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WEANING PREDICTION: ESOPHAGEAL PRESSURE MONITORING COMPLEMENTS READINESS TESTING

By

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ABSTRACT

Several variables are recommended for identifying if a patient is ready for a trial of weaning from mechanical ventilation, but there is no agreement as to whether monitoring any variable during the trial enhances patient management. To determine whether repeated measurements of esophageal pressure throughout a trial are more reliable than measurements of esophageal pressure or frequency-to-tidal volume ratio during the first minute of the trial, we studied 60 patients. A trend index that quantified esophageal pressure swings over time was more reliable than the first-minute measurements: sensitivity, 0.91, and specificity, 0.89. Area under receiver operating characteristic curve for trend index (0.94) was greater than for first-minute measurement of esophageal pressure (0.44, $p < 0.05$) and tended to be greater than that for frequency-to-tidal volume (0.78, $p = 0.13$). Likelihood ratio was highest for the trend index (8.2, $p < 0.05$). The advantage of the trend index may be related to the progressive increase in esophageal pressure throughout a failed weaning trial whereas breathing pattern changed little after two minutes of spontaneous breathing. In conclusion, continuous monitoring of esophageal pressure swings during a spontaneous breathing trial provides additional guidance in patient management over tests used for deciding when to initiate weaning.

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INTRODUCTION

Clinical decision making during weaning from mechanical ventilation consists of two stages (1). The first stage is for the clinician to decide whether or not a ventilator-supported patient has a reasonable likelihood of being able to breathe on his or her own. This decision on patient readiness is typically guided by measurement of physiological variables, termed weaning predictors (2,3). These variables are measured on a one-time basis, and before a formal weaning attempt is initiated. If the variables predict a reasonable likelihood of weaning success, clinicians progress to the second stage (4). The second stage consists of either a gradual reduction in the level of ventilator assistance, as with pressure support, or an abrupt decrease in mechanical ventilation, as with a spontaneous breathing trial (5,6).

A large number of physiological variables have been proposed for readiness testing (2,7,8). No agreement, however, exists as to what physiological variables should be monitored during the second stage. Indeed, there is no agreement as to whether the monitoring of any variable helps decide whether to continue a spontaneous breathing trial for an initially planned duration, prolong it, or curtail it. The contrast between the voluminous literature on predictors and the virtual absence of research on patient monitoring during the second stage of weaning is striking. Research into weaning pathophysiology has revealed that certain variables change progressively as patients fail a weaning trial (9-12). Specifically, we found that weaning failure patients develop marked increases in respiratory effort over the course of a spontaneous breathing trial (9). Accordingly, we wondered whether the monitoring of swings in esophageal pressure

(Pes) might provide guidance during the second stage of weaning and so enhance weaning prediction. We also wondered whether repeated measurements of the ratio of respiratory frequency to tidal volume (f/V_T) during a spontaneous breathing trial might predict weaning outcome more accurately than measuring it solely at the start of the trial (2,13).

A challenge for research on the clinical usefulness of repeated measurements of Pes is to develop a method for quantifying the change in Pes over time – its trend. To be applicable for clinical-decision making, the trend should ideally be captured in a single number. Physicians commonly say they base decisions on trends. In reality, however, methods for quantifying trends, such as those used in time-series research (14-17), have not been incorporated into everyday clinical practice. It is ironic that patients are commonly admitted to an intensive care unit for the sole purpose of repeatedly recording physiological variables over time, yet no attempt is made to quantify trends in a meaningful manner (18). Accordingly, an allied goal of the present study was to investigate methods for quantifying overall change in Pes and f/V_T over time. For this purpose, we tested several mathematical models for optimal capturing of these trends. We also investigated whether certain segments of the change in Pes and f/V_T over the course of a spontaneous breathing trial might prove superior for clinical-decision making over other segments.

Based on the above considerations, we hypothesized that repeated measurements of swings in Pes and f/V_T over the course of a trial of spontaneous breathing would be superior for predicting weaning outcome than one-time measurements of each variable.

METHODS

1. Online supplement

See online supplement for additional details.

2. Patients

Sixty patients (57 men, 3 women; age, 67 ± 2 (SE) years) who were clinically stable and whose primary physician considered them ready to undergo a weaning trial were recruited (Table 1). The patients had received 20 ± 4 days of ventilator support. The decision to extubate a patient or reinstitute mechanical ventilation was made solely by the primary physician. The study was approved by the Human Studies Subcommittee and informed consent was obtained from each patient. Some aspects of data on respiratory muscle function and mechanics have been included in reports that address different research questions (9,19,20).

3. Study Protocol

Endotracheal suctioning was performed before the study. Flow was measured between the endotracheal tube and the Y of the ventilator tubing with a pneumotachograph (9,19,21). From the flow signal, respiratory frequency was calculated and tidal volume was obtained by electronic integration. Pes was measured using balloon-tipped catheters connected to pressure transducers (9,19,21).

A trial of spontaneous breathing was initiated through a T-tube circuit, with the patient in a semi-recumbent position and fractional inspired oxygen concentration set at the same level as during mechanical ventilation. Breath-by-breath measurements of breathing pattern and Pes commenced immediately at the point of discontinuing mechanical ventilation and were continuously measured throughout the trial of spontaneous breathing. The a priori criteria for weaning failure were tachypnea, increased accessory muscle activity, diaphoresis, facial signs of distress, cyanosis, tachycardia, arrhythmias, and hypotension (9,19). Thirty-five patients met these criteria, were returned to the ventilator and were designated as weaning failure patients. Twenty-five patients met none of these criteria at the end of the trial, were extubated, and were designated as weaning success patients.

4. Data Analysis

4a General approach

To derive the new trend indices, three steps were taken: the first was to determine the equilibration time for swings in Pes and f/V_T; second was to characterize the trends in Pes swings and f/V_T (to determine whether the pattern differed between the two patient groups); and the third step was to derive the trend indices for Pes and f/V_T in an individual patient.

Patient data were assigned to one of two sets. A derivation data set was used for undertaking the three above-mentioned steps. This data set was derived from 31 patients (14 weaning success and 17 weaning failure patients); these were the patients in whom we previously reported that patient effort increases over the course of a failed weaning trial (9). A validation data set was used to assess the ability of the new indices to predict weaning outcome (Diagnostic accuracy and ROC analysis, see below). This validation data set was derived from 29 patients (11 weaning success and 18 weaning failure patients).

4b Derivation of new trend indices

4b.i Equilibration time for Pes swings and f/V_T: A swing in Pes was defined as the change between the point of rapid decrease in Pes and its nadir during a spontaneous breath. Swings in Pes were measured throughout the trial on a breath-by-breath basis. In each patient, Pes swings were then averaged on a minute-by-minute basis. The equilibration time for each patient was calculated as the time required for Pes swings to reach $\pm$ 10% of the average value of the last minute of the trial. The difference in equilibration time between failure and success patients was determined by Kaplan-Meier analysis. For the f/V_T data, all of the preceding analytic steps were repeated. Data on equilibration time are presented as medians with 25^{th} and 75^{th} percentile range.

4b.ii Trend analysis: Characterization of trend in both patient groups: To determine whether the pattern of change in Pes swings differed between the failure and success groups over the course of the trial, we first characterized the temporal pattern in each group using a mathematical model. Simple inspection of the data revealed that the data could not be fitted into a single linear model. Accordingly, a non-linear model, namely the multivariate adaptive regression spline (MARS) analysis, was employed to characterize the changes in Pes swings in the two groups (22).

The duration of spontaneous breathing varied from patient to patient, and nine minutes was the longest time sustained by all 31 patients of the derivation set. Accordingly, the MARS analysis was applied to the first nine minutes of the trial in the two groups. The two resulting equations for the failure patients and the success patients are graphed in **Figure 5**. Within 2 minutes of commencing spontaneous breathing, f/V_T values had equilibrated in both the success and failure patients **(See Figures 1 and 3);** accordingly, trend analysis was not appropriate.

