Intensive Care Med (2006) 32:1485–1493
DOI 10.1007/s00134-006-0338-8



**Martin J. Tobin**

# Remembrance of weaning past: the seminal papers

Received: 13 July 2006
Accepted: 24 July 2006
Published online: 8 August 2006


M. J. Tobin (✉)
Loyola University of Chicago Stritch School of Medicine,
Edward Hines Jr. VA Hospital,
Division of Pulmonary and Critical Care Medicine,
111N, 5th Avenue and Roosevelt Road,
Hines 60141, Illinois, USA
e-mail: mtobin2@lumc.edu
Tel.: +1-708-2022705
Fax: +1-708-2027907

**Abstract** The approach to ventilator weaning has changed considerably over the past 30 years. Change has resulted from research in three areas: pathophysiology, weaning-predictor testing, and weaning techniques. Physiology research illuminated the mechanisms of weaning failure. It also uncovered markers of weaning success. Through more reliable prediction, patients whose weaning would have been tedious in the 1970s are now weaned more rapidly. The weaning story offers several lessons in metascience: importance of creativity, the asking of heretical questions, serendipity, mental-set psychology, cross-fertilization, and the hazards of precocity. Weaning research also illustrates how Kuhnian normal (me-too) science dominates any field. Making the next quantum leap in weaning will depend on spending less time on normal science and more on the raising (and testing) of maverick ideas.

**Keywords** Mechanical ventilation · Weaning · Pathophysiology · Control of breathing · Respiratory muscles · Diagnostic testing · Monitoring · Randomized clinical trials · Metascience · Serendipity · Cross-fertilization

In the world of ideas, *seminal* refers to a thought pregnant with consequences. In science, to a paper that fostered new research. When judging a paper as seminal, a distinction arises between scientific and humanistic literature [1]. Whereas humanistic writing can retain interest centuries later (permanence), scientific literature is cumulative: a new paper that provides a better solution to a problem supersedes older papers. Researchers are prone to regard the latest paper more influential – a phenomenon known as "supersedure."

Is there a yardstick for rating a paper as seminal? Understandably, some use citation counts [2]. Scientometricians, however, have long recognized that authors often fail to cite the most ground-breaking work [3] and frequently cite papers of limited intellectual fiber or originality. Between 1961 and 1975, Watson and Crick's paper on DNA [4] was cited at one-hundredth the frequency of Lowry's report on a reagent for measuring protein [5]. The phenomenon of under-citation is known as "obliteration by incorporation" [6]. I say all this to justify my own subjective selection of seminal papers on weaning.

In writing on weaning history, the goal and hazards are clear. A mere chronicle of facts would be banal. Instead, the goal is to understand how events unfolded. A historian of science should keep one eye focused on contingencies faced by researchers of the day, while turning the other to subsequent developments. But there's the rub. It is impossible to capture accurately the minds of researchers who did not know what was going to happen next. Aware of the denouement, a historian is prone to exaggerate the rationality of those steps taken by researchers that were later proven correct. And to smugly list follies committed by other researchers.

My canvas contains only broad-brush strokes. Many contributions deserving pointillistic attention are omitted. At the end, I dilate on metascientific lessons offered by weaning research. That goal also influences my choice of seminal papers.

## Prologue

All discussion of modern ventilation dates to early-1950s Scandinavia [7]: Bjorn Ibsen's introduction of positive-pressure ventilation during the Copenhagen polio epidemic [8]; Carl-Gunnar Engström's first volume-oriented ventilator [9]; and Eric Nilsson's (1915–2004) management of barbiturate overdose [10]. Two Danes who earned their stripes bagging polio victims, Henrik Bendixin (1923–2004) and Henning Pontoppidan, later pioneered ventilator management in the United States [11]. After founding the first respiratory intensive care unit in the USA (at Massachusetts General Hospital) in 1961, they conducted much ventilator research [11].

In 1965, Bendixin, Pontoppidan and colleagues published the first textbook in the field, *Respiratory Care*. Its goal was to improve patient care "through the clinical application of the principles of respiratory physiology" [12]. At that time, the Boston unit was ventilating about 400 patients a year. Few were ventilated for longer than 2 days without a tracheotomy [13]: "It is our practice to limit endotracheal intubation to approximately forty-eight hours" [12]. The Bostonians articulated a principle that still holds: "To know the proper timing and rate of weaning from the respirator requires considerable judgment and experience. As a rule, weaning should start as soon as possible" [12].

Research over the ensuing 40 years can be divided into three areas: timing and prediction of weaning outcome, weaning techniques, and pathophysiology. To help readers see how findings in one area cross-fertilized research in other areas, I have broken discussion of each subfield into two phases.

## Predictor tests, phase I (1968–1983)

Weaning research begins with the development of diagnostic tests to identify the earliest time a patient might be safely disconnected from the ventilator. The first reports, from Pontoppidan's group (1968, 1972) [14, 15], are limited to abstracts. Thus, Sahn and Lakshminarayan's 1973 report [16] is the first detailed study. In 100 patients, they found that minute ventilation (< 10 l/min) and maximal inspiratory pressure (> 30 $cmH_2O$) "correlated well with the ability to discontinue mechanical ventilation."

In 1983, Tahvanainen and colleagues [17] reported on 47 patients who had been weaned to an intermittent mandatory ventilation (IMV) rate of zero. Minute ventilation, maximal inspiratory pressure, vital capacity and dead space did not differentiate between patients who required reintubation and the rest.

