1999 Donald F Egan Scientific Lecture

Weaning from Mechanical Ventilation: What Have We Learned?

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It is a pleasure and honor for me to give the 26th Annual Donald F Egan Scientific Lecture at the American Association for Respiratory Care. Much of my research career has focused on weaning from mechanical ventilation, and a major stimulus for my interest in this subject was an outstanding review article published in RESPIRATORY CARE by its current editor, Dave Pierson, in the early 1980s.[1] In that article, Dave made the subject of weaning exciting. More importantly, he pointed out many areas about which we knew nothing. To someone starting an academic career, the subject of weaning appeared particularly ripe for research.

While preparing for this morning's lecture, I took my copy of *Egan's Fundamentals of Respiratory Therapy* from the shelf. This was the first textbook directed primarily at respiratory therapists. It was first published in 1969, and the copy I own is the third edition, published in 1977.[2] In the 1977 edition, Dr Egan wrote that "The separation of a patient from his ventilator is very nearly pure art." Weaning is still an art in 1999. But over the next half hour, I hope I can show you that the approach to weaning has a more scientific basis than was the case 20 years ago.

Pathophysiology of Weaning Failure

A patient failing a weaning trial exhibits the physical signs of respiratory distress. We see heightened activity of the sternomastoid muscles, recession of the suprasternal fossa, recession of the intercostal spaces, paradoxical motion of the abdomen, tachypnea, and sometimes cyanosis.[3] These physical signs tell us the patient is not able to sustain spontaneous ventilation. But to understand *why* pa-

tients fail weaning trials, we need to delve into the underlying pathophysiological mechanisms. Four anatomical sites or functions may be involved: respiratory centers, respiratory muscles, lung mechanics, and gas exchange function of the lung.[4] I'll discuss data pertaining to each site and indicate how each is important in understanding why patients fail weaning trials.

We begin with the respiratory centers. A depressed respiratory center drive at the start of the weaning trial will cause hypoventilation, making weaning failure inevitable. Another possibility is for the drive to be normal at the start of the trial, but then to fall during the course of the trial. It's been suggested that it would be clever for the body to decrease respiratory center output as a way of avoiding contractile fatigue of the respiratory muscles. Such a strategy has even been called "central wisdom."[5] Figure 1 shows the total pressure generated by inspiratory muscles, expressed as pressure-time product, measured by Amal Jubran in 17 patients who failed a weaning trial.[6] All but one patient showed an increase in pressure generation between the beginning and end of the T-tube trial. As such, downregulation of respiratory motor output is not common in patients who fail a trial of weaning.

Next, we move to the respiratory muscles. We used to think that maximum inspiratory pressure, which reflects inspiratory muscle strength, was helpful in predicting which patients could come off the ventilator. In 100 patients undergoing a weaning trial, we found no difference in maximum inspiratory pressure between weaning success and weaning failure patients.[7] As such, respiratory muscle weakness doesn't appear to be a common cause for failure to wean. Might the respiratory muscles deteriorate between the beginning and end of a weaning trial? Yes, if they develop respiratory muscle fatigue.[8]

Is it important to know whether these patients develop muscle fatigue? It's *extremely* important. Darlene Reid[9] has demonstrated electron-microscopic evidence of severe muscle destruction in hamsters who developed diaphragmatic fatigue (Fig. 2). The same process may happen in weaning failure patients. Patients who fail a weaning trial already have problems before they commence the trial. Then, as they fail the trial, they may be developing a new

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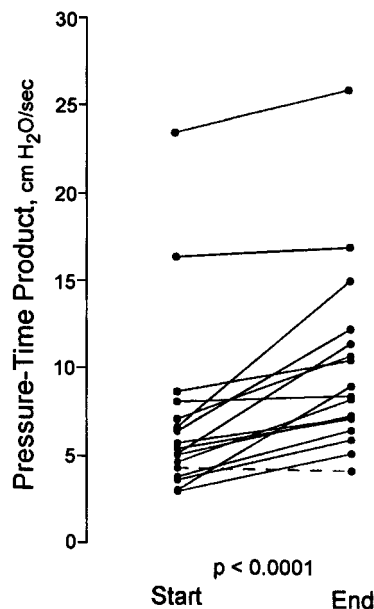
Fig. 1. Values of inspiratory pressure-time product at the start and end of an unsuccessful trial of weaning in 17 patients with chronic obstructive pulmonary disease. All but one patient showed an increase in pressure generation between the onset and end of the trial. (Based on data from Reference 6.)

separate problem—that is, structural damage resulting from contractile muscle fatigue.

To determine whether muscle fatigue is likely in such patients, Amal Jubran measured the tension-time index of the inspiratory muscles (Figure 3).[6] Tension-time index is the product of two fractions: the mean pressure per breath over maximum inspiratory pressure, and the time of inspiration over total respiratory cycle time. She made measurements at the start of a T-piece trial and at its end, about 45 minutes later. None of the weaning success patients developed a tension-time index above 0.15—the value that has been linked with muscle fatigue.[8] Five of the failure patients, however, had a tension-time index of 0.15 or higher by the end of the trial. This observation suggests that these five patients may have developed inspiratory muscle fatigue. Tension-time index is an indirect index, and it doesn't provide concrete evidence that fatigue actually occurred.

To convincingly detect fatigue, you need to stimulate the phrenic nerves and measure the contractile response of the diaphragm.[8] Figure 4 shows measurements obtained by Franco Laghi in a patient who failed a weaning trial. At the start of the trial, the patient's twitch transdiaphragmatic pressure was around 30 cm H_2O, which is normal. The patient then underwent a T-piece trial lasting a half hour. Franco repeated the measurements 15 min after completing the trial, and again at 30 and 60 min. The twitch pressures fell considerably compared with baseline. These data provide conclusive evidence of diaphragmatic fatigue.

This patient would have developed the type of structural injury I showed you in the hamster model. Of course, the data are from only a single patient. Franco is now studying a larger group of patients to determine the frequency of fatigue in patients undergoing weaning trials.

The data in Figures 5 and 6 show the stress on the respiratory muscles in weaning failure patients. This stress is related to the work the muscles perform. The information in Figure 5 represents a huge amount of compressed data.[6] The tracings are ensemble averages of several breaths from each individual patient. The failure patients had much larger swings in esophageal pressure by the end of the trial than at the beginning. Also, the swings in pressure were much greater in the failure patients than in the success patients.

Why is work of breathing (WOB) increased in patients who fail a weaning trial? To answer this question, Amal Jubran measured inspiratory resistance, dynamic elastance (which is the inverse of compliance), and auto positive end-expiratory pressure (auto-PEEP) (see Figure 6).[6] She found that the values for each variable were much higher in failure patients than in success patients over the course of a trial. Each variable also deteriorated over time in the failure patients. That is, patients who fail a weaning trial display a progressive worsening of their pulmonary mechanics, resulting in large increases in their WOB.

Might the pulmonary mechanics be more severely deranged in the failure patients even before they come off the ventilator? Could you tell, on the basis of mechanics, that weaning failure is going to be inevitable? To address this question, Amal Jubran looked at passive lung mechanics before taking patients off the ventilator.[10] Measurements of airway pressure, transpulmonary pressure, and esophageal pressure, combined with the end-inspiratory occlusion method, allow you to respectively characterize the overall respiratory system, the lung itself, and the chest wall. You can also divide respiratory resistance into the component resulting from ohmic resistance, reflecting airway resistance, and the component arising from stress inhomogeneities in the system, consequent to pendelluft and viscoelastic forces.