4b.iii Derivation of trend index for an individual patient: After demonstrating that the change in Pes swings over the nine minutes differed between the failure and success groups, we next determined whether change in Pes swings could reliably predict weaning outcome in an individual patient. To do this, we needed a single model that could accurately capture the change in Pes swings over the entire nine minutes for all patients. To derive such a model, the following 3 steps were undertaken:

(1) All of the data of each patient (in the two groups) were pooled together and the combined data were entered into another MARS analysis. The pattern of change in Pes swings varied considerably among patients, and a single MARS model could not accurately capture the change in Pes swings over the entire nine minutes for all patients. We then decided to focus on data available for all patients during the beginning and end

of the trial. Because nine minutes was the longest segment of data we had available in every patient (see above), we focused on two segments: the entire first minute and the entire ninth minute of the trial. (Please see online supplement for details).

(2) Linear regression analysis was then performed on swings in Pes during the first minute of the trial for each individual patient; the same analysis was repeated for the ninth minute. The change in Pes swings for the first minute was expressed as the slope of the regression equation. For the ninth minute, the slope and the intercept of the regression equation were used to estimate Pes at the transition between the ninth and tenth minute. Pes at the transition between the ninth and the tenth minute was estimated because not every patient had a data point at exactly the termination of the ninth minute, and because considerable breath-to-breath variability was evident among the patients.

(3) These two data sets -- the slope of the first minute and the estimated value of Pes swings at the transition between the ninth and tenth minute for all patients – were then entered into another MARS analysis. This analysis yielded an equation that proved successful in reliably predicting weaning outcome in an individual patient. We refer to this final model as the "Pes trend index". (Please see online supplement for details).

4c Diagnostic accuracy and ROC analysis

Standard formulas were used to calculate sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios of three variables in predicting weaning outcome: the average swing in Pes (calculated from all breaths during the first minute of the trial); f/V_T (calculated from all breaths during the first minute of the trial); and the Pes trend index. (Please see online supplement for details). Receiver operator characteristic (ROC) curves were generated to determine the relative accuracy of the above three variables in predicting weaning outcome (2). The probability of identifying weaning outcome correctly was calculated using a c-index, which is equivalent to the area under the ROC curve (23). The c-index values for the Pes trend index and the first-minute measurement of Pes swings were compared using confidence intervals analysis; Pes trend index and f/V_T were likewise compared (24).

RESULTS

Equilibration time for Pes swings and f/V_T

Time-series plots of Pes swings and f/V_T during a trial of spontaneous breathing in a representative failure patient are shown in Figure 1. The median time (plus interquartile range) to reach $\pm$ 10% of the final value was longer for swings in Pes, 7.5 (4.2-14.75) minutes, than for f/V_T, 2 (1-2) minutes ($p < 0.0001$ on Wilcoxson test; $p < 0.003$ on log rank rest) (Figure 2). For example, 77% of the failure patients reached $\pm$ 10% of the final value of f/V_T within 2 minutes whereas they needed 15 minutes to reach $\pm$ 10% of the final value for Pes swings.

Time-series plots of Pes swings and f/V_T for a success patient are shown in Figure 3. The median time (plus interquartile range) to reach $\pm$ 10% or higher of the final value was longer for swings in Pes, 5 (2-8.5) minutes, than for f/V_T, 2 (1-2) minutes ($p < 0.04$ on Wilcoxson test; $p = 0.07$ on log rank test) (Figure 4). For example, 73% of the success patients reached $\pm$ 10% of the final value of f/V_T within 2 minutes whereas they needed 8 minutes to reach $\pm$ 10% of the final value for Pes swings.

Characterization of trend in both patient groups

Figure 5 displays the change over time in Pes swings, as quantified by MARS analysis, in the success and failure patients. The success patients exhibited virtually no change in Pes swings over the first nine minutes of the weaning trial. In contrast, the failure patients displayed a progressive increase in Pes swings over time.

Prediction of weaning outcome

The derivation data set (31 patients) revealed three variables that discriminated between the success and failure patients: Pes swings during first minute, f/V_T during the first minute, and the Pes trend index. The threshold values providing greatest discrimination between the success and failure patients were: Pes swings during the first minute, $\geq$ 5.6 cm H_2O; f/V_T during the first minute, $\geq$ 101 breaths/min/L; and the Pes trend index, $\leq$ 0.44.

The accuracy of these three variables when tested in the prospective validation data set (29 patients) is listed in Table 2. The Pes trend index achieved the highest sensitivity (0.91), and the highest positive and negative predictive values (0.83 and 0.94, respectively). Specificity (0.89) of the trend index was equivalent to that achieved by swings in Pes during the first minute. The likelihood ratio – calculated solely from the validation data set -- was higher for the Pes trend index (8.2) than for either f/V_T (2.5, $p < 0.05$) or swings in Pes during the first minute (1.6, $p < 0.05$).

To avoid dependence on the threshold values of variables, receiver operating characteristic (ROC) curve analysis was performed (Figure 6). The area under the ROC curve for first-minute measurement of swings in Pes, 0.44 (0.23 to 0.66, 95% confidence intervals), was lower than the area for an arbitrary test that is expected a priori to have no discriminatory value (Figure 6). The area under the ROC curve for Pes trend index, 0.94 (0.73 to 0.99), tended to be more accurate than the area for f/V_T, 0.78 (0.55 to 0.91) ($p = 0.13$) (Figure 6). Because the areas under the curves for both the derivation and validation data sets were equivalent, the data were combined to assess the value of the Pes trend index in a larger group of patients. In the combined data sets, the area under the curve for the Pes trend index, 0.93 (0.82 – 0.98), was significantly higher than the area under the curve for f/V_T, 0.79 (0.66 – 0.88) ($p < 0.05$). Attaining significance with the combined data sets supports the view that the lack of statistical significance for the validation data set resulted from its relatively small size.

DISCUSSION

Repeated measurements of the swings in Pes (the Pes trend index) during a trial of spontaneous breathing were more accurate in predicting weaning outcome than was the average swing in Pes during the first minute of the trial. The Pes trend index also tended to provide more accurate prediction of weaning outcome than did f/V_T. The superiority of repeated measurements of Pes swings as a predictor may be related to the progressive increase in Pes swings over the course of a failed weaning trial whereas f/V_T shows little change after the first two minutes of spontaneous breathing.

Monitoring during second stage of weaning

Clinicians typically measure weaning predictors to see whether a patient is ready for a trial of spontaneous breathing (first stage of weaning); there is no agreement as to whether it is useful to obtain further measurements during the actual trial (second stage of weaning) to quantitatively assess patient progress (4). We found that monitoring the trend in Pes swings during a spontaneous breathing trial helped to discriminate between patients who failed and succeeded in a trial. This is the first study to show that repeated measurement of a physiological variable over the course of a spontaneous breathing trial (the second stage of weaning) provides additional guidance in patient management over tests used for deciding when to initiate weaning.

Previous studies of weaning prediction have been almost invariably confined to a one-time measurement of a physiological variable (2,4). A few investigators have obtained repeated measurements of some variable, but with a goal of enhanced pathophysiological understanding rather than clinical decision-making. For example, Chatilla et al (25) found that increases or decreases in the ST segment of the electrocardiogram of more than 1 mm tended to be more common in weaning failure patients than in weaning success patients. We previously reported that weaning failure patients are more likely to exhibit a decrease in mixed venous oxygen saturation during a spontaneous breathing trial than are weaning success patients (11). In neither study, however, were the variables investigated for their usefulness in clinical decision making

The Pes trend index was more accurate in predicting weaning outcome than first-minute measurement of Pes. This finding is consistent with current understanding of the pathophysiology of weaning failure. We have previously shown that respiratory pressure output (quantified by pressure-time product) was similar in weaning success and failure patients at the start of a spontaneous breathing trial (9). Over the course of the trial, weaning failure patients developed marked and progressive increases in the mechanical load on the respiratory muscles. By the end of the trial, respiratory resistance increased to about seven times the normal value; lung elastance increased to about five times the normal value; and intrinsic PEEP more than doubled (9). To cope with the increase in mechanical load, weaning failure patients increased their pressure-time product to more than four times the normal value by the end of the trial (9). Pressure-time product assesses both the magnitude and duration of an inspiratory muscle contraction, and thus more closely reflects oxygen consumption by the respiratory muscles than do swings in Pes (26). From a monitoring perspective, however, swings in Pes show larger changes over the course of a failed weaning trial than does the duration of inspiratory muscle contraction (9,27), and they provide a simpler method for monitoring changes in patient effort.

