and Extubation (n = 56)	P
Respiratory rate (breaths/min)				
Baseline	28 ± 8	28 ± 6	25 ± 7	.12
At end of hypercapnia test	33 ± 8	34 ± 6	32 ± 7	.68
$\dot{V}_E$ (L/min)				
Baseline	9.9 ± 2.8	9.5 ± 2.9	10.9 ± 3.1	.18
At end of hypercapnia test	15.0 ± 4.4*	16.1 ± 3.3	19.1 ± 4.2	< .001
$P_{0.1}$ (cm H_2O)				
Baseline	3.4 ± 2.3	2.4 ± 1.1	2.9 ± 1.8	.26
At end of hypercapnia test	8.2 ± 3.8	8.1 ± 3.5	9.8 ± 3.8	.10
P_{aCO_2} (mm Hg)				
Baseline	44.7 ± 10.4*	45.6 ± 10.2	38.9 ± 7.9	.005
At end of hypercapnia test	63.3 ± 13.7*	60.0 ± 10.7	54.3 ± 9.9	.001
pH				
Baseline	7.39 ± 0.07*	7.39 ± 0.04	7.43 ± 0.05	.002
At end of hypercapnia test	7.27 ± 0.07*	7.29 ± 0.04	7.32 ± 0.05	< .001
Baseline standard bicarbonate (mmol/L)	26.8 ± 2.8	25.8 ± 2.8	26.6 ± 2.8	.60
MIP (cm H_2O)	42 ± 16	49 ± 16	51 ± 20	.07
Hypercapnia-test $P_{0.1}$/baseline $P_{0.1}$	3.0 ± 1.8*	3.7 ± 1.3	4.3 ± 2.7	.03
$\dot{V}_E/P_{0.1}$ (L/min/cm H_2O)	4.0 ± 2.3	4.5 ± 1.6	4.9 ± 2.8	.26
$P_{0.1}$/MIP	0.13 ± 0.08	0.14 ± 0.11	0.15 ± 0.08	.49
$\Delta\dot{V}_E/\Delta P_{aCO_2}$ (L/min/mm Hg)	0.31 ± 0.21*	0.50 ± 0.26	0.60 ± 0.35	< .001
$\Delta P_{0.1}/\Delta P_{aCO_2}$ (cm H_2O/mm Hg)	0.27 ± 0.15*	0.42 ± 0.19	0.48 ± 0.24	< .001

* Statistically significant difference between SBT/extubation success and SBT failure
SBT = spontaneous breathing trial
V_E = minute volume
$P_{0.1}$ = occlusion pressure 0.1 s after beginning of inspiratory effort
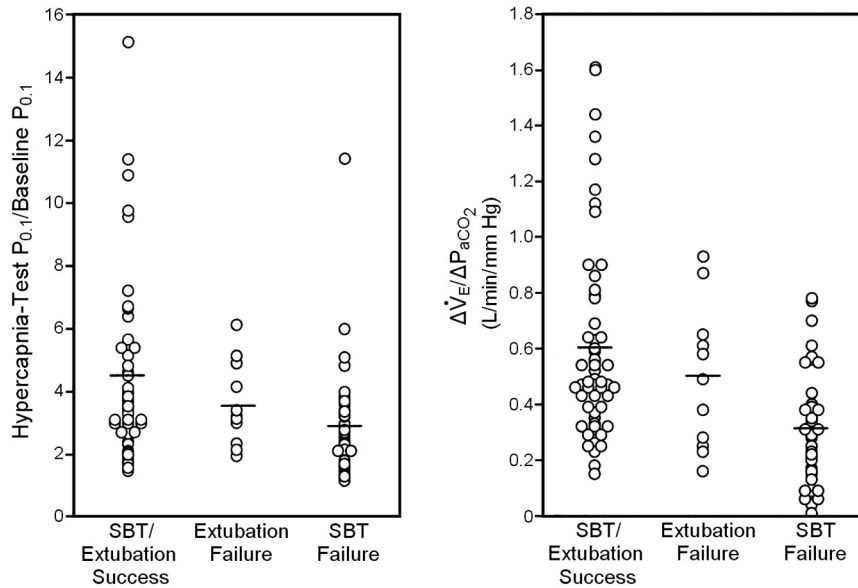MIP = maximum inspiratory pressure

Fig. 1. Individual values for the ratio of hypercapnia-test $P_{0.1}$ (airway occlusion pressure 0.1 s after the beginning of inspiration) to baseline $P_{0.1}$, and the ratio of the change in minute volume [$\Delta \dot{V}_E$] to the change in P_{aCO_2} (hypercapnic ventilatory response), relative to success or failure in the spontaneous breathing trial (SBT) and extubation. The horizontal lines represent the mean value of each group.

Table 3.   Accuracy of the Indexes in Predicting Success of Spontaneous Breathing Trial and Extubation

	Sensitivity and 95% CI	Specificity and 95% CI	Positive Predictive Value	Negative Predictive Value
Hypercapnia-test $P_{0.1}$/baseline $P_{0.1} \geq 2.52$	0.80 (0.71–0.88)	0.47 (0.37–0.57)	0.64	0.67
$\Delta \dot{V}_E / \Delta P_{aCO_2} \geq 0.31$ L/min/mm Hg	0.86 (0.77–0.92)	0.53 (0.43–0.63)	0.69	0.76
$\Delta P_{0.1} / \Delta P_{aCO_2} \geq 0.27$ cm H_2O/mm Hg	0.82 (0.73–0.89)	0.55 (0.45–0.65)	0.69	0.72

CI = confidence interval
$\dot{V}_E$ = minute volume
$P_{0.1}$ = occlusion pressure 0.1 s after beginning of inspiratory effort

in the SBT/extubation-success group, and 78.3 ± 38.2 in SBT/extubation-failure group. The values for the area-under-the-receiver-operating-characteristic curve (0.67 ± 0.5 at baseline versus 0.69 ± 0.5 at the end of the hypercapnia test) show that the ratio of respiratory rate to V_T was not a useful predictor.