The Tahvanainen paper represented a major advance. Unlike Sahn and Lakshminarayan, who did not express results as statistical quantities, they presented complete two-by-two tables (true positives, true negatives, false positives, false negatives) for all variables. They, however, based conclusions about diagnostic-test reliability on chi-square comparisons of group means. Neither group used expressions such as sensitivity or specificity to judge a test's reliability.

## Weaning techniques, phase I (1965–1988)

The 1960s approach to weaning is given in Bendixin's book: "weaning is started by taking the patient off the respirator for three to four minutes every half hour and, if this is tolerated, by gradually increasing the period off the respirator as rapidly as is tolerated" [12]. In 1977, Egan advised: "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" [18].

Compared with the preceding tedium, no imagination is needed to see how nurses and therapists regarded dialing an IMV rate as a major advance [19]. And by the mid-1980s, IMV was triumphant: being used for more than 90% of weaning attempts in the US [20]. Europe was little different. In 1988, Lemaire wrote: "Despite the lack of evidence that IMV shortens the weaning period, IMV is extensively used in the majority of ICUs" [21].

## Pathophysiology, phase I (1977–1989)

Throughout the 1970s, authors emphasized the challenge posed by difficult-to-wean patients. But attempts to elucidate underlying mechanisms were almost non-existent. An exception was a 1977 study by Henning, Shubin and Weil [22]. Using esophageal-balloon catheters, these investigators made detailed measurements of work of breathing. Ventilator-dependent patients had higher work readings. The mechanism, however, was not clear. In particular, dynamic pulmonary compliance was equivalent to that in weaning-success patients.

In 1982, Cohen, Roussos, Macklem and colleagues [23] reported electromyographic recordings in difficult-to-wean patients. Six patients developed power-spectral features of diaphragmatic fatigue. Electromyographic abnormalities were accompanied by abdominal paradox (inward motion during inspiration) and respiratory alternans (alternating predominance of rib-cage and abdominal breathing) (Fig. 1).

For the first time, there was a framework with which to investigate weaning pathophysiology. Attention turned from the lungs per se to the respiratory muscle pump. In 2006, this seems a trivial turn. In 1982, it was revolutionary. Most provocative was the suggestion that simple physical signs, paradox and alternans, could detect fatigue