Before performing the T-piece trials, she passively ventilated the patients. Respiratory system resistance was equivalent in the weaning success and weaning failure patients (Figure 7).[10] Moreover, partitioning of resistance into the components reflecting airway resistance and stress inhomogeneity revealed no difference between the groups. That the respiratory mechanics were similar in the two groups before the start of a trial implies that something in the *act* of spontaneous breathing causes the weaning failure patients to deteriorate over the course of the trial. We can speculate about mechanisms by which spontaneous breathing could worsen respiratory mechanics, but to find the real reason we need further research.
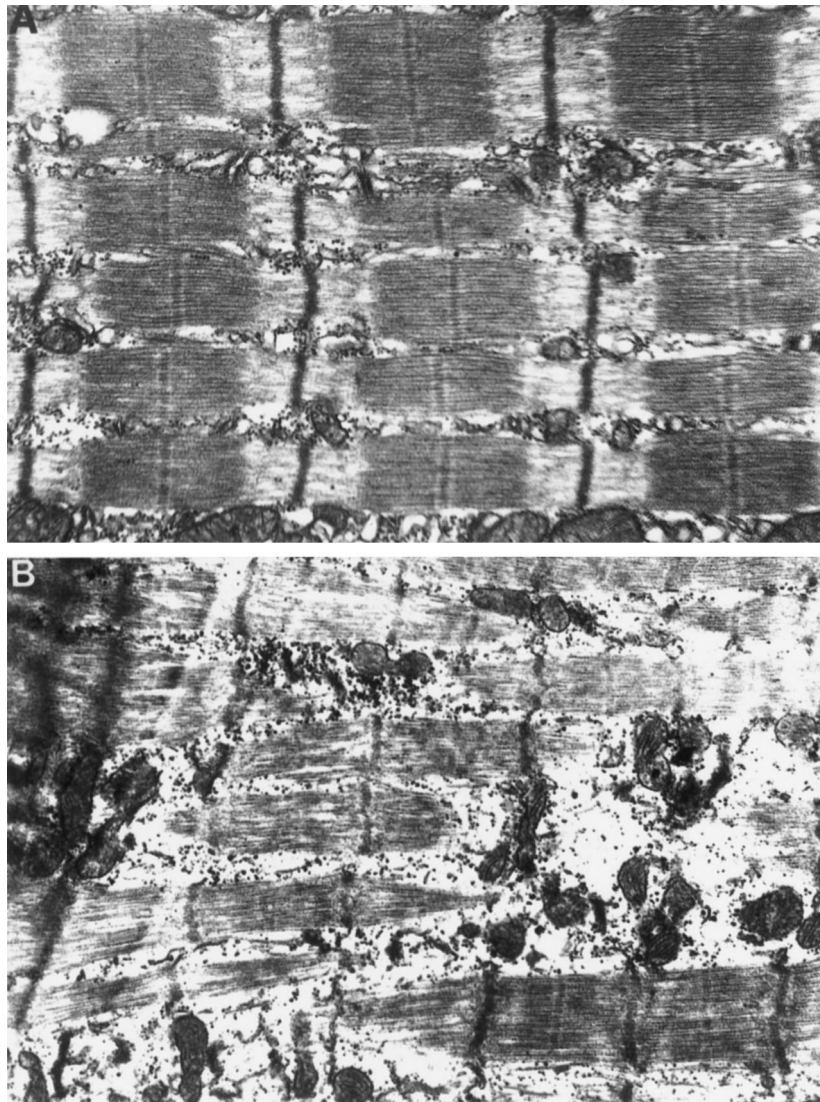
Fig. 2. Electron micrograph of the diaphragm in a control hamster (upper) and in a hamster that had breathed through a resistive load for 6 days (lower). Loading was achieved by tightening a polyvinyl band around the trachea until swings in esophageal pressure were ~20% of maximal inspiratory pressure; pulmonary resistance was increased 6.5 fold. Compared with the normal structure, the loaded animals developed sarcomere disruption with loss of distinct A bands and I bands and development of Z line streaming. (From Reference 9, with permission.)

The fourth, and final, aspect of the pathophysiology is gas exchange. Some patients fail a weaning trial with no change in their arterial blood gases, whereas others develop increases in carbon dioxide tension (P_{CO_2}) or decreases in oxygen tension. The term hypoventilation is used synonymously with hypercapnia. But when you see an increase in P_{CO_2}, it doesn't mean that minute ventilation has necessarily fallen. In a group of patients failing a weaning trial, we found no relationship between P_{CO_2} and minute ventilation.[11] Instead, we found that more than 80% of the variance in P_{CO_2} could be explained by the patients' tidal volume (V_T) and respiratory frequency (Figure 8). The P_{CO_2} rose because the patients developed rapid shallow breathing—with inevitable increase in dead-space ventilation. Alveolar ventilation went down but overall minute ventilation didn't change.

The hypoxemia that occurs in some patients failing a weaning trial is usually associated with an increase in venous admixture. A further factor contributing to the hypoxemia is a decrease in mixed venous oxygen saturation (Figure 9).[12] The fall in mixed venous oxygen saturation is partly the result of the considerable cardiovascular demand experienced by weaning failure patients, as first shown by François Lemaire.[13] In a classic study, François
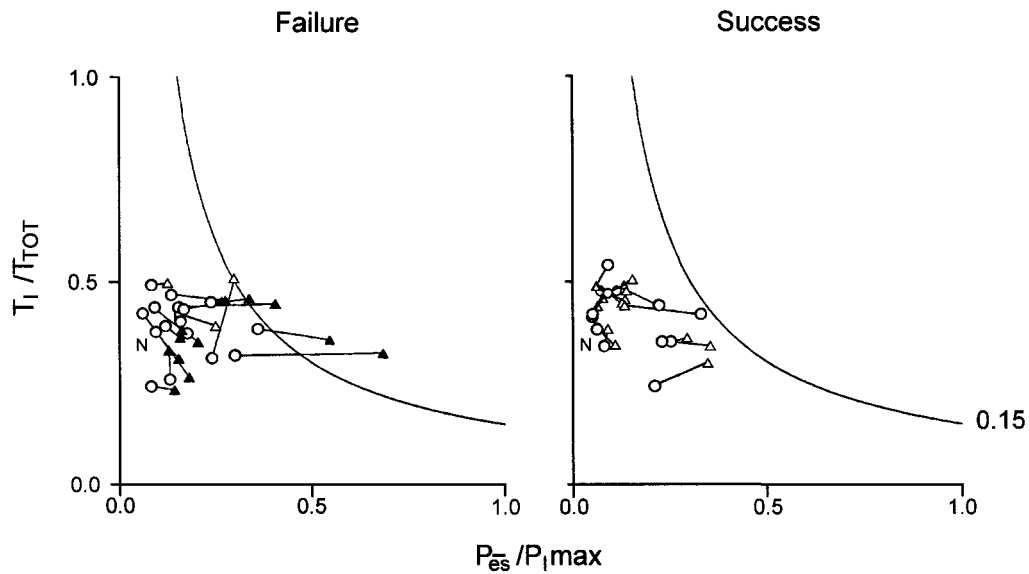
Failure   Success

Fig. 3. The relationship between the ratio of mean esophageal pressure to maximum inspiratory pressure ($P_{\bar{es}}/P_{I}max$) and duty cycle (T_I/T_{TOT}) in 17 ventilator-supported patients with chronic obstructive pulmonary disease who failed a trial of spontaneous breathing and 14 patients who tolerated the trial. Circles and triangles represent values at the start and end of the trial, respectively; closed symbols indicate patients who developed an increase in P_{aCO_2} during the trial. Five of the 17 patients in the failure group developed a tension-time index of > 0.15 (indicated by the isopleth), suggesting respiratory muscle fatigue. N represents the value in a normal subject. (From Reference 6, with permission.)
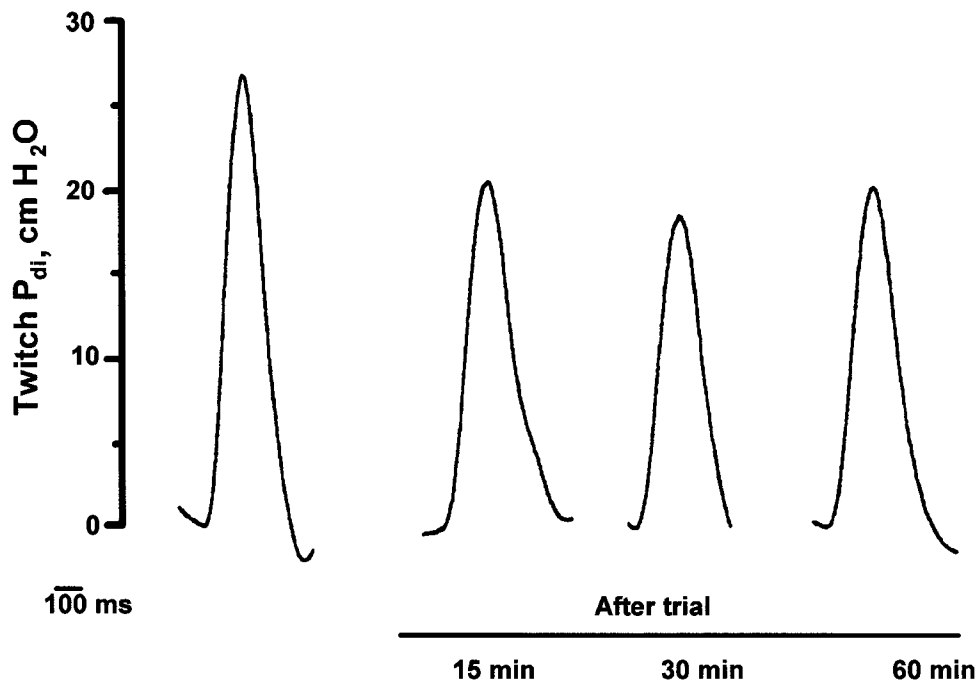