Mathematical computation of trend

To investigate the usefulness of repeated measurements of Pes, researchers have to contend with several obstacles: the enormous amount of data generated by such monitoring; determining whether certain segments are more reliable than other segments in clinical decision making; and discovering a mathematical method that best expresses the trend in Pes. We first investigated whether some segment or segments of repeated measurements of Pes swings might discriminate between weaning success and weaning failure patients. For this purpose, we used the MARS (multivariate adaptive regression spline) analysis (22). MARS analysis has an advantage over other mathematical models because it segments data strings of varying length, and thus is able to identify the most promising variables in each segment. As such, the shape of any nonlinearities is determined by the data, and is not imposed by the data analyst. The MARS approach also employs a cross-validation technique, which generates a model of optimal size and avoids overfitting of the data. We investigated other mathematical models before concluding that the MARS approach was optimal.

Time-course of Pes trend and f/V_T

That repeated measurements of Pes swings were more reliable than f/V_T in predicting weaning outcome may be related to the different time scales needed for equilibration of these two variables. Within two minutes of commencing spontaneous breathing, f/V_T had reached $\pm$ 10% of the average value during the last minute of the trial in the failure patients. In contrast, patients took 15 minutes for swings in Pes to equilibrate to an equivalent extent. Research into weaning pathophysiology indicates that patients show substantial alterations in many (9,11,25), but not all (19,27), physiological variables over time. Thus, a variable, such as the Pes trend index, which captures change in a patient's condition over time, has the greatest likelihood for demonstrating the usefulness of monitoring during a spontaneous breathing trial. Conversely, a variable that attains close to its final value shortly after a patient is disconnected from a ventilator may be most helpful in guiding when to undertake a weaning trial (readiness testing), but will have little if any value in monitoring the performance of a patient during such a trial. Because no physiological variable provides perfect prediction of weaning outcome, the combination of a variable that indicates when to undertake a trial of spontaneous breathing and another variable that quantifies patient progress during the trial is appealing.

The precise mechanism as to why weaning failure patients exhibit an immediate increase in f/V_T is not known. Alterations in mechanical load are likely to be important. We have previously reported that patients failing a weaning trial develop progressive increases in both inspiratory resistive and inspiratory elastic load (9). These loads have opposing effects on breathing pattern. A resistive load slows respiratory frequency while preserving tidal volume, thereby producing a decrease in f/V_T (17,28,29). An elastic load increases respiratory frequency accompanied by a decrease in tidal volume, both of which will produce an increase in f/V_T (30,31). These opposing influences of resistive and elastic loads on breathing pattern may account for the relative constancy of f/V_T.

The development of dynamic hyperinflation in weaning failure patients – as suggested by progressive increase in dynamic intrinsic PEEP (9,19) – may also contribute to the relative constancy of f/V_T. An increase in end-expiratory lung volume is expected to slow respiratory frequency without causing an increase in tidal volume, producing a decrease in f/V_T (32). The muscle weakness that accompanies hyperinflation, however, is likely to increase respiratory frequency (32), and thus cause an increase in f/V_T. These opposing influences of dynamic hyperinflation and muscle weakness on breathing pattern is another possible reason that f/V_T reaches a constant value soon after the commencement of spontaneous breathing.

Swings in Pes took between 8 and 15 minutes to reach $\pm$ 10% of their final magnitude in most failure patients. The progressive increase in Pes, which reflects increase in respiratory motor output, may have resulted in part from an increase in $PaCO_2$. We have previously reported that patients develop an increase of $PaCO_2$ of 13 mm Hg over the course of a failed weaning trial. Increases in PCO_2 are known to produce proportional increases in respiratory effort (33,34).

Frequency-to-tidal volume ratio

The area under the ROC curve for f/V_T in this study, 0.78, is lower than the value of 0.89 that we originally reported (2). The discrepancy may relate to three or more factors. One, the patients in the present study received an average of 20 days of mechanical ventilation as compared with an average of 8 days in the previous study. In our original report, we pointed out that f/V_T was less accurate in predicting weaning outcome in patients requiring 8 or more days of mechanical ventilation than in patients being ventilated for a shorter time (2). Two, the method for measuring f/V_T differed in the two studies. In the original report, f/V_T was measured using a hand-held spirometer while the patient inspired room air. In the current study, breathing pattern was measured using a pneumotachograph attached to a T-piece while the patient inspired supplemental oxygen. Three, and most importantly, clinical decision making of physicians in the first study was not influenced by the measurement of f/V_T – because its usefulness as a clinical test had not been reported.

Clinical implications of Pes trend index

Commercial systems that enable the monitoring of Pes swings have been available for more than a decade. Only one group of investigators, however, has attempted to quantify Pes tracings into a numeric value that can be used for clinical-decision making. Gluck et al (35) evaluated the usefulness of a commercial system, Bicore (Bicore Monitoring Systems, Irvine, CA), for expediting the weaning process. The Bicore protocol consisted of measurements of work of breathing, airway occlusion pressure ($P_{0.1}$) and f/V_T; the conventional protocol consisted of frequency, tidal volume, minute ventilation, static compliance, respiratory resistance, and maximum inspiratory pressure. The Bicore protocol resulted in a more aggressive pace of weaning than did the conventional protocol in 40% of instances. Unfortunately, the investigators did not distinguish between the efficacy of simple measurements, such as f/V_T, and the more complex measurement of work of breathing in the Bicore protocol. Moreover, the pace of weaning in the conventional arm was estimated rather than directly measured. Furthermore, weaning was primarily achieved by decreasing intermittent mandatory ventilation, which is the least efficient weaning technique (5,6). Finally, measurements of work of breathing were based on an average of 10 breaths.

Combining breath-by-breath measurements of Pes swings and sophisticated mathematical modeling, we found that monitoring of the trend in Pes swings (quantified as the Pes trend index) during the first nine minutes of a spontaneous breathing trial was more accurate in predicting weaning outcome than first minute measurements of either Pes swings or f/V_T. In particular, a Pes trend index of less than or equal to 0.44 after nine minutes of spontaneous breathing was 8.2 times more likely to occur in a patient who went on to fail the trial than in a patient who was subsequently successfully weaned. If confirmed by subsequent investigators, measurement of Pes trend index could provide a useful clinical tool for patient assessment during weaning. More accurate prediction of weaning outcome should help to minimize failed extubation and unnecessary prolongation of mechanical ventilation. Moreover, increases in Pes swings during the trial should alert a physician to institute therapy, such as bronchodilators, inotropics or diuretics, at a time that might enable an unsuccessful trial to be converted into a successful trial.

Although monitoring of the Pes trend index during weaning looks promising, its implementation in clinical practice poses some challenges. First, accurate measurements of Pes swings requires minimizing the artifact caused by the heartbeat and optimizing the frequency response of the measuring system; these limitations can be circumvented through careful attention to the length, diameter, and the position of the catheter (36). Second, the derivation of the Pes trend index involves sophisticated mathematical modeling such as MARS; the mathematical computation involving linear regression analysis, could be automated through commercial software packages such as Excel.