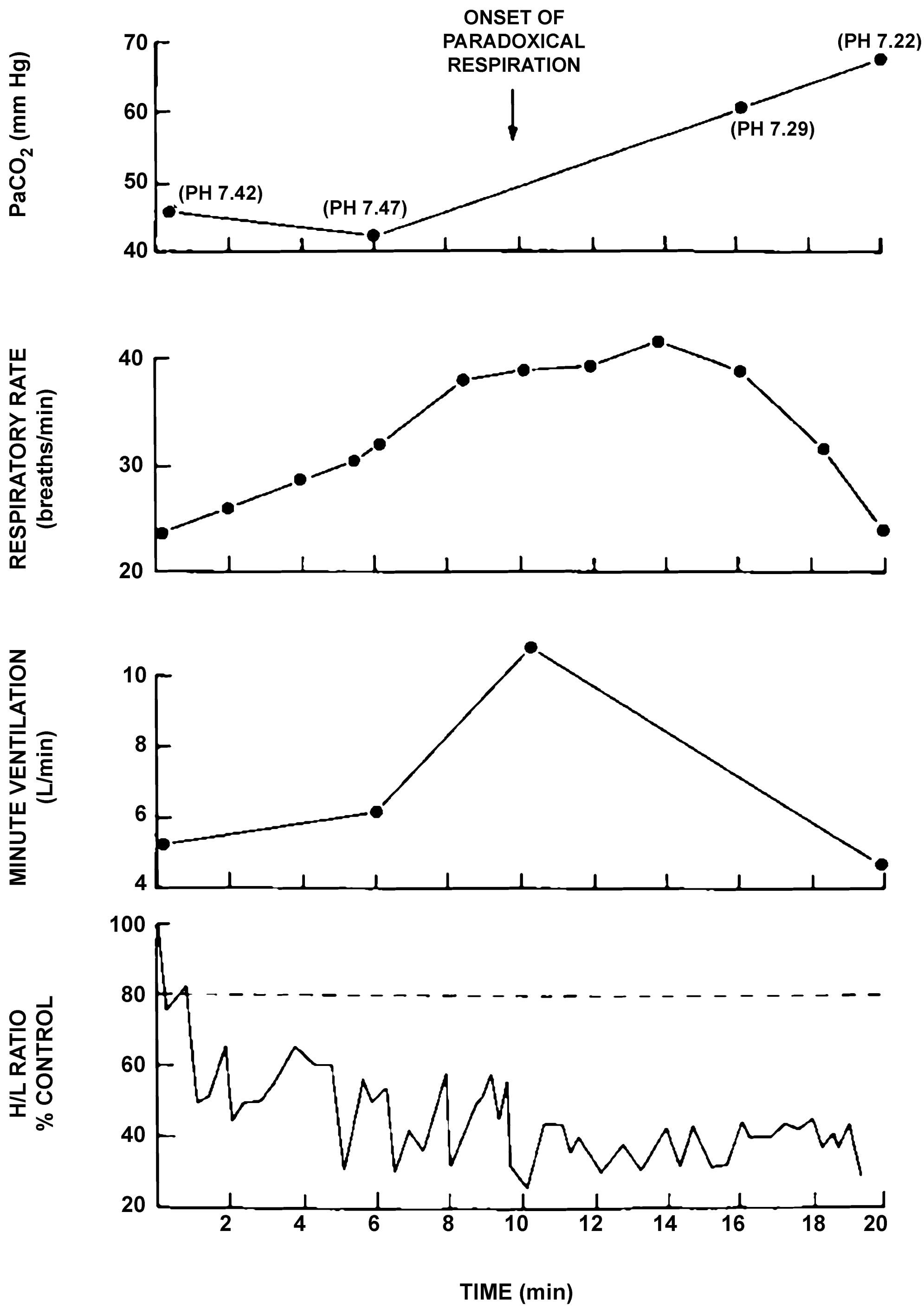


**Fig. 1** Sequence of changes in arterial carbon dioxide tension ($PaCO_2$), respiratory rate, minute ventilation, and high/low ($H/L$) ratio of power spectrum of the diaphragmatic electromyogram in a patient who failed a weaning trial. Ventilator discontinuation was followed by an immediate change in the high/low ratio, followed by a slow increase in respiratory rate, then abdominal paradox (and alternans), and finally hypercapnia. (From Cohen et al. [23])

and provide a means for minute-by-minute monitoring of weaning progression. But Cohen [23] did not attempt to quantify chest-wall motion.

Stirred by these findings, we used inductive plethysmography to obtain quantitative indices of chest-wall motion [24]. Abnormal motion, however, turned out to be common in both success and failure patients [24]. Moreover, motion did not worsen over time in weaning-failure patients, suggesting it did not reflect fatigue (a negation subsequently confirmed [25]).

Although our study was undertaken to quantify chest-wall motion, we also analyzed breathing pattern (since the data were available) [26]. We expected acute hypercapnia to result from a fall in respiratory drive, whereas drive rose. Rather, 81% of the variance in $PaCO_2$ was accounted for by development of rapid shallow breathing [26]. Alveolar–arterial oxygen gradient did not widen. These findings suggested a number of mechanisms were unlikely to cause weaning failure: respiratory center depression, respiratory muscle fatigue, and ventilation–perfusion abnormality [26]. Instead, rapid shallow breathing dominated.

Before 1986, several investigators had reported that tidal volume and respiratory frequency did not discriminate between weaning-success and weaning-failure patients [15, 17, 19, 27]. Since 1986, researchers have repeatedly confirmed their discriminatory power [28]. How could such a striking distinction have gone undetected? In previous studies, we had documented considerable breath-to-breath variability in breath components, and thus used large breath samples in our breathing-pattern studies [29, 30] (Fig. 2). Most importantly, we believed that subtle differences in breathing pattern could yield as much pathophysiologic insight as data generated by more sophisticated methodology. In the mid-1980s, physicians did not focus on respiratory rate. Rate was a nursing measurement, along with charting of temperature and

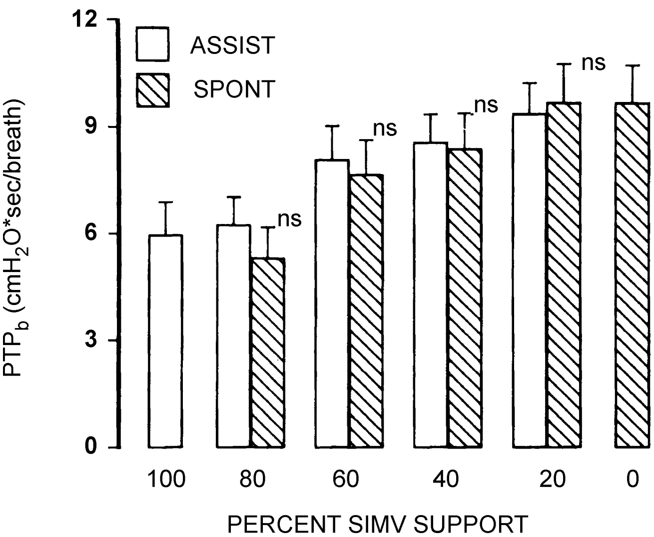


**Fig. 3** Inspiratory pressure-time product per breath for assisted, mandatory breaths (*open bars*) and intervening spontaneous breaths (*cross-hatched bars*). Patient effort was equivalent for mandatory and spontaneous breaths at every level of synchronized intermittent mechanical ventilation (*SIMV*). (From Marini et al. [33])