Discussion

Our results confirm the blunted ventilatory and $P_{0.1}$ response to hypercapnia test in critically ill patients who failed SBT/extubation, compared to those who succeeded in SBT/extubation, as has been suggested in previous studies with fewer patients.[12,21,22] However, the hypercapnia test does not appear to be a predictor of SBT/extubation success.

The mean values of hypercapnic ventilatory response and hypercapnic-respiratory-drive response in our study and in other studies in critically ill intubated patients[12,21,22] are clearly lower than those in non-intubated healthy sub-

jects, especially for hypercapnic ventilatory response, in whom a hypercapnic ventilatory response increase of 2.6 ± 1.2 L/min/mm Hg and a hypercapnic-respiratory-drive response increase of 0.6 ± 0.5 cm H_2O/mm Hg have been described.[23,24]

There have been few studies[12,21,22,25] in which the hypercapnia test was done in intubated, critically ill patients ready for SBT/extubation. Montgomery et al[12] found good specificity and sensitivity with the hypercapnia test as a predictor of SBT/extubation success in 14 SBT/extubation attempts in 11 patients, but the results from Pourriat et al,[22] who studied 13 patients with chronic obstructive pulmonary disease, were similar to ours.

In our study the ratio of hypercapnia-test $P_{0.1}$ to baseline $P_{0.1}$, hypercapnic ventilatory response, and hypercapnic-respiratory-drive response showed low accuracy for SBT/extubation prediction (see Table 3), as has been described for other SBT/extubation predictors.[26,27] The low accuracy of SBT/extubation predictors has many causes, pulmonary

and non-pulmonary, that contribute to SBT/extubation failure. Only 5 of our 11 reintubated patients had a pulmonary etiology for reintubation. The other causes of extubation failure would not be expected to be detected by the hypercapnia test.

The hypercapnia test may help identify whether a defect in the metabolic respiratory system, the respiratory neural system, or the ventilatory apparatus is contributing to SBT/extubation failure. To interpret our results we must account for the following facts. First, the mean baseline $P_{0.1}$ values were higher than those in resting normal subjects and close to values reported in other studies in patients ready for SBT/extubation.[16,28] This suggests that disorders of respiratory-center activity are probably not a cause of SBT/extubation failure in most patients. However, according to a study by Holle et al,[29] in which the hypercapnic-respiratory-drive response was preserved in severe diaphragmatic weakness induced by curare, the blunted hypercapnic-respiratory-drive response in our patients who failed the SBT could indicate a greater disorder in the respiratory drive system (brainstem motoneurons, spinal cord, or respiratory nerves). Second, the $\dot{V}_E/P_{0.1}$ ratio, which provides excellent differentiation between normal subjects and patients with lung disease, and that in normal subjects is > 8.0 L/min/cm H_2O,[19] had low values in our study. There was no significant $\dot{V}_E/P_{0.1}$ difference between the SBT/extubation-success and SBT/extubation-failure patients, which indicates that the groups may have had similarly altered ventilatory systems.

Other studies have given conflicting results about the $P_{0.1}$/MIP ratio.[5,16,28] Because of the overlap of values from SBT/extubation-success and SBT/extubation-failure patients (see Fig. 1), the $P_{0.1}$/MIP ratio was not helpful in predicting SBT/extubation success.

Finally, the $\dot{V}_E/P_{0.1}$ ratio (an index of resting respiratory function)[19] was not different between the SBT/extubation-success and SBT/extubation-failure groups.

Limitations

Our method of producing hypercapnia (by adding a dead space similar to the V_T) has the advantage of being easy, and can increase P_{aCO_2} by > 10 mm Hg within 5 min, similar to the usual rebreathing test.[23] During the hypercapnia test the patients received a low level of pressure support. Neuromuscular response to CO_2 is similar at different levels of inspiratory assistance or with unassisted ventilation.[30,31] Differences in methods between studies (eg, increased dead space instead of inhaling a fixed level of CO_2, or measuring P_{aCO_2} instead of end-tidal CO_2) could slightly alter the hypercapnia test results,[17,18] but that would not explain the differences between the groups. The hypercapnia test was conducted after a period of hyperoxia,

for patient safety, and to avoid hypoxic chemoreceptor stimulus.

The interpretation of the hypercapnia test response, in general, and in our study in particular, has several limitations. First, the normal ranges are wide;[23,24] there is large day-to-day intra-individual variation in breathing-pattern variables[32] and within-day variability of hypercapnic ventilatory response; and the coefficient of variation ranges from 8.3% to 26.3% (average 17.9%).[33]

Second, the ventilator's accuracy in measuring the respiratory variables we studied is not as good as certain other methods, such as pneumotachography, so relying on the values reported by the ventilator may risk misclassifying patients who have borderline measurements.

Third, our findings cannot be extrapolated to all intensive care patients because we excluded patients with chronic obstructive pulmonary disease and neuromuscular disease (who may have reduced response to the hypercapnia test), and the duration of mechanical ventilation before the first SBT was substantial.

Conclusions

SBT/extubation-failure patients have less response to hypercapnia test than do SBT/extubation-success patients. In the patients we studied, the hypercapnia test was not useful in predicting SBT/extubation success.

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