Fig. 4. Recordings of transdiaphragmatic twitch pressure (P_{di}) in a patient with a C_4 spinal cord injury 10 min before a trial of spontaneous breathing and at several intervals after the end of the failed trial that lasted 30 min. The nadir in twitch pressure was reached 30 min after the end of the trial, and at 60 min twitch pressure was still less than that recorded 10 min before the trial. This finding indicates the development of contractile muscle fatigue.
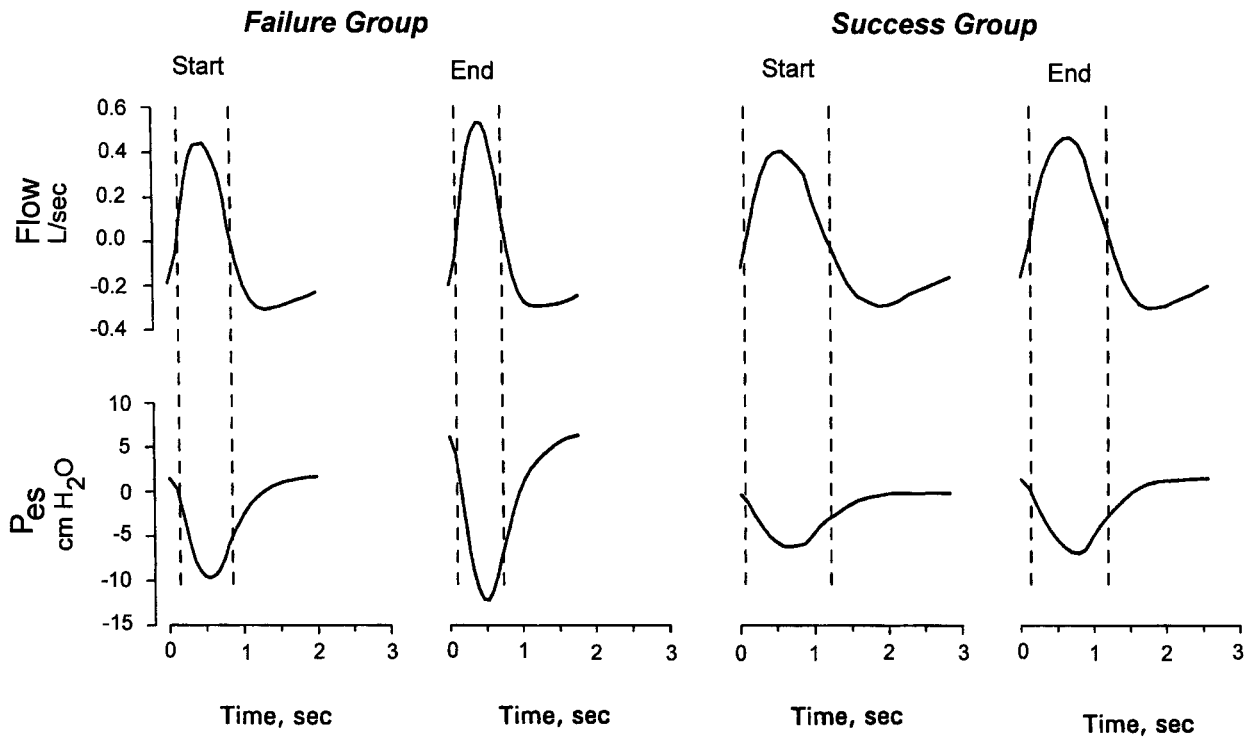
Fig. 5. Ensemble average plots of flow and esophageal pressure (P_{es}) at the start and end of a trial of spontaneous breathing in 17 ventilator-dependent patients with chronic obstructive pulmonary disease who failed the trial and 14 patients who tolerated the trial and were extubated. At the start of the trial, the inspiratory excursion in P_{es} was greater in the failure group, and it showed a further increase by the end of the trial. To generate these plots, flow and P_{es} tracings were divided into 25 equal time intervals over a single respiratory cycle for each of the 5 breaths for each patient in the two groups. For a given patient, the 5 breaths from the start of the trial were then superimposed and aligned with respect to time, and the average at each time point was calculated. The group mean tracings were then generated by ensemble averaging of the individual mean from each patient. The same procedure was performed for breaths at the end of the trial. (From Reference 6, with permission.)

showed that weaning failure patients develop an increase in their pulmonary artery wedge pressure and left-ventricular end-diastolic volume. The increased stress on the cardiovascular system probably resulted from the increased WOB. When intrathoracic pressure becomes more negative, the afterload of the left ventricle increases, which, in turn, makes it more difficult to maintain cardiac output.[12,13]

Prediction of Weaning Outcome

I will now discuss how good we are at predicting weaning outcome. The predictive indices listed by Dr Egan in 1977 are similar to those you see listed today.[1,3] One difference is his inclusion of a dead space-to-V_T ratio of less than 0.60 as a helpful predictor of weaning success; few people today would recommend this measurement. Over the last 20 years, we have found that the classic variables, such as maximum inspiratory pressure, minute ventilation, and vital capacity have very high rates of false positives and false negatives.[3,7] Many indices don't help in telling us whether or not an individual patient is likely to come off the ventilator. They are useful, however, in our assessment of the patient who has already failed a trial—to understand why that patient failed.

In the past, it was felt that the gestalt of an experienced clinician at the bedside was better at predicting weaning outcome than physiologic indices. The accuracy of this gestalt had never been studied until recently. Randy Stroetz and Rolf Hubmayr[14] asked attending physicians in the intensive care units of the Mayo Clinic to predict whether their patients were likely to succeed in a weaning trial. Of the 31 patients in the study, the physicians predicted that 22 would fail the trial. Yet, half of the 22 patients were successfully weaned. This doesn't mean that clinical assessment is useless. It remains necessary, but it's not sufficient. We need something in addition to clinical assessment.

Some people say you can dispense with weaning predictors completely, and go directly to some weaning method, such as a T-tube trial or pressure support. But to use any weaning approach you have to first *think* of the possibility that the patient might tolerate it. In the study
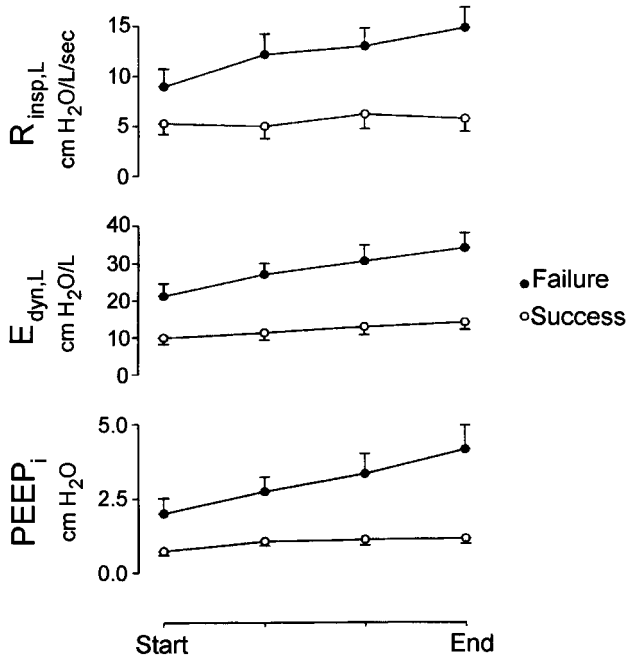
Fig. 6. Inspiratory resistance of the lung ($R_{insp,L}$), dynamic lung elastance ($E_{dyn,L}$), and intrinsic positive end-expiratory pressure ($PEEP_i$) in 17 weaning failure patients and 14 weaning success patients. Data were obtained during the second and last minute of the trial, and at one third and two thirds of the trial duration. Between the onset and end of the trial, the failure group developed increases in $R_{insp,L}$ ($p < 0.009$), $E_{dyn,L}$ ($p < 0.0001$), and $PEEP_i$ ($p < 0.0001$), and the success group developed increases in $E_{dyn,L}$ ($p < 0.006$) and $PEEP_i$ ($p < 0.02$). Over the course of the trial, the failure group had higher values of $R_{insp,L}$ ($p < 0.003$), $E_{dyn,L}$ ($p < 0.006$), and $PEEP_i$ ($p < 0.009$) than the success group. (From Reference 6, with permission.)

from the Mayo Clinic, we see that half the patients that physicians thought not ready for weaning actually succeeded.[14] As such, the systematic use of predictors alerts us to the possibility that some of the patients we think not ready for weaning are in fact much better than they appear. From my discussion of the pathophysiology of weaning failure, it's clear that patients failing a weaning trial experience huge stresses on their respiratory muscles and cardiovascular system. These stresses might damage their heart or respiratory muscles and also cause considerable anxiety and distress. The measurement of predictive indices—provided they are reasonably reliable—avoids subjecting patients prematurely to such stresses before they are able to cope with them.