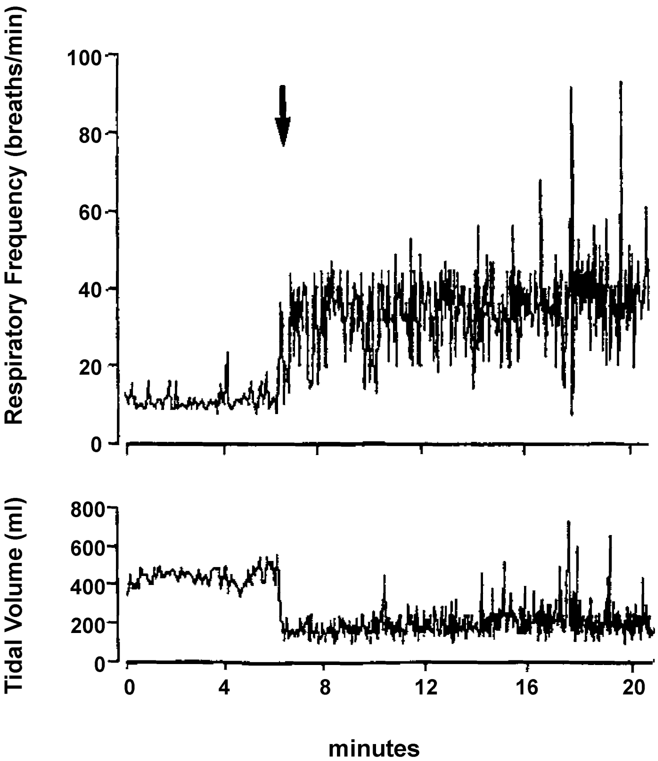


**Fig. 2** A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. Discontinuation of ventilator support (*arrow*) resulted in almost immediate rapid shallow breathing. Note the marked breath-to-breath variability in the data. (From Tobin et al. [26])

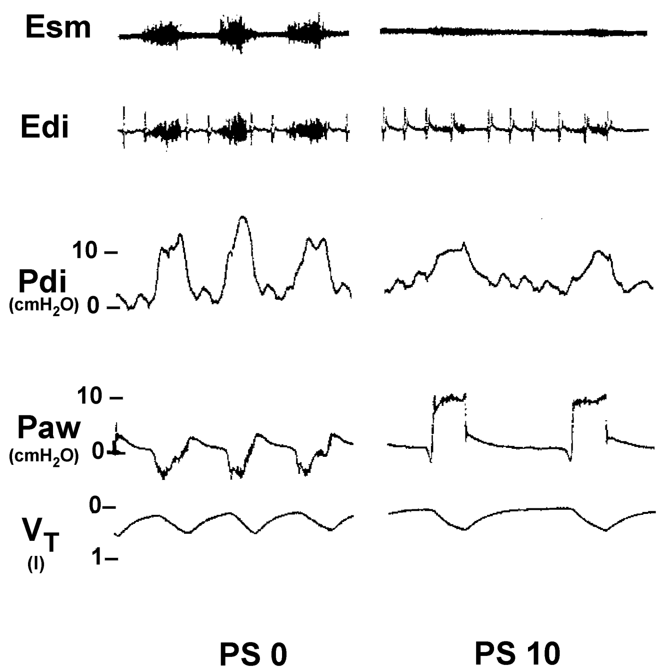


**Fig. 4** Electromyographic recordings of the sternomastoid muscle (*Esm*) and diaphragm (*Edi*), transdiaphragmatic pressure (*Pdi*), airway pressure (*Paw*), and tidal volume ($V_T$) in a ventilator-supported patient. Compared with 0, pressure support of 10 $cmH_2O$ decreased (but did not abolish) sternomastoid and diaphragmatic electrical activity, decreased Pdi, increased $V_T$, and slowed respiratory rate. (From Brochard et al. [35])

number of bowel motions [31]. And bedside spirometers measured total minute ventilation – spontaneous tidal volume did not become part of bedside testing until the 1990s [31].

Research into patient–ventilator interaction also advanced (weaning) understanding. In 1985, Marini and colleagues reported that subjects receiving assist-control ventilation performed half as much work as done by the ventilator [32]. This was heresy. It had been dogma that connecting a patient to a ventilator lessened work to near zero. In 1988, Marini reported that patient effort was virtually the same during mandatory IMV breaths as during the intervening spontaneous breaths (Fig. 3) [33]. This was blasphemy. By the late 1980s, IMV had been deified as the nonpareil weaning technique [20].

The importance of rigorous evaluation was recognized by the time pressure support was launched. In 1987 and 1989, Brochard, Lemaire, Harf and colleagues reported recordings of transdiaphragmatic pressure, electromyography, and work of breathing (Fig. 4) [34, 35]. Armed with such data, they delineated the pressure-support level that avoided fatigue but still maintained diaphragmatic activity. These studies ensured that misunderstanding about a mode's ability to assuage work, as with IMV, did not recur.

## Predictor tests, phase II (1985 and after)

The mid-1980s saw a flurry of reports on airway occlusion pressure ($P_{0.1}$). Herrera (1985) [36], Sassoon (1987) [37] and colleagues reported that low $P_{0.1}$ (low respiratory drive) was superior to conventional tests in predicting weaning success.

Montgomery, Pierson and colleagues [38] reported that $P_{0.1}$ was reliable only when expressed as ratio of $P_{0.1}$ during $CO_2$ stimulation to baseline $P_{0.1}$. These authors were the first to discuss results in terms of sensitivity and specificity. They noted that ventilatory response to $CO_2$ was higher in success patients, "although overlap occurred indicating that this predictor could neither be 100 percent sensitive or specific" [38]. In contrast, ratio of $P_{0.1}$ during $CO_2$ stimulation to baseline $P_{0.1}$ "separated all weaning failure patients from all those who succeeded and was thus, a completely specific and sensitive test."

The quotations are revelatory. They portray a mindset where a test is judged reliable only if it attains 100% sensitivity and 100% specificity. The authors made no distinction between desirability of high sensitivity versus high specificity [38]. This monolithic orientation pervades to this day.