Thus, it is feasible to incorporate Pes trend index into a commercial monitor at patient's bedside. Third, the major limitation of using the Pes trend index is the invasiveness of inserting an esophageal balloon-catheter. Although the Pes trend index fared better in predicting weaning outcome than measurement of f/V_T at the start of a weaning trial, its superiority is rather small. Thus, the risk of inserting an esophageal catheter in an individual patient has to be balanced against the benefit of being able to more accurately predict weaning outcome. Inserting a balloon may be unnecessary in a patient who can be weaned within three or so days; many patients, however, require many additional days of ventilation before weaning is attempted. Of note, our patients had received on average 20 days of mechanical ventilation.

In summary, repeated measurements of swings in Pes over the first nine minutes of a spontaneous breathing trial were more accurate in predicting weaning outcome than were measurements of Pes swings or f/V_T during the first minute of the trial. The superiority of Pes swings as a predictor may be related to the longer time that patients took to achieve Pes equilibration whereas f/V_T showed little change after the first two minutes of spontaneous breathing. In conclusion, continuous monitoring of Pes swings during the second stage of weaning provides additional guidance in patient management over tests used for deciding when to initiate weaning.

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LEGENDS

Figure 1: Time-series plot of swings in esophageal pressure (Pes) (*left panel*) and frequency-to-tidal volume ratio (f/V_T) (*right panel*) during a trial of spontaneous breathing in a weaning failure patient. Black dots represent one-minute averages. The solid line indicates the average value of Pes swings and f/V_T of the final minute of the trial. The dashed lines indicate $\pm$ 10% of the final minute values of Pes swings and f/V_T. The time taken to reach $\pm$ 10% of the final value was 14 minutes for Pes swings and 2 minutes for f/V_T.

Figure 2: Probability of weaning failure patients reaching equilibration time ($\pm$10% of final value) for frequency-to-tidal volume ratio (f/V_T) and swings in esophageal pressure (Pes) at progressive points in time over the course of a spontaneous breathing trial. Pes swings took a longer time to reach $\pm$10% of their final value than did f/V_T ($p < 0.003$ on log rank rest).

Figure 3: Time-series plot of swings in esophageal pressure (Pes) (*left panel*) and frequency-to-tidal volume ratio (f/V_T) (*right panel*) during a trial of spontaneous breathing in a weaning success patient. Black dots represent one-minute averages. The solid line indicates the average value of Pes swings and f/V_T of the final minute of the trial. The dashed lines indicate $\pm$ 10% of the final minute value of Pes swings and f/V_T. The time taken to reach $\pm$ 10% of the final value was 6 minutes for Pes swings and 2 minutes for f/V_T.

Figure 4: Probability of weaning success patients reaching equilibration time ($\pm$10% of final value) for frequency-to-tidal volume ratio (f/V_T) and swings in esophageal pressure (Pes) at progressive points in time over the course of a spontaneous breathing trial. Pes swings tended to take a longer time to reach $\pm$10% of their final value than did f/V_T ($p = 0.07$ on log rank rest).

Figure 5: Esophageal pressure swings (Pes) in weaning failure (solid line) and weaning success groups (dashed lines) that were generated by the multiple adaptive regression spline (MARS) analysis. See text for details. The greatest rate of increase in Pes swings in the failure patients occurred during the first minute. The greatest difference in Pes swings between the failure (14.5 cm H_2O, 95% confidence intervals 18.9 to 11.2) and success groups (7.9 cm H_2O, 95% confidence intervals 11.8 to 0.8) was at the transition between the ninth and tenth minute.

Figure 6: Receiver operator characteristic (ROC) curves for esophageal pressure (Pes) during the first minute of a spontaneous breathing trial (*upper left panel*), frequency-to-tidal volume ratio (f/V_T) during the first minute of the trial (*upper right panel)*, and esophageal pressure (Pes) trend index (*lower pane*l) of the validation data set. The diagonal line represents a test that is expected *a priori* to have no discriminatory value. The area under the curve is expressed (in box) as a proportion of the total area of the curve. The area under the curve for one-minute measurement of Pes

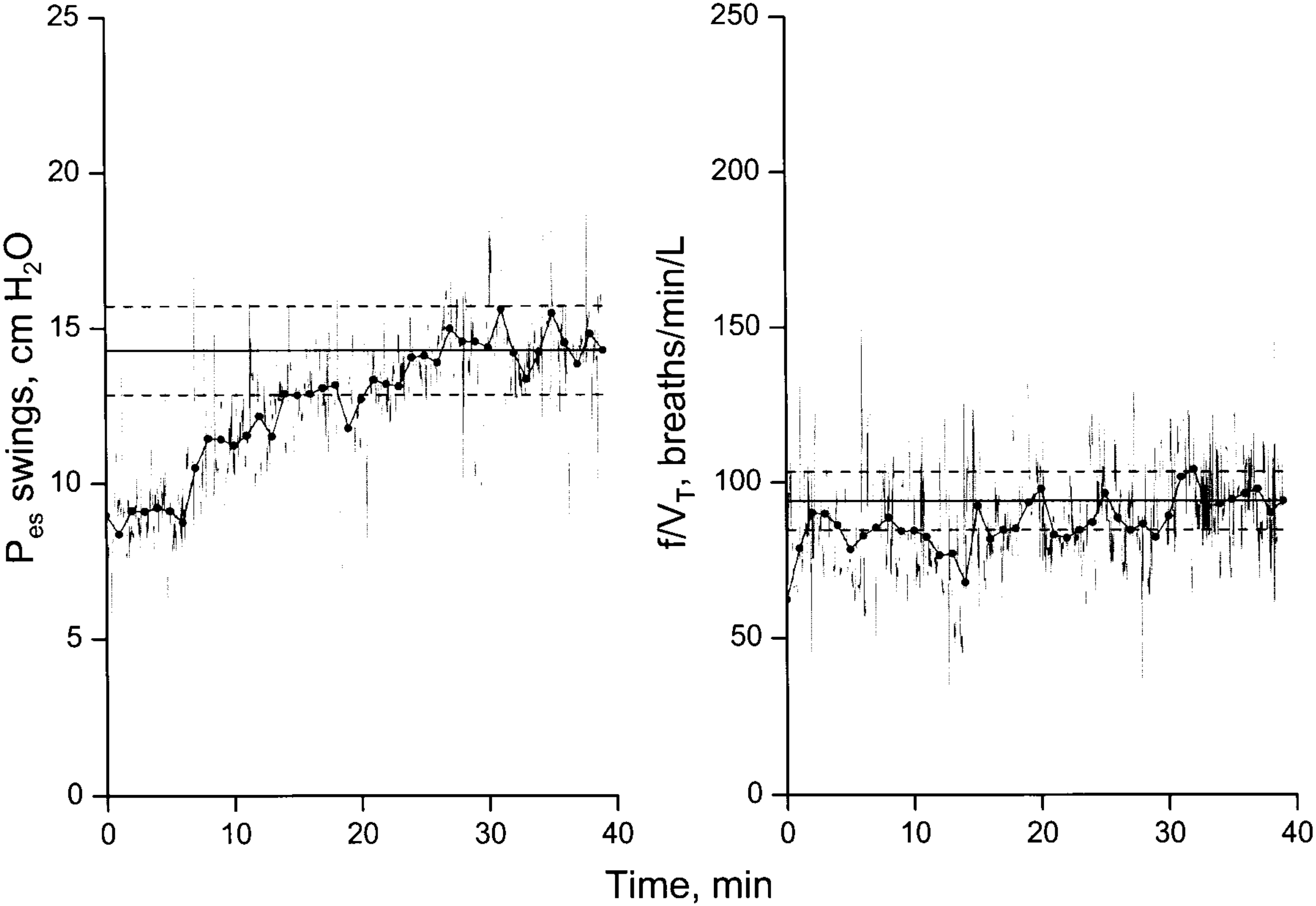
swings was 0.44, which is less than chance alone. The area under the curve for Pes trend index (0.94) was significantly higher than that for one-minute measurement of Pes swings ($p = 0.05$) and tended to be higher than that for f/V_T ($p = 0.13$).