Several years ago, we noted that patients who went on to fail a weaning trial developed an increase in respiratory frequency and a fall in V_T as soon as we took them off the ventilator (Figure 10).[11] We reasoned that measuring these changes might be useful in forecasting weaning outcome.

We subsequently undertook a study, where we measured frequency and V_T with simple instrumentation—a hand-held spirometer—over one minute.[7] The measurements were made while patients were disconnected from the ventilator and breathing room air. We combined the measurements into an index of rapid shallow breathing, the frequency-to-V_T ratio. The higher the ratio, the more severe the rapid shallow breathing, and the greater the likelihood that the patient would fail a weaning trial. We tested the accuracy of this index in 100 patients, and found a ratio of 100 breaths/min per liter gave the best separation of the groups—a value that's easy to remember.

One of the best ways of evaluating the accuracy of any diagnostic test is to use receiver operating characteristic curves.[3] These curves are created by taking multiple values of a test measurement, and plotting the true positive rate against the false positive rate (Figure 11). You then measure the area under the curve, and this tells you the overall accuracy of the test. A perfect test has an area under the curve of 1.0. A test that's no better than chance has an area under the curve of 0.50. For our patients, the area under the curve for minute ventilation was 0.40, meaning that minute ventilation was worse than flipping a coin at the patient's bedside in predicting weaning outcome. The other classic index, maximum inspiratory pressure, had an area of 0.61; it's slightly better than chance in predicting outcome. The CROP index, which integrates a number of physiologic variables, was substantially better, with an area of 0.78. The frequency-to-V_T ratio had an area of 0.89. This simple index turned out to be the most accurate predictor.

We answer research questions by making measurements in groups of patients. But when we leave research and go back to clinical practice, our focus shifts to a single patient. That relationship between one patient and one clinician is the soul of clinical medicine. What you *really* want to answer is what's the likelihood that the patient in front of you can come off the ventilator? Let's take a situation where you have no clue whether a patient is likely to come off the ventilator. In the language of statisticians, this is a pre-test probability of 50 per cent.[15] If you measure the frequency-to-V_T ratio and the value is above 100, you draw a line on Figure 12 between the pre-test probability, 50 per cent, and the likelihood ratio, which we know is 0.04 for a frequency-to-V_T ratio above 100.[16] Then, you continue the line to get the post-test probability, and you find it's less than 5 per cent. Here you have a patient about whom you're in *total* doubt as to clinical outcome; if you find that the frequency-to-V_T ratio is above 100, the information changes your post-test probability to a less than 5 per cent likelihood that the patient will come off the ventilator. If the frequency-to-V_T ratio is 80, this has a likelihood ratio of 7.5,[16] which changes the post-test probability to nearly 95 per cent. This example illustrates the
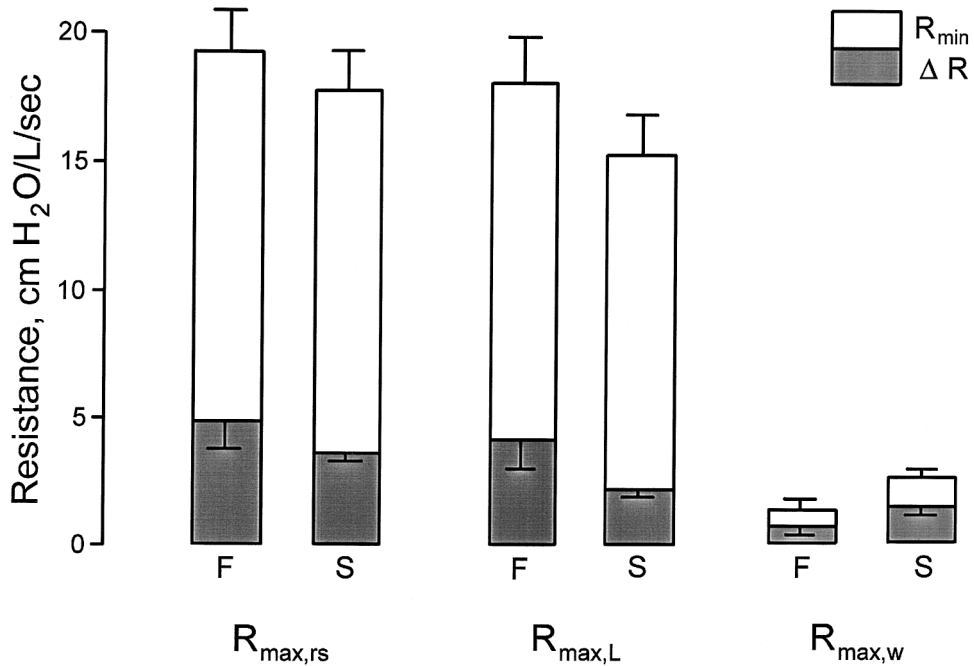
Fig. 7. Maximal resistance (overall column height) of the respiratory system ($R_{max,rs}$), lung ($R_{max,L}$), and chest wall ($R_{max,w}$) in weaning failure (F) and weaning success (S) patients during passive ventilation; the clear portions of the columns represent minimum resistance (R_{min}) while the shaded portions represent additional resistance (ΔR). No differences in $R_{max,rs}$, $R_{min,rs}$, or ΔR_{rs} were observed between the groups, nor between the lung and chest wall components. Upward directed bars represent $\pm$ SE (standard error) of R_{min}, while downward directed bars represent $\pm$ SE of ΔR. (From Reference 10, with permission.)
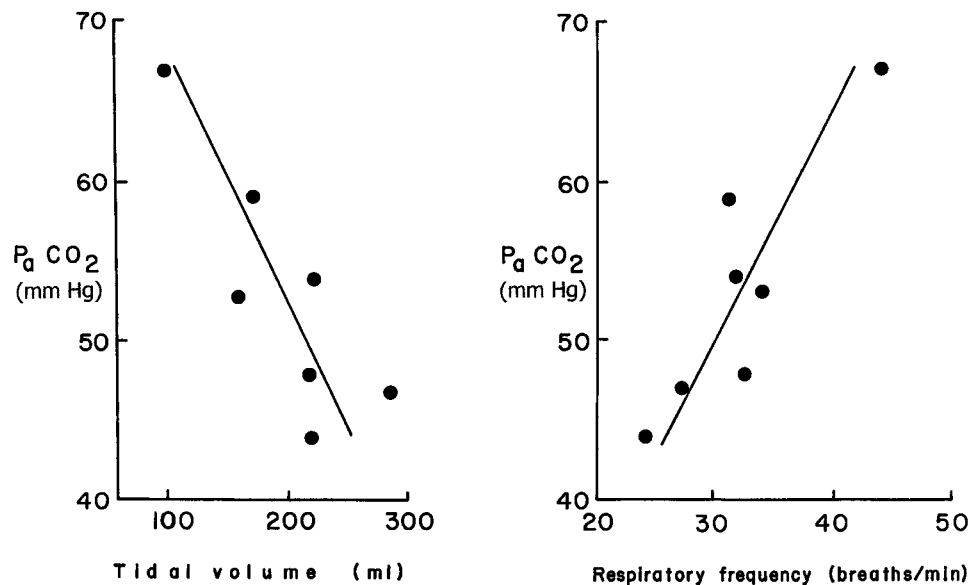
Fig. 8. Relationship between tidal volume (V_T) and respiratory frequency with carbon dioxide tension (P_{aCO_2}) in seven patients who failed a spontaneous breathing trial. P_{aCO_2} was significantly correlated with V_T ($r = 0.84$, $p < 0.025$) and frequency ($r = 0.87$, $p < 0.025$); 81% of the variance in P_{aCO_2} could be explained by the changes in these two variables (From Reference 11, with permission.)
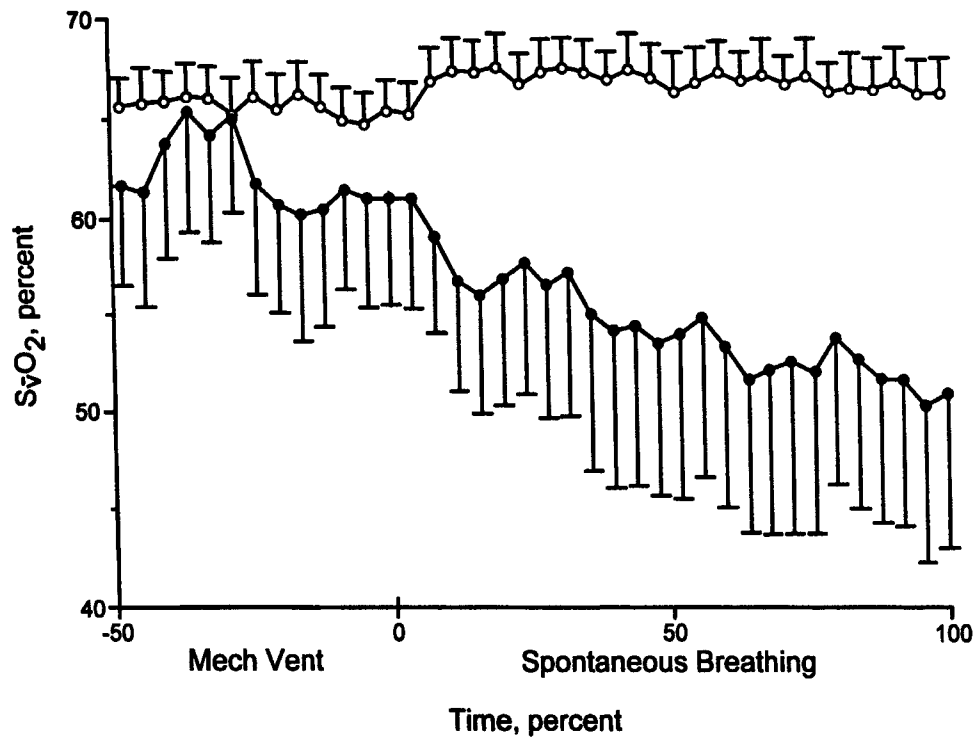
Fig. 9. Ensemble averages of interpolated values of mixed venous oxygen saturation ($S_{\bar{v}O_2}$) during mechanical ventilation and a trial of spontaneous breathing in patients who succeeded in the trial (open symbols) and patients who failed the trial (closed symbols). During mechanical ventilation, $S_{\bar{v}O_2}$ was similar in the two groups (p = 0.28). Between the onset and end of the trial, $S_{\bar{v}O_2}$ decreased in the failure group (p < 0.01), whereas it remained unchanged in the success group (p = 0.48). Over the course of the trial, $S_{\bar{v}O_2}$ was lower in the failure group than in the success group (p < 0.02). Bars represent standard errors. (From Reference 12, with permission.)