In 1986, Milic-Emili [39] proposed an index that integrated several respiratory muscle characteristics. We followed his suggestion, and developed the CROP index, which integrated *c*ompliance, *r*ate, *o*xygenation, and (maximal inspiratory) *p*ressure [40]. CROP proved superior to conventional tests. Cognizant that rapid shallow breathing was the dominant finding in our 1986 pathophysiology study [26], we quantified this phenomenon as frequency-to-tidal volume ratio ($f/V_T$). This test proved superior to all others [40].

The 1991 $f/V_T$ paper [40] is typically cited as the source for usefulness of rapid shallow breathing in weaning prediction. In reality, this paper has much less intellectual content than our 1986 pathophysiological study [26]. The merit of the 1991 paper was its experimental design. First, all studies up to then involved post-hoc data analysis (which inflates test reliability). Instead, we first determined threshold values for each predictor test in a "training-data set", and then investigated reliability in a prospective "validation-data set." Second, clinicians were blinded to CROP and $f/V_T$. Third, results were expressed in terms of sensitivity, specificity, positive-predictive value, negative-predictive value, and receiver-operating-characteristic (ROC) curves [40].

Since 1991, $f/V_T$ has been evaluated in more than 25 studies [41]. Unfortunately, many authors have not complied with the canons for diagnostic-test evaluation, grounded on Bayes' theorem. In particular, many have ignored conditional independence, pre-test probability, test-referral bias, and spectrum bias – each of which can corrupt reported measures of test reliability [41].

## Pathophysiology, phase II (1989 and after)

The multiple inert-gas technique paints vivid pictures of pulmonary gas exchange. This technique enabled Torres, Rodriguez-Roisin and colleagues (1989) [42] to show that acute hypercapnia and ventilation–perfusion maldistribution in weaning-failure patients results from rapid shallow breathing. Using the same technique, Beydon, Harf, Lemaire and colleagues (1991) [43] confirmed shallow breathing as the major cause of ventilation–perfusion maldistribution. Years later, we studied tissue gas exchange using mixed-venous oxygen saturation [44]. Saturation fell progressively in failure patients consequent to a relative decrease in convective oxygen transport combined with an increase in tissue oxygen extraction.

In a series of studies, Bates, Rossi, Milic-Emili and colleagues [45, 46, 47, 48] used the rapid airway-occlusion technique to characterize respiratory mechanics. Through inventive mathematical modeling, they partitioned the relative roles of ohmic resistance, viscoelastic behavior, and time-constant inhomogeneity. The main abnormality in ventilator-dependent patients resulted from airway resistance, with less contribution from time-constant inhomogeneities and abnormal viscoelastic behavior of the lung. Chest-wall contribution was negligible. With this methodology, it was possible to find out whether severe disturbance of mechanics made weaning failure little more than enactment of a predestined state.

In 1997, we found that passive respiratory mechanics were severely disturbed in patients who failed subsequent weaning, but no worse than in patients who weaned successfully [49]. This contrasted with findings during an ensuing 30–60-min T-tube trial. Inspiratory effort was much higher in weaning-failure patients consequent to marked increases in resistance, elastance and auto-PEEP [50]. That mechanics were markedly worse in failure patients during the weaning trial, but equivalent to those in success patients immediately beforehand, indicated that some mechanism associated with spontaneous breathing caused the abnormalities. That mechanism is still unidentified.

More deranged mechanics in failure patients was confirmed by Vassilakopoulos et al. [51]. They studied a group of patients at two points: shortly after failing a T-tube trial, and about 9 days later, shortly before successful extubation. Over this interval, airway resistance and auto-PEEP decreased substantially. Multiple logistic regression uncovered two determinants of weaning failure: tension–time index and $f/V_T$.

After the 1982 Cohen study [23], the role of muscle fatigue in weaning failure was not reexamined directly until 1994. Goldstone, Moxham and Green [52] reported slowing of maximum relaxation rate (of transdiaphragmatic pressure), a harbinger for fatigue, in failure patients but not in success patients. Stimulating the phrenic nerves and recording transdiaphragmatic pressure provides the most direct measure of diaphragmatic fatigue. Using this technique, we were surprised to find that not even one weaning-failure patient developed fatigue [53]. Related analyses disclosed why. Failure patients became progressively distressed during the trial, leading clinicians to reinstate ventilator support before patients had breathed long enough to develop fatigue. That is, monitoring clinical signs of distress provides sufficient warning to avoid fatigue.

## Weaning techniques, phase II (1994 and after)

The year 1994 ushered in a new era of weaning research: Brochard and colleagues published the first randomized controlled trial (RCT) [54]. They randomized 109 difficult-to-wean patients to T-tube trials, IMV, or pressure support. At 21 days, ventilator dependency was less with pressure support than with other techniques. This report was revolutionary. Its main message was that steps chosen for weaning influenced duration of ventilator dependency. Second, 76% of 456 patients entered into the study passed the first T-tube trial (without "weaning"). Third, a 2-hr limit was imposed on T-tube trials; back then, trials often lasted 24 h [55, 56].

The major contribution of RCTs to clinical research is the elimination of susceptibility bias, a source of major disparity in baseline states of compared groups. "Beyond this achievement," notes Feinstein [57], "randomization itself makes no other scientific contribution". Despite the name, use of control groups is not limited to RCTs. Investigators studying weaning-failure pathophysiology have commonly included success patients as controls.

Knowledge gained through research depends ultimately on the ingenuity of the hypothesis under interrogation. RCTs are typically designed by research groups. Committees are hardly renowned for maverick ideas. So questions subjected to RCT testing are characterized by their sameness. Our 1995 RCT copied the general design of the Brochard trial, though we specified different steps [58]. T-tube trials proved superior to pressure support. The different outcomes in the two RCTs primarily reflected different steps in the algorithms of the two studies [54, 58].