Table 1. Baseline Characteristics of Patients

	Derivation set (n = 31)	Validation set (n = 29)
Age – years	68.5 ± 1.9	65.6 ± 2.8
Male sex, numbers (%)	29 (94)	28 (97)
Days on mechanical ventilation, mean ± SE	21.9 ± 6.4	18.8 ± 5.5
Reason for initiating mechanical ventilation, numbers (%)		
Acute-on-chronic COPD	20 (65)	17 (59)
Pneumonia	4 (13)	3 (10)
Heart failure	0	4 (14)
Post-op respiratory failure	2 (6)	2 (7)
Miscellaneous	5 (16)	3 (10)

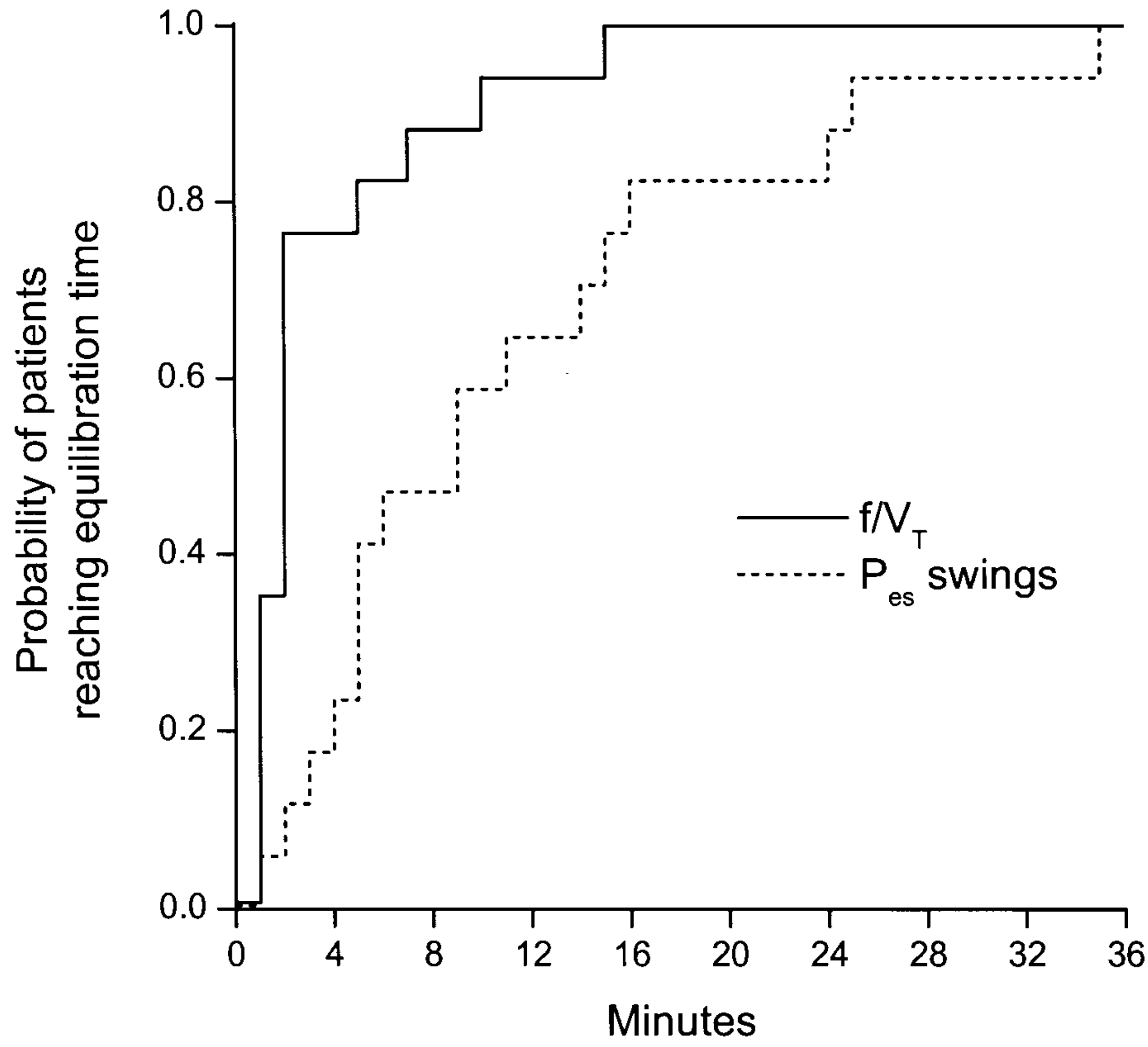
Table 2. Accuracy of the indexes used to predict weaning outcome in the validation data set

Index	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio (95% C.I.)
P_{es} swings during first minute, cm H_2O	0.18	0.89	0.50	0.64	1.6 (0.3 – 8.3)
f/V_T breaths/min/liter	0.82	0.67	0.60	0.86	2.5 (1.2 – 5.2)
P_{es} trend index, a.u.	0.91	0.89	0.83	0.94	8.2 (2.7 – 29.6)



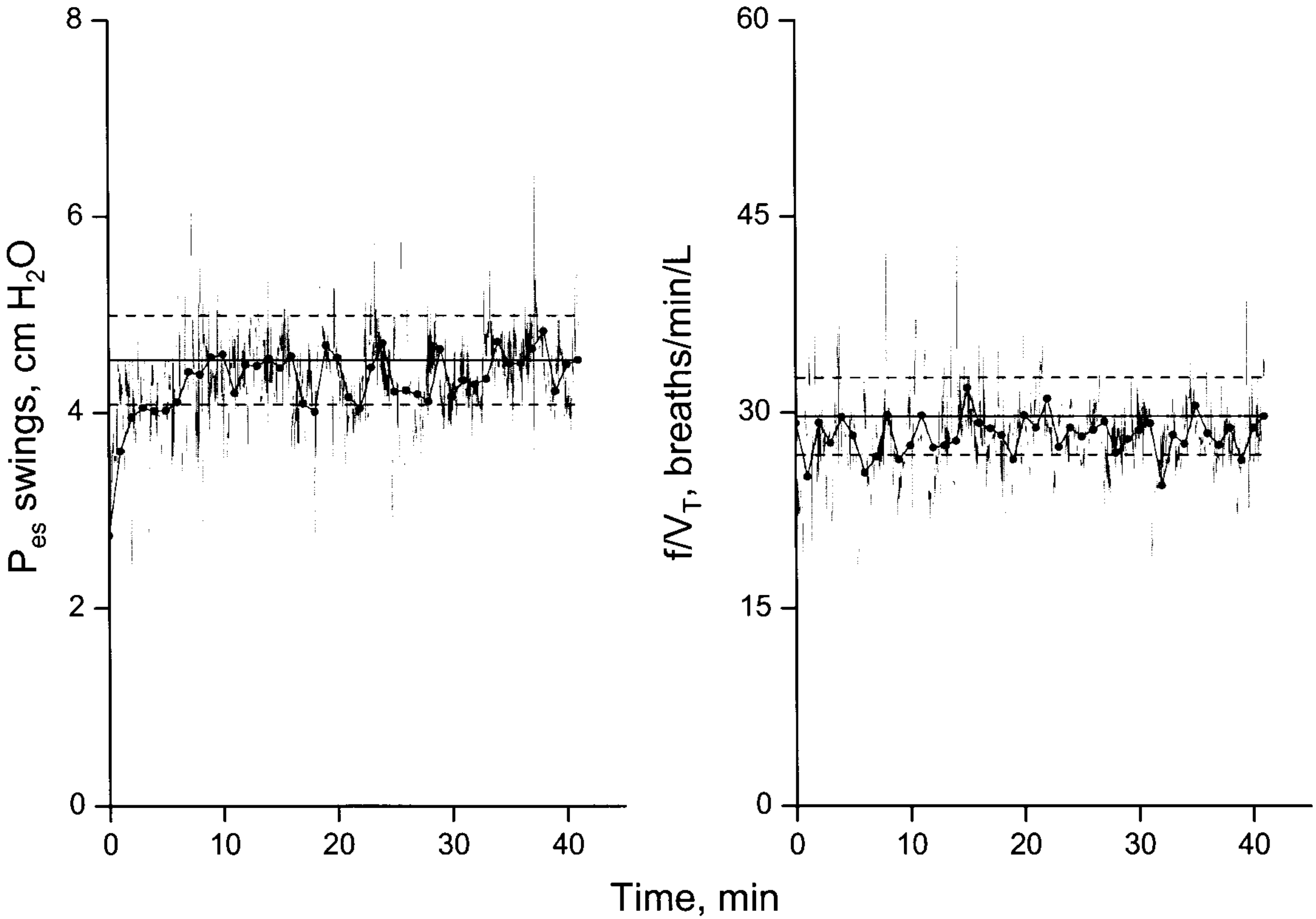
25
20
15
10
5
0
P_{es} swings, cm H_2O
0
10
20
30
40
250
200
150
100
50
0
f/V_T, breaths/min/L
0
10
20
30
40
Time, min