value of combining your clinical judgment, which is your pre-test probability, with a test, in this case the frequency-to-V_T ratio, and seeing how it alters your post-test probability.

Weaning Techniques

For the remaining portion of my presentation, I'll focus on the different methods used for weaning. We have four approaches. With pressure support and intermittent mandatory ventilation (IMV), you decrease the support from the ventilator and force the patient to undertake more of the work needed for a given minute ventilation. The third and oldest approach is to perform T-piece trials several times a day. Dr Egan described how this approach was being used in 1977: "Some experts advocate removing the patient from his ventilator for a fixed short period of time and gradually shorten the intervals between. As an example, this might mean letting the patient breathe unassisted for 2 minutes of an hour, then 2 minutes every half-hour, quarter-hour, and so on, until mechanical ventilation is discontinued." That approach involves a huge amount of work for the intensive care unit staff, and it's not hard to

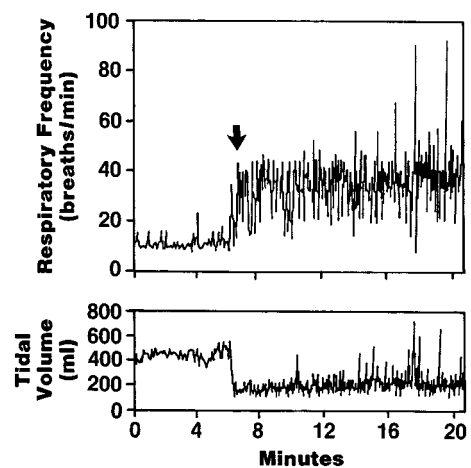Fig. 10. Breath-by-breath plot of respiratory frequency and tidal volume (V_T) in a patient who failed a weaning trial. The arrow indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately, suggesting the prompt establishment of a new steady state. (From Reference 11, with permission.)
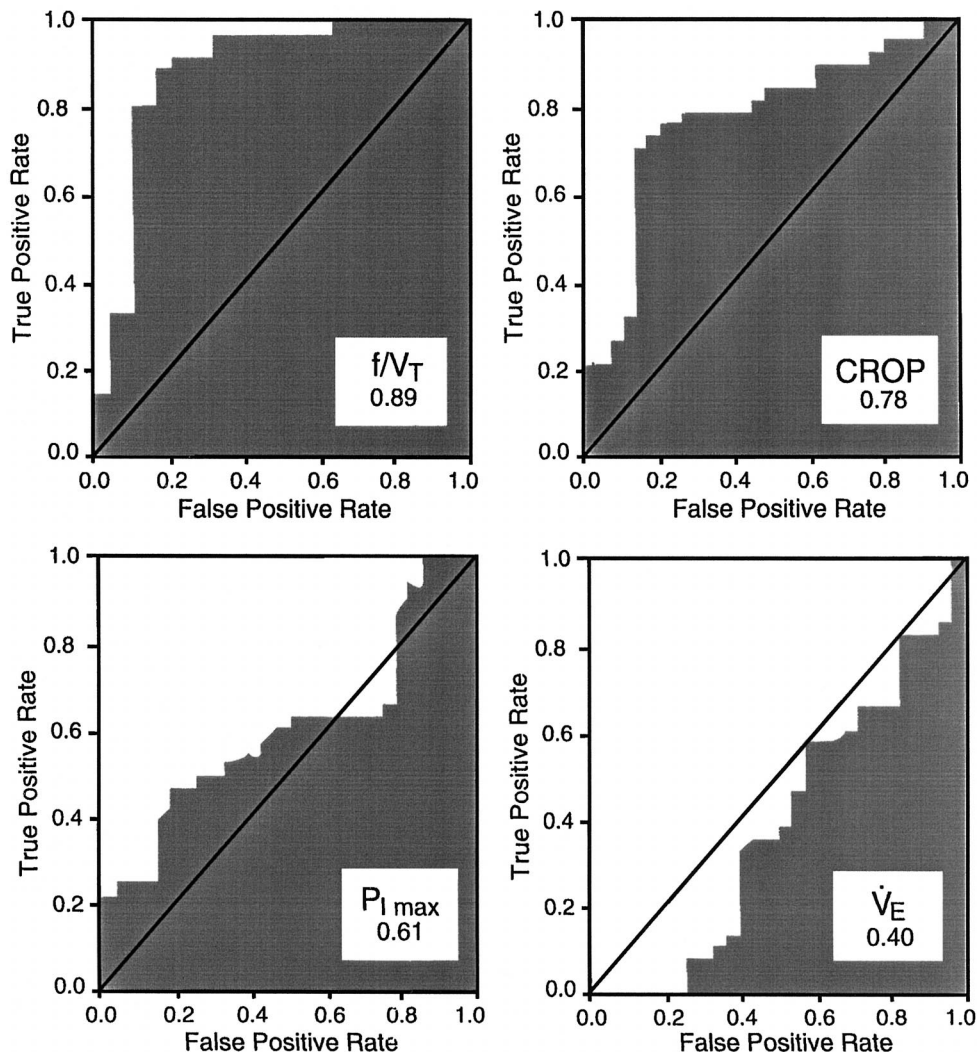
Fig. 11. Receiving-operating-characteristic (ROC) curves for frequency-to-tidal volume ratio (f/V$_T$), CROP index (acronym for *compliance*, *rate*, *oxygenation*, and *pressure*, which integrates factors associated with risk of respiratory failure), maximum inspiratory pressure (P$_{Imax}$), and minute ventilation ($\dot{V}_E$) in weaning success and weaning failure patients. The ROC curve is generated by plotting the proportion of true positive results against the proportion of false positive results for each value of a test. The curve for an arbitrary test that is expected *a priori* to have no discriminatory value appears as a diagonal line, whereas a useful test has an ROC curve that rises rapidly and reaches a plateau. The area under the curve (shaded) is expressed (in box) as a proportion of the total area. (From Reference 7, with permission.)

see why multiple T-piece trials became very unpopular. The fourth approach, and the one I personally prefer, is to perform a T-piece trial once a day. If patients are breathing comfortably after a half hour, they're extubated. Patients who fail go back on the ventilator for at least 24 hours before we make another weaning attempt.