In 1997, Ely et al. [59] borrowed two steps from previous studies: measurement of $f/V_T$ (and other predictors), followed by a T-tube trial. The two-step approach achieved faster weaning than usual care. This study has since been portrayed as a comparison of weaning-by-protocol versus usual care. But this portrayal flouts a fundamental requirement for sound science: need for internal validity. Of patients in the usual-care arm, 76% were managed with IMV [59]. Not one protocol patient was so managed. To conclude that protocols are superior, weaning methods need to be the same in the protocol and usual-care arms.

## Lessons in metascience

It would be naïve to regard the weaning story as a microcosm of the entire scientific process. Nonetheless, it offers several metascientific lessons.

The steam in science's engine is the novel question. Medical practice today depends on what questions our predecessors asked. But questions are not there for the picking, like apples on a tree. People have to formulate them. The reason why one researcher makes greater contributions to science than an equally talented coeval is courage to raise antinomial questions [60]. To think the unthinkable. As did Marini, when he suspected that ventilated patients might be performing prodigious respiratory work, and that IMV was largely ineffectual [32, 33]. But getting heresies published is not easy – the acceptance date on Marini's 1995 paper provides a clue to that effect.

Being too novel poses other problems. The 1977 report by Henning, Shubin, and Weil incorporated the most advanced scientific techniques [22]. But others did not build on their findings. The paper's sophistication was about a decade ahead of its time. Yes, researchers live in constant dread of being pipped at the post. But if they arrive before the zeitgeist, others cannot build on their work. The most famous example is Gregor Mendel's paper in 1866 [61]. Not for another thirty years did general biological theory find a slot in which to fit the abbot's discovery [6].

Allied to discovery is serendipity. We did not set out to show that rapid shallow breathing is a hallmark of weaning failure [26]. Rather, our motivation was to quantify rib cage–abdominal motion [24]. But serendipity per se does not produce discoveries [60]. Instead, it produces opportunities for making discoveries. The person making the serendipitous connection is already primed to appreciate its significance. "Luck favors only the prepared mind," mused Pasteur.

Before the mid-1980s, rapid shallow breathing went unheeded by weaning researchers [15, 17, 19, 27, 37]. After it was pronounced a hallmark of weaning failure, the connection was reported over and over again [28]. The switch from non-detection to repeated confirmation is a consequence of *mental set* (as labeled by psychology researchers). Mental set describes the set of beliefs that determines what a person perceives (the prepared mind). With a mental set, a goal (detecting rapid shallow breathing) selects and shapes what it is a researcher sees. Without a mental set, the obvious becomes invisible. The researcher is distracted and blinded by a blizzard of other possible observations. In his magisterial history of the Scientific Revolution, Herbert Butterfield (1900–1979) [62] concluded, "of all forms of mental activity, the most difficult to induce ... is the art of handling the same bundle of data as before, but placing them in a new system of relations with one another by giving them a different framework, all of which virtually means putting on a different kind of thinking-cap for a moment."

The mid-1980s opened a new chapter in the weaning story. Like elsewhere in critical care, greater emphasis was placed on RCTs – in the belief that this was the only science that improved patient outcome. The purpose of science, however, is to enhance *understanding*, not simply accumulate facts [60]. Facts generated through research improve patient outcome only if they enhance physician understanding. Tanenbaum [63] undertook an ethnographic study of how clinicians think. For only a small fraction of time did clinicians engage in probabilistic reasoning – based on results of RCTs. The vast majority of reasoning involved models with moving parts, like heart valves – the type of understanding gained through physiology research.

Few seminal advances in the *understanding* of weaning originated in RCTs. Take weaning techniques. It was Marini's study of patient–ventilator interaction that highlighted the limitations of IMV [33]. Brochard's group, already steeped in pathophysiology methods [34, 35], built on Marini's understanding and undertook the first RCT [54]. The blending of different research disciplines among the Parisians exemplifies how cross-fertilization leads to scientific progress. New ideas rarely arise out of the blue. More often, they represent novel combinations of existing ideas [60]. To make a connection, a researcher has to traverse interdisciplinary boundaries. For the Parisians, this involved combining knowledge gained through physiology research with knowledge of trial design. Cognitive psychologists view cross-fertilization as a major source of mental creativity [60].

The introduction of $f/V_T$ as a weaning-predictor test provides another example of cross-fertilization. For years before the 1991 report [40], we had been studying control of breathing in various settings – including weaning failure [26, 29, 30]. Independently, we had a specific interest in ICU monitoring [31]. Monitoring fundamentally boils down to the serial application of diagnostic tests. An understanding of the principles of diagnostic testing (garnered through expertise in monitoring) combined with immersion in physiology research gave birth to the $f/V_T$ test [40].

The framework posited by Thomas Kuhn (1922–1996) in *The Structure of Scientific Revolutions* helps select which papers were seminal in advancing a field [64]. Kuhn averred that inquiry is dominated by long periods of *normal science*, punctured intermittently by sharp revolutions (*paradigm shifts*). Normal science, quantified by the amount of me-too research, makes few demands on an individual's intellect and psyche [60]. Kuhn concluded, "Few people who are not actually practitioners of a mature science realize how much mop-up work" there is to do. And, "Mopping-up operations are what engage most scientists throughout their careers" [64]. The seminal advances in weaning *understanding* (and thus management) resulted from pathophysiology research on respiratory muscles and breathing pattern [23, 26, 32, 33, 34], and cross-fertilization between pathophysiology research and fundamentals of diagnostic testing [40] and principles of RCT design [54]. The many RCTs published after the first [54] fit the category of *normal science*: they help with the dotting of i's and crossing of t's. But they have not seeded ideas on how to make the next quantum leap in this field.