Figure 1



Probability of patients reaching equilibration time
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24
28
32
36
Minutes
f/V_T
P_es swings

Figure 2



8
6
4
2
0
Pes swings, cm H2O
0
10
20
30
40
60
45
30
15
0
f/VT, breaths/min/L
0
10
20
30
40
Time, min

Figure 3

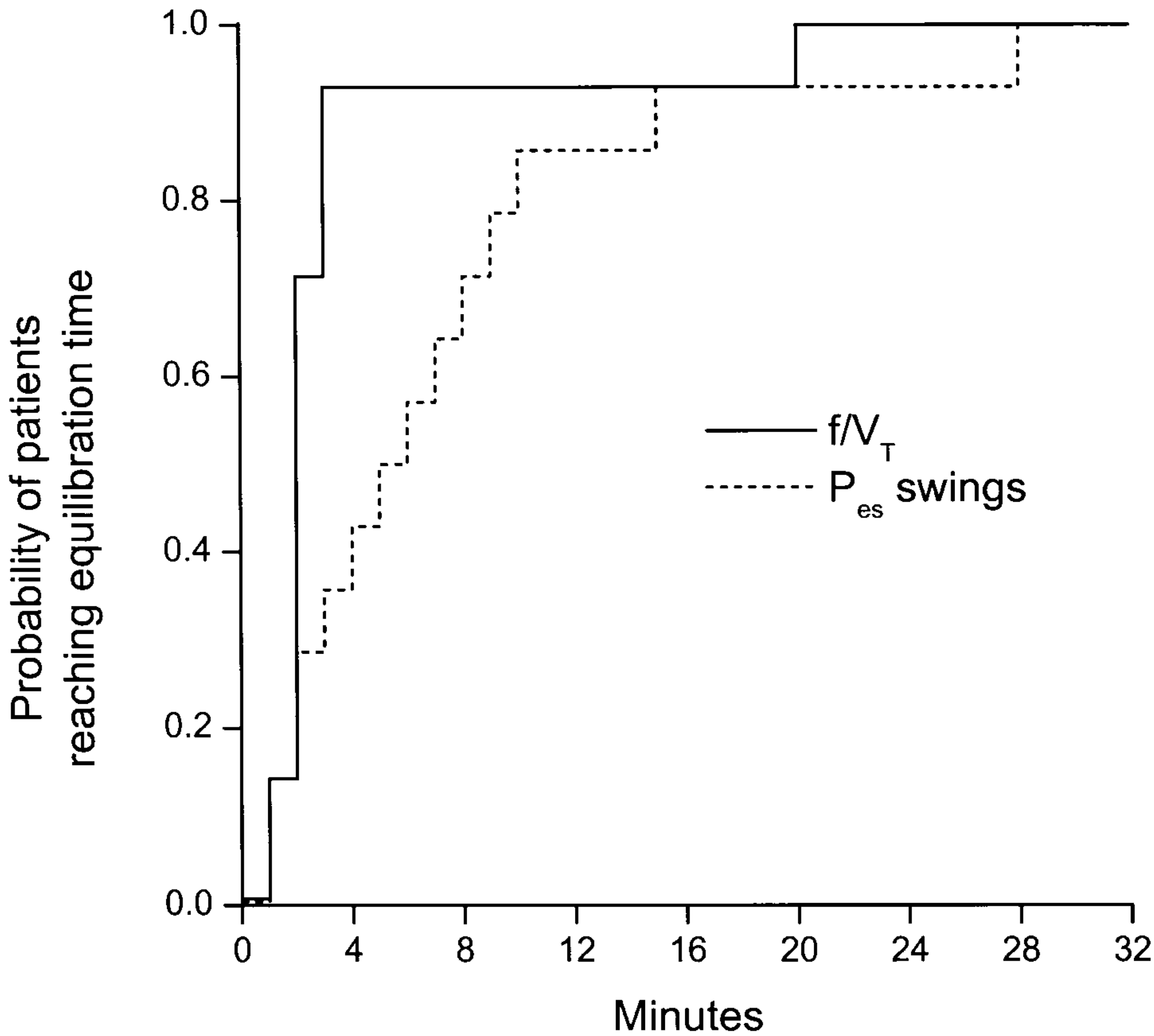

Probability of patients reaching equilibration time
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
16
20
24
28
32
Minutes
f/V_T
P_es swings