Studies from our lab show that WOB is enormous in patients who fail a weaning trial.[6] A major goal of mechanical ventilation is to decrease this work.[17] But if the respiratory muscles get too much rest might they develop atrophy? Antonio Anzueto[18] has shown that 11 days of

controlled ventilation in baboons causes a decrease in contractility of the diaphragm, suggesting the development of muscle atrophy. With mechanical ventilation, we want to achieve rest without causing muscle atrophy. The ideal amount of rest needed by a patient has never been studied. Franco Laghi[19] addressed this issue in healthy human volunteers (Figure 13). He induced muscle fatigue by having the subjects breathe through a resistive load. He stimulated the phrenic nerves and measured transdiaphragmatic twitch pressure (P$_{di}$). The subjects started off with a baseline twitch value in the high 30s, which is normal. When the
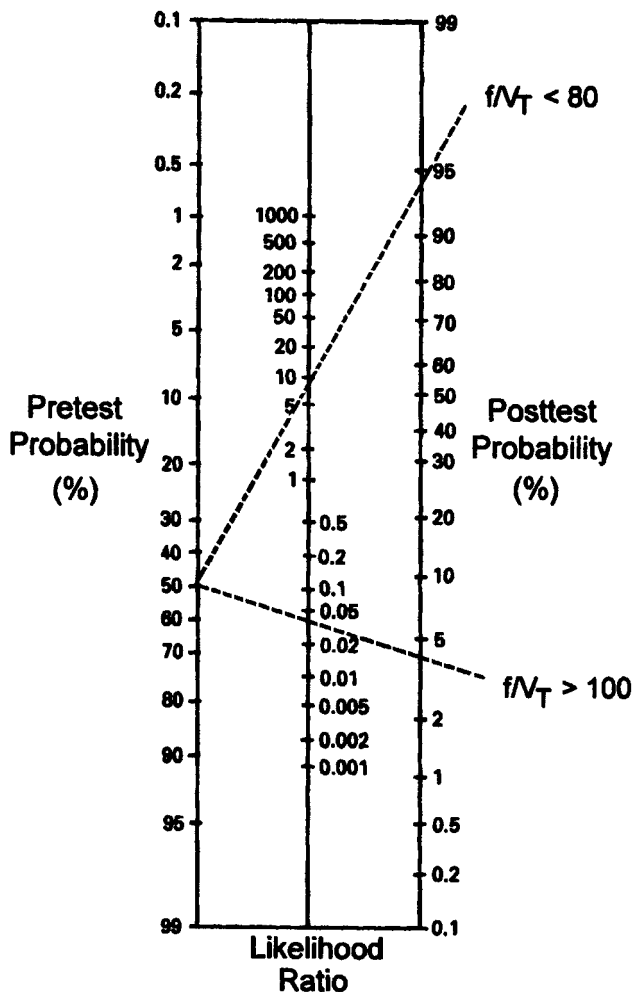
Fig. 12. The effect of frequency-to-V_T ratio measurements on clinical equipoise, ie, a pre-test probability of 50 per cent. A frequency-to-V_T ratio of > 100 breaths/min per liter has a likelihood ratio of 0.04. The post-test probability is obtained by drawing a line between the pre-test probability, 50 per cent, and the likelihood ratio, 0.04, and then extending the line; this results in a post-test probability value of less than 5%. A frequency-to-V_T ratio of less than 80, which is known to have a likelihood ratio of 7.5, results in a post-test probability approaching 95 per cent. (Modified from Reference 15.)

subjects breathed through a resister, the twitch pressure fell to about 25 cm H_2O. Several investigators had previously shown that twitch pressures fall after resistive loading. What's new here is that Franco measured the change in the contractile properties of the diaphragm over the subsequent 24 hours.[19] He observed some recovery over the first 8 hours. Between 8 and 24 hours, there was no further recovery. Compared with baseline, the twitch pressures at 24 hours were significantly depressed. This observation tells us that a considerable period of rest is needed for recovery from diaphragmatic fatigue. That's the reason I prefer performing a T-piece trial just once a day. When patients fail, I fear that they may have respiratory muscle

fatigue and it'll require at least 24 hours to recover from that.

When introduced, IMV looked like the ideal way to wean patients from the ventilator. It took into account the need for rest to avoid muscle fatigue and also the idea that too much rest might cause atrophy.[20] By allowing the patient to take some spontaneous breaths, IMV should prevent muscle atrophy. By resting the patient during the mandatory breaths, fatigue should be avoided. The balance between these two factors makes it theoretically possible to customize the approach for each individual patient.

Unfortunately, IMV doesn't work according to plan. Figure 14 shows measurements in a single patient.[21] According to the theory, we'd expect a decrease in diaphragmatic and sternomastoid activity during the assisted breaths. But we can't tell these tracings from the spontaneous breaths. That the effort performed by the patient is the same for the mandatory and spontaneous breaths was first pointed out by John Marini.[22] A patient doesn't know whether the ventilator is going to provide assistance on the next breath. As such, the patient fires his respiratory centers at the onset of the breath. When the ventilator starts to assist him, he's unable to switch off his respiratory centers. As a result, the effort he performs is the same for the ventilator breaths as for the spontaneous breaths.

Pressure support is the other commonly used method of weaning.[23] Pressure support was popularized as a means of overcoming the resistance of the endotracheal tube. The story goes that if patients are able to breathe comfortably at that level of pressure support, they should be able to breathe without difficulty following extubation. The problem is to figure out what's the level of pressure support that overcomes the resistance of the endotracheal tube. Various levels, such as 6 or 8 cm H_2O, have been suggested.

The people who proposed the addition of pressure support to overcome the resistance of the endotracheal tube appear to have forgotten that when a tube is in the airway for some time it causes inflammation and edema. When the tube is removed, the resistance of the upper airway will be higher than normal. This point was nicely shown by Christian Strauss.[24] He found that WOB in patients following extubation was virtually identical to what it had been while they breathed on a T-piece. *Any* amount of pressure support causes you to underestimate the work a patient will have to perform following extubation—which is what you're trying to forecast.

Another problem arises with pressure support in patients with chronic obstructive pulmonary disease—the most challenging group to wean from the ventilator. This problem relates to the off-cycling of the time of inflation. Mechanical inflation is switched off when inspiratory flow falls to some value, such as 25 per cent of the peak value.[23] Patients with chronic obstructive pulmonary disease have
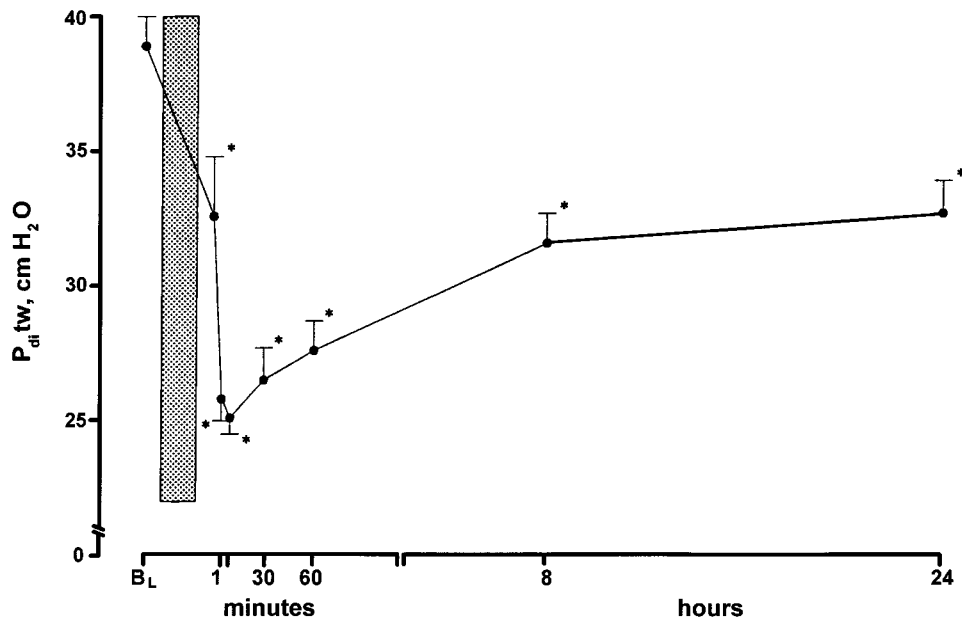
Fig. 13. Induction of diaphragmatic fatigue (stippled bar) produced a significant fall in transdiaphragmatic twitch pressure (P_{di}) elicited by twitch stimulation of both phrenic nerves. Significant recovery of twitch pressure was noted in the first 8 hours after completion of the fatigue protocol; no further change was observed between 8 and 24 hours, and the 24-hour value was significantly lower than baseline. The delay in reaching the nadir of twitch P_{di} probably results from twitch potentiation, induced by repeated contractions, which was present at the end of the protocol. Values are mean $\pm$ standard error. * Significant difference compared with baseline value, $p < 0.01$. (From Reference 19, with permission.)
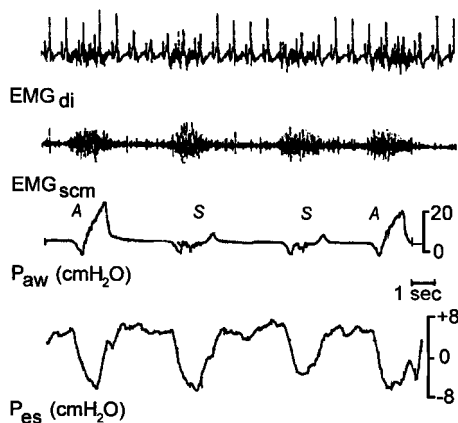