## Conclusion

As long as ventilators are used, the impetus for greater understanding of weaning will continue. We do a better job of weaning easy patients than in the 1970s, but more complex patients populate today's units. As a practicing intensivist, nothing taxes my intellect more than the difficult-to-wean patient. I know of no problem where connoisseurship of the individual intensivist has a greater influence on patient wellbeing and outcome.

**Acknowledgements.** Supported by a Merit Review grant from the Veterans Administration Research Service and by the National Institute of Health (RO1 NR008782).

## References


1. Kronick DA (1962) A history of scientific and technical periodicals: the origins and development of the scientific and technological press 1665–1790. Scarecrow Press, New York, pp 16–17
2. Tremblay LN, Slutsky AS (2006) Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 32:24–33
3. Garfield E (1998) From citation indexes to infometrics: is the tail now wagging the dog? Libri 48:67–80
4. Watson JD, Crick FH (1953) Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature 171:737–738
5. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. J Biol Chem 193:265–275
6. Kronick DA (1985) The literature of the life sciences: reading, writing, research. Philadelphia: ISI Press: 1, 66
7. Colice GL (2006) Historical perspective on the development of mechanical ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill, New York, pp 1–36
8. Ibsen B (1952) The anesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen. Proc R Soc Med 47:72–74
9. Bjork VO, Engstrom CG (1955) The treatment of ventilatory insufficiency after pulmonary resection with tracheostomy and prolonged artificial ventilation. J Thorac Surg 30:356–367
10. Nilsson E (1951) On treatment of barbiturate poisoning; a modified clinical aspect. Acta Med Scand Suppl 253:1–127
11. Pontoppidan H (2003) The development of respiratory care and the respiratory intensive care unit (RICU): a written oral history. In: Ritz RJ (ed) This is no humbug! Reminiscences from the Department of Anesthesia at the Massachusetts General Hospital – a history. Massachusetts General Hospital, Boston, pp 151–177
12. Bendixin HH, Egbert LD, Hedley-Whyte J, Laver MB, Pontoppidan H (1965) Respiratory Care. Mosby, St Louis, pp 149–150
13. Harrison GA, Tonkin JP (1968) Prolonged (therapeutic) endotracheal intubation. Br J Anaesth 40:241–249
14. Berry PR, Pontoppidan H (1968) Oxygen consumption and blood gas exchange during controlled and spontaneous ventilation in patients with respiratory failure. Anesthesiology 29:177–178
15. Browne AGR, Pontoppidan H, Chiang H, Geffin B, Wilson R (1972) Physiological criteria for weaning patients from prolonged mechanical ventilation. Abstracts of scientific papers, Annual meeting of the American Society of Anesthesiologists, pp 69–70
16. Sahn SA, Lakshminarayan S (1973) Bedside criteria for discontinuation of mechanical ventilation. Chest 63:1002–1005
17. Tahvanainen J, Salmenpera M, Nikki P (1983) Extubation criteria after weaning from intermittent mandatory ventilation and continuous positive airway pressure. Crit Care Med 11:702–707
18. Egan DF (1977) Fundamentals of respiratory therapy. 3rd ed. Mosby, St Louis, pp 456–458
19. Downs JB, Klein EF Jr, Desautels D, Modell JH, Kirby RR (1973) Intermittent mandatory ventilation: a new approach to weaning patients from mechanical ventilators. Chest 64:331–335
20. Venus B, Smith RA, Mathru M (1987) National survey of methods and criteria used for weaning from mechanical ventilation. Crit Care Med 15:530–533
21. Lemaire F (1988) Weaning from mechanical ventilation. In: Ledingham I McA, editor. Recent advances in critical care medicine. Churchill Livingstone, New York, pp 15–30
22. Henning RJ, Shubin H, Weil MH (1977) The measurement of the work of breathing for the clinical assessment of ventilator dependence. Crit Care Med 5:264–268
23. Cohen CA, Zagelbaum G, Gross D, Roussos C, Macklem PT (1982) Clinical manifestations of inspiratory muscle fatigue. Am J Med 73:308–316
24. Tobin MJ, Guenther SM, Perez W, Lodato RF, Mador MJ, Allen SJ, Dantzker DR (1987) Konno–Mead analysis of ribcage–abdominal motion during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 135:1320–1328
25. Tobin MJ, Perez W, Guenther SM, Lodato RF, Dantzker DR (1987) Does rib cage–abdominal paradox signify respiratory muscle fatigue? J Appl Physiol 63:851–860
26. Tobin MJ, Perez W, Guenther SM, Semmes BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR (1986) The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 134:1111–1118
27. Gilbert R, Auchincloss JH Jr, Peppi D, Ashutosh K (1974) The first few hours off a respirator. Chest 65:152–157
28. Tobin MJ, Jubran A (2006) Weaning from mechanical ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill New York, pp 1185–1220
29. Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA (1983) Breathing patterns. 2. Diseased subjects. Chest 84:286–294
30. Tobin MJ, Jenouri G, Birch S, Lind B, Gonzalez H, Ahmed T, Sackner MA (1983) Effect of positive end-expiratory pressure on breathing patterns of normal subjects and intubated patients with respiratory failure. Crit Care Med 11:859–867
31. Tobin MJ (1988) State-of-the-art: Respiratory monitoring in the intensive care unit. Am Rev Respir Dis 138:1625–1642
32. Marini JJ, Capps JS, Culver BH (1985) The inspiratory work of breathing during assisted mechanical ventilation. Chest 87:612–618
33. Marini JJ, Smith TC, Lamb VJ (1988) External work output and force generation during synchronized intermittent mechanical ventilation. Effect of machine assistance on breathing effort. Am Rev Respir Dis 138:1169–1179
34. Brochard L, Pluskwa F, Lemaire F (1987) Improved efficacy of spontaneous breathing with inspiratory pressure support. Am Rev Respir Dis 136:411–415
35. Brochard L, Harf A, Lorino H, Lemaire F (1989) Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis 139:513–521
36. Herrera M, Blasco J, Venegas J, Barba R, Doblas A, Marquez E (1985) Mouth occlusion pressure (P0.1) in acute respiratory failure. Intensive Care Med 11:134–139
37. Sassoon CS, Te TT, Mahutte CK, Light RW (1987) Airway occlusion pressure. An important indicator for successful weaning in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 135:107–113
38. Montgomery AB, Holle RH, Neagley SR, Pierson DJ, Schoene RB (1987) Prediction of successful ventilator weaning using airway occlusion pressure and hypercapnic challenge. Chest 91:496–499
39. Milic-Emili J (1986) Is weaning an art or a science? Am Rev Respir Dis 134:1107–1108
40. Yang KL, Tobin MJ (1991) A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med 324:1445–1450