Figure 4

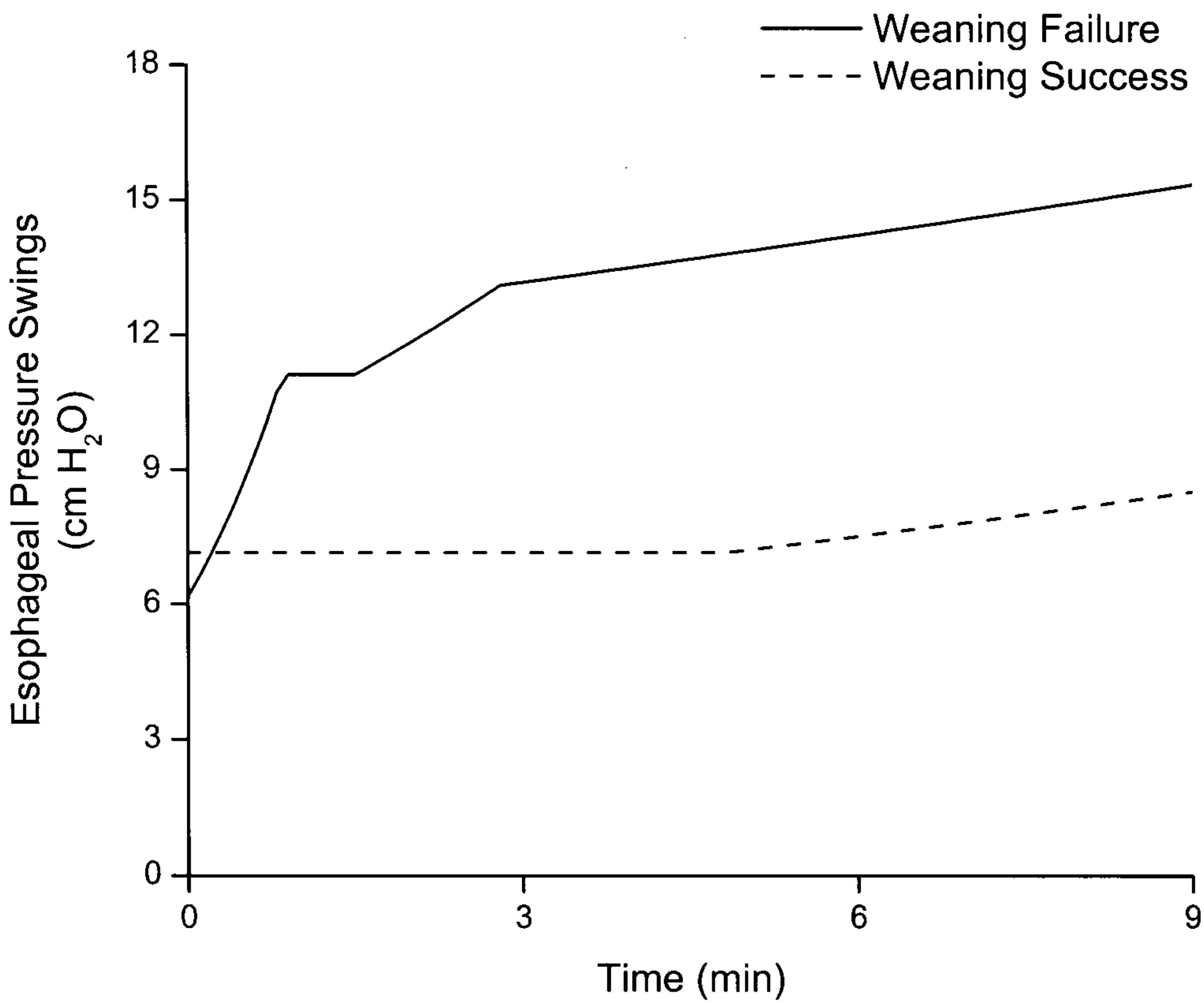
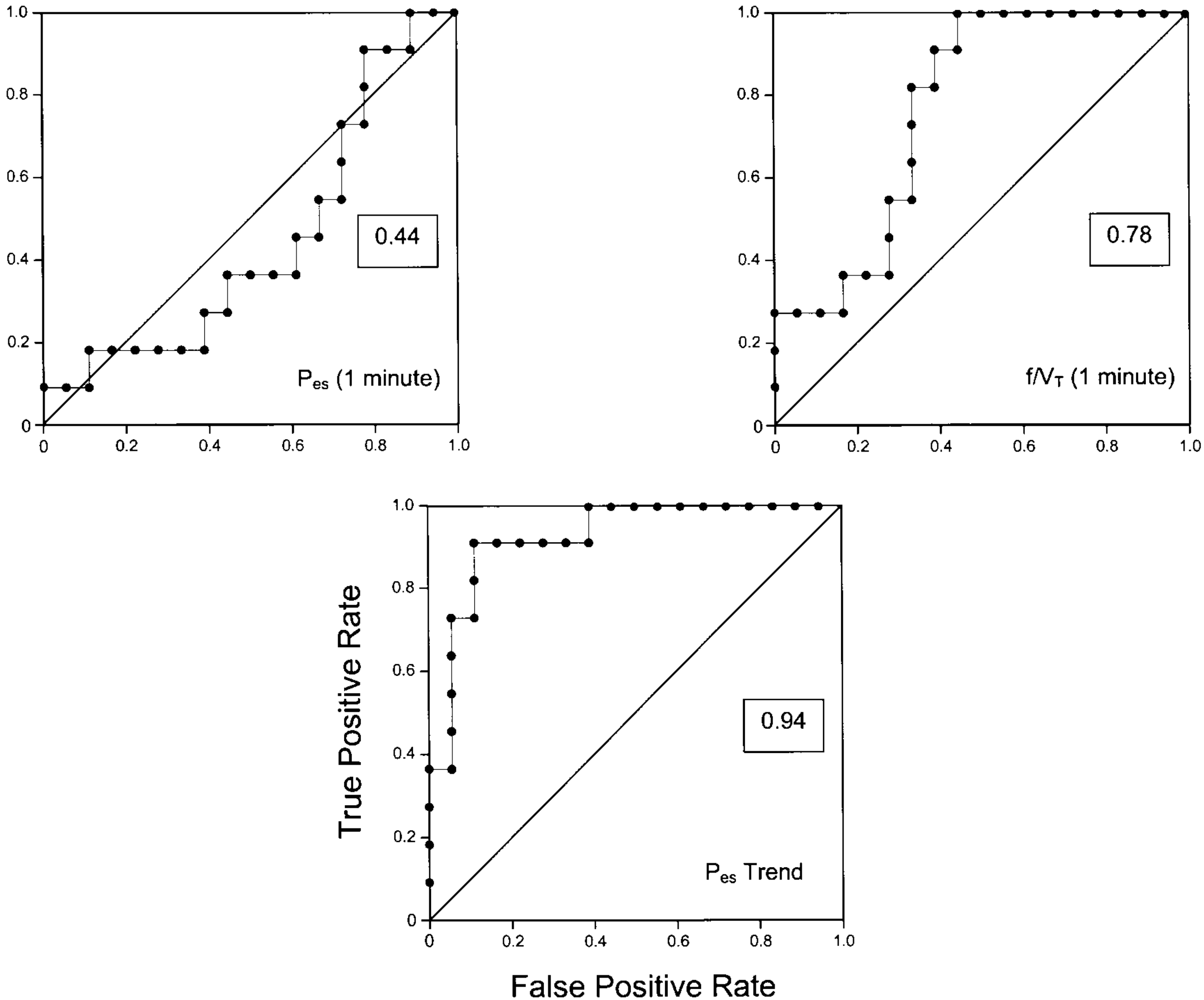

Weaning Failure
Weaning Success
18
15
12
9
6
3
0
Esophageal Pressure Swings
(cm H_2O)
0
3
6
9
Time (min)

Figure 5



1.0
0.8
0.6
0.4
0.2
0
0.44
Pes (1 minute)
0.78
f/VT (1 minute)
0.94
Pes Trend
True Positive Rate
False Positive Rate

Figure 6

WEANING PREDICTION: ESOPHAGEAL PRESSURE MONITORING

COMPLEMENTS READINESS TESTING

By

Amal Jubran MD, Brydon J.B. Grant*, Franco Laghi, Sairam Parthasarathy

and Martin J. Tobin

SUPPLEMENTARY MATERIAL FOR ON-LINE ONLY REPOSITORY

METHODS

Text that is highlighted in yellow represents materials that is not present in the print version

1. Online supplement:

2. Patients

Sixty patients (57 men, 3 women; age, 67 ± 2 (SE) years) who were clinically stable and whose primary physician considered them ready to undergo a weaning trial were recruited (Table 1). The patients had received 20 $\pm$ 4 days of ventilator support**.** The patients were ventilated in the assist-control mode, using either a Servo 900C (Siemens; Schaumburg, IL) or Puritan Bennett 7200a (Puritan-Bennett; Los Angeles, CA) ventilator, through cuffed endotracheal (n=50) or tracheostomy tubes (n= 10). The decision to extubate a patient or reinstitute mechanical ventilation was made solely by the primary physician. The study was approved by the Human Studies Subcommittee and informed consent was obtained from each patient. Some aspects of data on respiratory muscle function and mechanics have been included in reports that address different research questions (E1-E3).

3. Study Protocol

Endotracheal suctioning was performed before the study. Flow was measured between the endotracheal tube and the Y of the ventilator tubing with a pneumotachograph (E1,2,4). The data for the first 31 patients were obtained using a variable orifice pneumotachograph/pressure transducer (Bicore, Irving, CA) (E1). The company (Bicore) that manufactured the pneumotachograph/pressure transducer went out of business during the data-collecting phase of the study. Accordingly, the data of the remainder of the patients (n=29) were obtained using a heated pneumotachograph (Hans Rudolph, Kansas City, MO) (E2,E3). In separate studies against a reference standard, we found that the two pneumotachographs yielded equivalent values of flow (E5). From the flow signal, respiratory frequency was calculated and tidal volume was obtained by electronic integration. Esophageal pressure (Pes) was measured with balloon-tipped catheters connected to pressure transducer; the Bicore system was used in the first 31 patients (E1) and the Validyne system (MP-45; Validyne, Northridge, CA) in the remaining 29 patients (E2,E4).