Fig. 14. Electromyograms of the diaphragm (EMG_{di}) and the sternocleidomastoid muscles (EMG_{scm}) in a patient receiving synchronized intermittent mandatory ventilation. Intensity and duration of electrical activity is similar during assisted (A) and spontaneous (S) breaths. P_{aw} = airway pressure. P_{es} = esophageal pressure. (From Reference 21, with permission.)

increases in resistance and compliance. The product of these two variables is the time constant of the respiratory system.[25] An increase in the time constant means it'll take longer for air to move in and out of the bronchi. Specifically, it'll take longer for flow to drop from its peak down to 25 per cent of that value. As a result, the expiratory neurons in the brainstem become impatient. They're saying, "The ventilator is still pumping gas into the lungs, but we think it's time to breathe out." The expiratory neurons get switched on, and the patient fights the ventilator. This is not something you want to do in a patient with preexisting weaning difficulties.

Amal Jubran investigated this issue in critically ill patients. The interrupted tracing in Figure 15 represents the chest wall recoil.[26] Halfway during the period of mechanical inflation, we see that esophageal pressure was higher than the chest wall recoil. This means that the patient had switched on his expiratory muscles while the ventilator was still pumping gas into the lungs. The measurements in her study were based on a number of assumptions, particularly the positioning of the chest wall recoil line. One of our fellows, Sai Parthasarathy, readdressed the question by inserting needle electrodes into the transversus abdominis—the major muscle of expiration.[27] Again, about halfway during the period of mechanical inflation he found that the patients recruited their abdominal muscles. This problem with pressure support arises because of the algorithm used for cycling off the inflation phase. As a result, most patients with chronic obstructive pulmonary disease receiving a high level of pressure support will be forced to fight the ventilator.
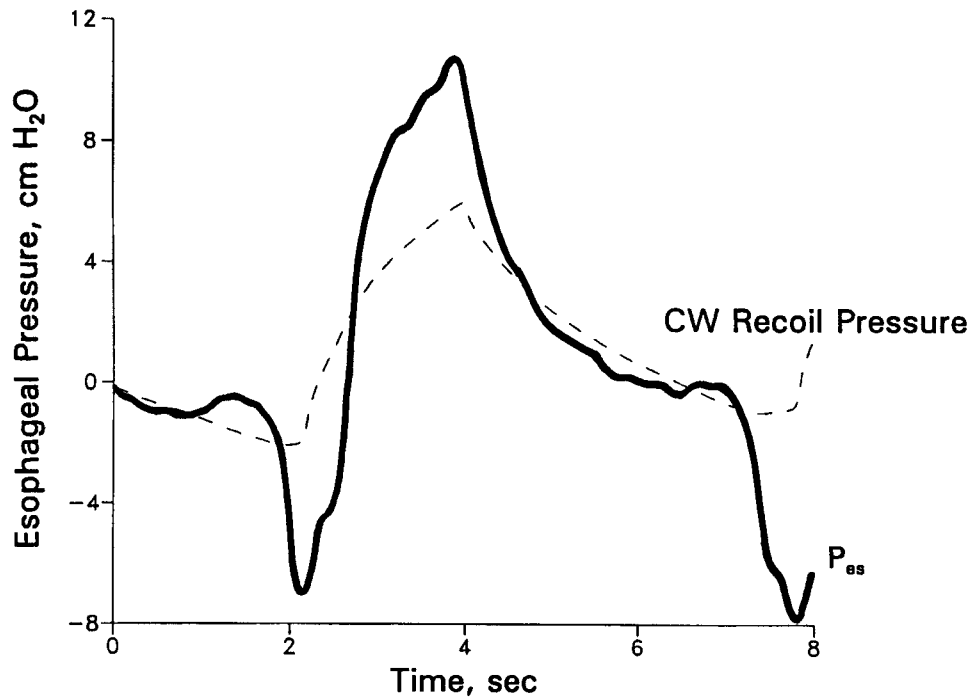
Fig. 15. Esophageal pressure (continuous line) in a patient with chronic obstructive pulmonary disease receiving pressure support of 20 cm H_2O. The interrupted line represents the estimated recoil pressure of the chest wall. The tracings have been superimposed so that chest wall recoil pressure is equal to esophageal pressure at the onset of the rapid fall in esophageal pressure in late expiration (right of figure). Times at which esophageal pressure is higher than chest wall pressure signify a minimal estimate (lower bound) of expiratory effort. The expiratory muscles become active about halfway during the period of mechanical inflation. (From Reference 26, with permission.)

In patients who fail a weaning trial, we want to rest their respiratory muscles. Clinicians often assume that simply connecting a patient to a ventilator is sufficient to achieve rest. But patients can have difficulty even in triggering the machine (Figure 16). One of our fellows, Phil Leung, found that up to 30 per cent of attempts made by patients fail to trigger the ventilator.[28] Why do patients have difficulties in triggering? To understand this phenomenon, Phil looked at the characteristics of the breaths that immediately preceded the triggering and nontriggering attempts. The breaths before nontriggering attempts had a higher V_T and a lower expiratory time. When you inhale a large V_T, the elastic recoil pressure at the peak of inspiration will be high. If the time for exhalation is also shorter, the pressure in your system—the elastic recoil pressure—will be above normal when you finish trying to exhale. We quantify this pressure in terms of auto-PEEP. And Phil found that auto-PEEP was higher before attempts that failed to trigger the ventilator than for the attempts that triggered the machine. That is, the real trigger sensitivity—not the set sensitivity—is much higher in patients who fail to trigger the machine.

A problem in talking about the subject of weaning is the word itself. "Weaning" implies a gradual reduction in the level of ventilator support. In recent randomized, controlled trials of weaning techniques, however, 70 to 80 per cent of patients tolerated their first T-piece trial.[29,30] Patients went from full ventilator support, consisting of assist-control ventilation, to a T-piece trial, without a gradual decrease in the level of support.

A major milestone in weaning research was the first randomized, controlled trial carried out by Laurent Brochard.[29] He compared three different methods: IMV, T-pieces, and pressure support. Before this study, most commentators said it really didn't matter what technique you used for weaning—that they're all the same. Laurent showed it clearly matters. For the first time, he showed that one technique, IMV, was markedly inferior to the other weaning approaches. People often misinterpret the results of Laurent's study, and say that he showed that pressure support was better than T-pieces. Pressure support was better than the combination of the T-piece group and the IMV group. There was no difference between pressure support and T-pieces, when the T-piece group was analyzed separately from the IMV group.