41. Tobin MJ, Jubran A (2006) Variable performance of weaning-predictor tests: role of Bayes' theorem and spectrum and test-referral bias (submitted for publication)
42. Torres A, Reyes A, Roca J, Wagner PD, Rodriguez-Roisin R (1989) Ventilation–perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. Am Rev Respir Dis 140:1246–1250
43. Beydon L, Cinotti L, Rekik N, Radermacher P, Adnot S, Meignan M, Harf A, Lemaire F (1991) Changes in the distribution of ventilation and perfusion associated with separation from mechanical ventilation in patients with obstructive pulmonary disease. Anesthesiology 75:730–738
44. Jubran A, Mathru M, Dries D, Tobin MJ (1998) Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med 158:1763–1769
45. Bates JH, Baconnier P, Milic-Emili J (1988) A theoretical analysis of interrupter technique for measuring respiratory mechanics. J Appl Physiol 64:2204–2214
46. Polese G, Rossi A, Appendini L, Brandi G, Bates JH, Brandolese R (1991) Partitioning of respiratory mechanics in mechanically ventilated patients. J Appl Physiol 71:2425–2433
47. Guerin C, Coussa ML, Eissa NT, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J (1993) Lung and chest wall mechanics in mechanically ventilated COPD patients. J Appl Physiol 74:1570–1580
48. Tantucci C, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J (1991) Flow resistance in patients with chronic obstructive pulmonary disease in acute respiratory failure. Effects of flow and volume. Am Rev Respir Dis 144:384–389
49. Jubran A, Tobin MJ (1997) Passive mechanics of lung and chest wall in patients who failed or succeeded in trials of weaning. Am J Respir Crit Care Med 155:916–921
50. Jubran A, Tobin MJ (1997) Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med 155:906–915
51. Vassilakopoulos T, Zakynthinos S, Roussos C (1998) The tension–time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med 158:378–385
52. Goldstone JC, Green M, Moxham J (1994) Maximum relaxation rate of the diaphragm during weaning from mechanical ventilation. Thorax 49:54–60
53. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ (2003) Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 167:120–127
54. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F (1994) Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 150:896–903
55. Krieger BP, Ershowsky PF, Becker DA, Gazeroglu HB (1989) Evaluation of conventional criteria for predicting successful weaning from mechanical ventilatory support in elderly patients. Crit Care Med 17:858–861
56. Thorens JB, Kaelin RM, Jolliet P, Chevrolet JC (1995) Influence of the quality of nursing on the duration of weaning from mechanical ventilation in patients with chronic obstructive pulmonary disease. Crit Care Med 23:1807–1815
57. Feinstein AR (1987) The intellectual crisis in clinical science: medaled models and muddled mettle. Perspect Biol Med 30:215–230
58. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, Fernandez R, de La Cal MA, Benito S, Tomas R (1995) A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 332:345–350
59. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF (1996) Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 335:1864–1869
60. Ziman J (2000) Real science: what it is, and what it means. Cambridge University Press, Cambridge, pp 182–245
61. Mendel G (1866) Versuche über Pflanzenhybriden (Experiments on plant hybrids). Verhandl Naturforsch Ver Brunn, Bd IV für das Jahr 1865, Abhandl:3–47
62. Butterfield H (1949) The origins of modern science 1300–1800. Bell, London, p 1
63. Tanenbaum SJ (1994) Knowing and acting in medical practice: the epistemological politics of outcomes research. J Health Politics, Policy and Law 19:27–44
64. Kuhn TS (1962) The structure of scientific revolutions, 3rd edn. University of Chicago Press, Chicago, p 24