A trial of spontaneous breathing was initiated through a T-tube circuit, with the patient in a semi-recumbent position and fractional inspired oxygen concentration set at the same level as during mechanical ventilation. Breath-by-breath measurements of breathing pattern and Pes commenced immediately at the point of discontinuing mechanical ventilation and were continuously measured throughout the trial of spontaneous breathing. The a-priori criteria for weaning failure were tachypnea, increased accessory muscle activity, diaphoresis, facial signs of distress, cyanosis, tachycardia, arrhythmias, and hypotension (E1,2). Thirty-five patients met these criteria, were returned to the ventilator and were designated as weaning failure patients. Twenty-five patients met none of these criteria at the end of the trial, were extubated, and were designated as weaning success patients.

4. Data Analysis

4a General approach

To derive the new trend indices, three steps were taken: the first to determine the equilibration time for swings in Pes and f/V_T; second was to characterize the trends in Pes and f/V_T (to determine whether the pattern differed between the two patient groups); and the third step was to derive the new trend indices for Pes and f/V_T in an individual patient.

Patient data were assigned to one of two sets. A derivation data set was used for undertaking the three above-mentioned steps. This data set was derived from 31 patients (14 weaning success and 17 weaning failure patients); these were the patients in whom we previously reported that patient effort increases over the course of a failed weaning trial (E1). A validation data set was used to assess the ability of the new indices to predict weaning outcome (Diagnostic accuracy and ROC analysis, see below). This validation data set was derived from 29 patients (11 weaning success and 18 weaning failure patients).

4b Derivation of new trend indices

4b.i Equilibration time for Pes swings and f/V_T: Swings in Pes were measured throughout the trial on a breath-by-breath basis. A swing in Pes was defined as the change between the point of rapid decrease in Pes and its nadir during a spontaneous breath. In each patient, Pes swings were then averaged on a minute-by-minute basis. The equilibration time for each patient was calculated as the number of seconds it took for Pes swings to reach $\pm$ 10% of the average value of the last minute of the trial. The difference in equilibration time between failure and success patients was determined by Kaplan-Meier analysis. For the f/V_T data, all of the preceding analytic steps were repeated. Data on equilibration time are presented as medians with 25^{th} and 75^{th} percentile range.

***4b.ii Trend* analysis*: Characterization of trend in both patient groups*:** To determine whether the pattern of change in Pes swings differed between the failure and success groups over the course of the trial, we first characterized the temporal pattern in each group using a mathematical model. Simple inspection of the data revealed that the data could not be fitted into a single linear model. Accordingly, a non-linear model, namely the multivariate adaptive regression spline (MARS) analysis, was employed to characterize the changes in Pes swings in the two groups (E6). The MARS technique is a predictive tool that builds flexible regression models with a series of adjoining linear regressions for a given predictor variable. This approach facilitates consideration of any shape for the regression model, and, thus, an investigator does not need to prejudge the form of the model. By employing a cross-validation technique, the MARS technique generates a model of optimal size and avoids overfitting of the data.

The duration of spontaneous breathing varied from patient to patient, and nine minutes was the longest time sustained by all 31 patients of the derivation set. Accordingly, the MARS analysis was applied to the first nine minutes of the trial in the two groups. Specifically, all data points of Pes swings of every patient in the failure group over the entire nine minutes were pooled together, and then entered into a MARS analysis. This analysis yielded an equation that captured the changes in Pes swings for the failure group. The same analysis was carried out for the success group. The two resulting equations for each group are graphed in **Figure 5**. Within 2 minutes of commencing spontaneous breathing, f/V_T values had equilibrated in both the success and failure patients **(See Figures 1 and 3);** accordingly, trend analysis was not appropriate.

4b.iii Derivation of trend index for an individual patient: After demonstrating that the change in Pes swings over the nine minutes differed between the failure and success groups, we next determined whether change in Pes swings could reliably predict weaning outcome in an <u>individual</u> patient. To do this, we needed a single model that could accurately capture the change in Pes swings over the entire nine minutes for all patients. To derive such a model, the following 3 steps were undertaken:

(1) All of the data of each patient (in the two groups) were pooled together and the combined data were entered into another MARS analysis. The pattern of change in Pes swings varied considerably among patients, and a single MARS model could not accurately capture the change in Pes swings over the entire nine minutes for all patients. We then decided to focus on data available for all patients during the beginning and end of the trial. Because nine minutes was the longest segment of data we had available in every patient (see above), we focused on two segments: the entire first minute and the entire ninth minute of the trial. In other words, the commencement of analysis for the first minute was the transition between mechanical ventilation and the start of the spontaneous breathing trial; the termination of the analysis for that first minute was the transition between the first and

second minute. Likewise, the commencement of analysis for the ninth-minute was the transition between the eighth and ninth minute of the trial; the termination of analysis for that ninth-minute was the transition between the ninth and the tenth minute.

(2) Linear regression analysis was then performed on swings in Pes during the first minute of the trial for each individual patient; the same analysis was repeated for the ninth minute. The change in Pes swings for the first minute was expressed as the slope of the regression equation. For the ninth minute, the slope and the intercept of the regression equation were used to estimate Pes at the transition between the ninth and tenth minute. Pes at the transition between the ninth and the tenth minute was estimated because not every patient had a data point at exactly the termination of the ninth minute, and because considerable breath-to-breath variability was evident among the patients.

(3) These two data sets -- the slope of the first minute and the estimated value of Pes swings at the transition between the ninth and tenth minute for all patients – were then entered into another MARS analysis. This analysis yielded an equation that proved successful in reliably predicting weaning outcome in an individual patient. We refer to this final model as the "Pes trend index".

$$\text{Pes trend index} = 0.240 + 0.241 * X1 - 0.111 * X2 - 0.067 * X3 + 0.055 * X4$$

where $X1 = \max(0, 7.411 - \Delta Pes_9)$;

$X2 = \max(0, \Delta Pes_9 - 15.967)$;

$X3 = \max(0, \Delta Pes_1 - 0.094) * \max(0, \Delta Pes_9 - 7.411);$

$X4 = \max(0, \Delta Pes_1 + 1.679) * \max(0, \Delta Pes_9 - 10.729)$

and where ΔPes_9 represents the estimated value of Pes at the ninth-to-tenth minute transition, and ΔPes_1 represents the slope of the swings in Pes throughout the first minute.

4c Diagnostic accuracy and ROC analysis

Standard formulas were used to calculate sensitivity, specificity, positive predictive value and negative predictive value of three variables in predicting weaning outcome: the average swing in Pes (calculated from all breaths during the first minute of the trial); f/V_T (calculated from all breaths during the first minute of the trial); and the Pes trend index (E7). The likelihood ratios of the above three variables were also calculated (E8). Likelihood ratios are a powerful means of determining the predictive value of a diagnostic test, because they relate the probability of a test result to the presence or absence of a disorder and are thus particularly applicable to clinical decision-making. The 95% confidence intervals (95% CI) of sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios were computed using an iterative method (E8). Receiver operator characteristic (ROC) curves were generated to determine the relative accuracy of the above three variables in predicting weaning outcome (E9). The probability of identifying weaning outcome correctly was calculated using a c-index, which is equivalent to the area under the ROC curve (E10). The c-index values for the Pes trend index and the first-minute measurement of Pes swings were compared using confidence intervals analysis; Pes trend index and f/V_T were likewise compared (E11).

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