The following year we published a randomized controlled trial conducted with collaborators in Spain.[30] We looked at the four approaches I mentioned earlier: single
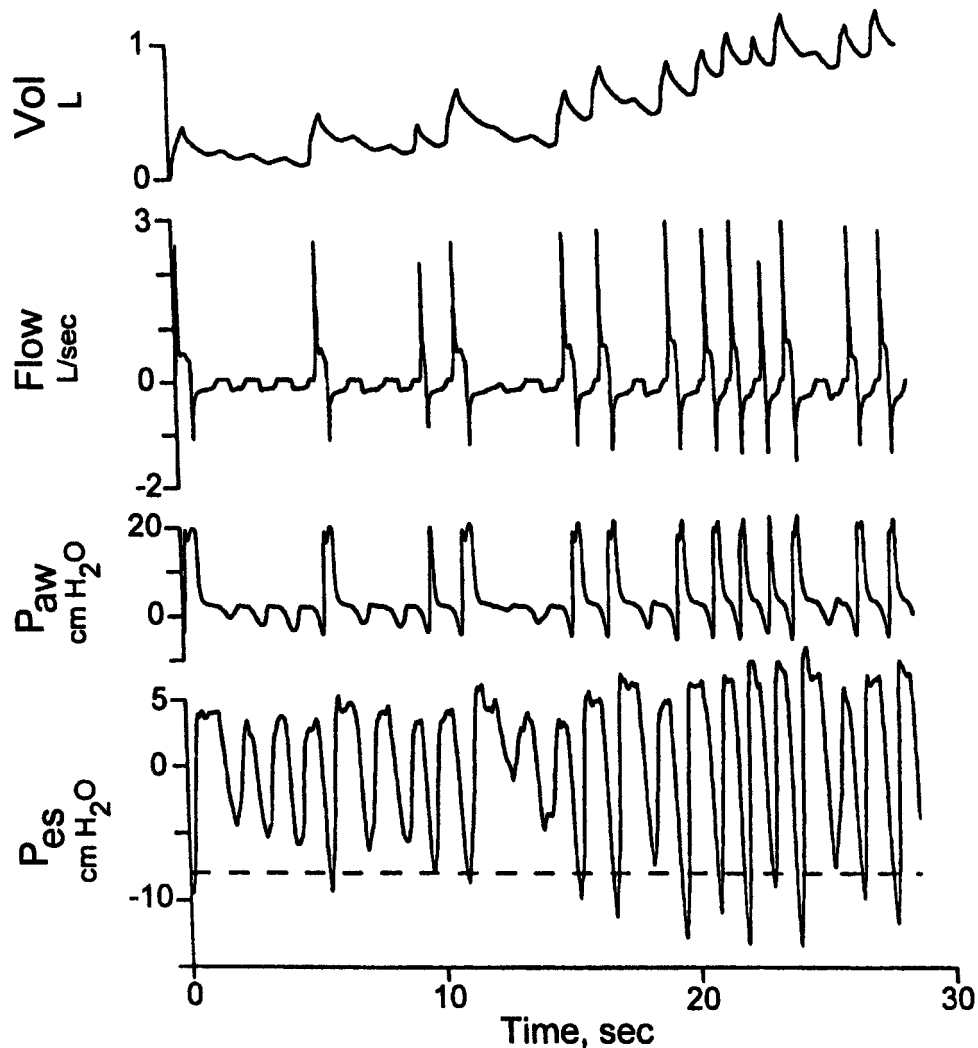
Fig. 16. Recordings of tidal volume, flow, airway pressure (P_{aw}), and esophageal pressure (P_{es}) in a patient with chronic obstructive pulmonary disease receiving pressure support ventilation. Approximately half of the patient's inspiratory efforts do not succeed in triggering the ventilator. Triggering occurred only when the patient generated a P_{es} more negative than -8 cm H_2O (indicated by the interrupted horizontal line), which was equal in magnitude to the opposing elastic recoil pressure. Each ineffective triggering attempt is signalled by a braking of expiratory flow, whereby flow returns to zero due to the action of the inspiratory muscles. Thus, monitoring of expiratory flow provides a more accurate measurement of the patient's intrinsic respiratory rate than the number of machine cycles displayed on the bedside monitor. (From Reference 4, with permission.)

daily trials of spontaneous breathing, multiple trials of spontaneous breathing, pressure support, and IMV. Like Laurent Brochard, we found that IMV had the worse outcome. Using a Cox proportional-hazards regression model, we found that the single daily trial of spontaneous breathing resulted in a three-fold increase in the rate of successful weaning compared with IMV, and a two-fold increase in the rate of successful weaning compared with pressure support.

Wes Ely[31] subsequently undertook a study that combined two aspects of our previous research: the use of weaning predictors[7] and the use of spontaneous breathing trials.[30] He studied 300 patients who underwent a daily screen by respiratory therapists. The daily screen consisted of looking at the patient's oxygenation, the level of PEEP, the absence of rapid, shallow breathing (a frequency-to-V_T ratio of less than 105),[7] the presence of a good cough on suctioning, and lack of infusions of pressors or sedatives. Patients passing the screen were randomized to an intervention group and a control group. The control group was managed in the usual manner by the attending physicians, largely consisting of pressure support or IMV. Patients in the intervention group underwent a two-hour trial of spontaneous breathing,[30] without getting permission from the

attending physician. The attending physicians of patients passing the two-hour trial were contacted verbally and a note to that effect was also written in the chart.

Although the patients in the intervention group were sicker, with higher acute physiology and chronic health evaluation and lung injury scores, they were weaned twice as fast as the control group. That is, a two-step strategy, consisting of the systematic measurement of weaning predictors[7] combined with a spontaneous breathing trial,[30] achieved a better outcome. Looking at the details, 59 per cent of the patients tolerated the trial. In general, about 10 to 15 per cent of extubated patients require reintubation. If the investigators had been aggressive and extubated every patient who passed the spontaneous breathing trial, you'd expect about 50 per cent of patients to have tolerated extubation. In contrast, 32 per cent were actually extubated. Despite this nonaggressive approach, the rate of successful extubation was more than double that in the control group.

In early 1999, we published a study conducted with collaborators in Spain to determine if patient outcome was different for a spontaneous breathing trial lasting a half hour versus two hours.[32] To emphasize how thinking has changed about the right length for a T-piece trial, I refer to what Dr Egan wrote in 1977: "When the patient can breathe unassisted around the clock, and is moving a reasonable amount of air without undue effort, and can walk for short distances consistent with his general physical condition, and when ventilation is satisfactory and stable by blood gas values, it is time to consider removal of the endotracheal tube." When we work in a field, we often don't notice how much it advances. In another 20 years, I expect people will think some of my statements today as strange—probably much sooner than 20 years! Returning to our recent study, patient outcome was the same for spontaneous breathing trials lasting for two hours or a half hour.[32] Contrasted with the previous recommendation that T-piece trials should last 24 hours, being able to make a decision within a half hour frees up time for staff to take care of other tasks and simplifies the approach to weaning.

In our recent study, the intensive care unit mortality was 5 per cent in patients who succeeded in a trial and didn't require reintubation.[32] In contrast, patients who succeeded in the trial, were extubated, but then required reintubation had a mortality rate of 33 per cent—a similar experience has been reported by Scott Epstein.[33] We found that respiratory frequency was high in the patients who failed the spontaneous breathing trial, but the values were similar in the patients who were successfully extubated and in those requiring reintubation. A superficial assessment of these data might lead you to conclude that weaning indices do not predict the need for reintubation. The design of our study, however, was not adequate to reach a conclusion on this issue. The patients in our study who failed the weaning trial had a much higher frequency, and, if extubated, it is likely that many of them would have required reintubation. To properly answer the question, you'd need to take a group of patients, measure the predictive indices, and then extubate every patient irrespective of whether or not they tolerated a weaning trial.

Reintubation represents a major new frontier for research. We need to find out what exactly is going on in these patients. To date, we don't have a single study probing the pathophysiology of reintubation.

In summary, the major reason that patients fail weaning trials is their enormous respiratory work load. We're still unsure whether these patients develop respiratory muscle fatigue. We need to answer this question because it has major implications for patient management. In deciding the right time to take a patient off the ventilator, we've learned that the judgment of an experienced clinician is not enough. You need weaning predictors. And when they're measured systematically, predictors result in more effective management. Of the weaning techniques available, a number of randomized, controlled trials have shown that one of the most ingrained approaches, IMV, is the least effective. A single daily trial of spontaneous breathing appears to be the most expeditious weaning technique. When looking at the story of weaning research over the last 20 years, one is reminded of the saying of the French essayist, Michel de Montaigne:

> Whenever a new discovery is reported to the scientific world, they say first, "it is probably not true." Thereafter, when . . . demonstrated beyond question, they say "yes, it may be true, but it is not important." Finally, when a sufficient time has elapsed, they say "Yes, surely it is important, but it is no longer new.

That statement was made more than 400 years ago—*plus ça change, plus c'est la même chose.*

I will finish by returning to Dr Egan's book. He pointed out that weaning is very nearly a pure art. As critical care shifts increasingly toward a focus on technology, more than ever is there a need for the personal interaction between two human beings: the clinician and the patient. Respiratory therapists play a key role at the bedside of the patient who's frightened by the process of weaning. This interplay between one human being and another will remain the dominant factor in determining which patients are successfully weaned from the ventilator.

Thank you.

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