

Of Principles and Protocols and Weaning

Half the patients in an intensive care unit receive mechanical ventilation and almost half of intubated time is devoted to weaning. Accordingly, weaning constitutes an enormous workload for intensive care staff (1).

Two deliberate steps are involved in weaning. First, patient readiness is tested with physiological measurements, usually called weaning predictors (2, 3). Second, the patient is evaluated while ventilator support is decreased, gradually or abruptly (4, 5). This two-step approach has been found more dependable than allowing physicians wean in a desultory fashion (6).

But findings reported in this issue of the *Journal* (pp. 673–678) appear to turn accepted wisdom on its head.

In a prospective controlled trial, Krishnan and coworkers (7) compared protocolized weaning with usual care. Patients assigned to protocolized weaning were screened in the morning by a respiratory therapist and stable patients had frequency-to-tidal volume ratio measured. If the ratio was 105 or less, respiratory and nursing staff undertook a spontaneous breathing trial (without physician intervention). If the patient passed the one-hour trial, the physician was informed. Patients failing the assessment were rested until the following day. In the usual care arm, patients were managed at the discretion of their physicians. Patients did not undergo any scheduled screening, although physicians were free to make measurements at the bedside.

Clinical outcomes did not differ between the two groups. Duration of mechanical ventilation, the primary outcome, was equivalent for protocolized weaning and usual care (60.4 versus 68.0 hours), as was the rate of successful weaning (74.7 versus 75.2%).

At first glance, the findings of Krishnan and coworkers (7) suggest that previous research on weaning has not improved clinical practice. But interpretation of information depends on context. In research, special trouble is taken to ensure relevant context by studying a comparison group. Yet data from control groups have served mainly as backdrop, and the spotlight has been shone mostly on the treated group. Today, however, selection of control groups is moving more and more to center stage (8). It is no longer acceptable to compare a new bronchodilator agent against placebo (instead, the new agent must be compared against the best preexisting treatment) (8). Likewise, interpretation of research findings with a new ventilator strategy depends on how the control group is ventilated (9).

Close examination of the control group of Krishnan and coworkers (7) tells us what questions we can and cannot answer with the new data. Do patients weaned according to the usual practice of Hopkins physicians do as well as patients subjected to protocolized weaning? Yes. Do the data indicate that the two-step approach to weaning (testing patient readiness followed by evaluation of the patient as ventilator assistance is deliberately decreased) is unhelpful? No—because that question was not tested. And it is doubtful whether the question could have been satisfactorily tested. To do so, the investigators would have had to compare their 2000–2001 usual care group with matched

patients weaned in their unit before the late 1980s—before the emergence of physiological principles used when weaning a patient today (2–5, 10).

Quantification of usual care is a subject of increasing interest to intensivists (8, 11, 12). It is not easy to capture it in a manner that enables meaningful comparison with a new management strategy. Usual care also changes constantly—as every malpractice attorney knows. To see how care of the weaning patient has changed over time, I opened a text from my fellowship years. Discussing weaning prediction and readiness for extubation, the author writes: “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” (13). Today, we know that most patients can be extubated after a spontaneous breathing trial lasting only a half hour (14).

What other lessons can we learn from the new data? One, the study shows that it’s possible to include usual care as a control group when doing research on ventilator protocols in an intensive care unit—the second such study by Krishnan and collaborators. These investigators previously reported the outcome of patients with the acute respiratory distress syndrome ventilated according to usual practice (from their study of patients refusing to participate in the ARDS Network trial) (15).

Two, we need to make a distinction between the use of algorithms in research protocols and their subsequent application in everyday practice. When formulating a research algorithm, each step must be specified with exacting precision (16). In the trial of Krishnan and coworkers, patients who had a frequency-to-tidal volume ratio of 104 or less progressed to a spontaneous breathing trial whereas patients with a ratio of 105 or higher were returned to the ventilator (for another day). And this is exactly how a protocol for a controlled trial must be specified and followed (16). No flexibility. No weasel words. But a competent clinician would think it daft to slavishly comply with a protocol that decided an entire day of ventilator management on a one-unit difference in a single measurement of frequency-to-tidal volume ratio. An intelligent physician who customizes knowledge generated by a previous research protocol to the particulars of each patient is expected to outperform the inflexible application of that protocol—as reflected by the longer time between initiation of a spontaneous breathing trial and extubation in the protocolized versus usual care group: 3.0 versus 1.6 hours. It is not the inflexibility of an algorithm that we want when caring for patients, but the new physiological principles that arise from successful testing of the algorithm.

In the study of Krishnan and coworkers, the question is not what went wrong with protocolized weaning but what was right with usual care. Physicians are adept at extracting principles that emerge from research studies and incorporating them into their everyday practice. Once these principles have crept into a clinician’s brain, they cannot be extirpated surgically. To interpret the study as saying it’s not necessary to undertake weaning in a deliberate manner would be to throw a physiological baby out with the protocolized bath water.

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Lung Infection and the Diaphragm

Placing Basic Research in Clinical Perspective

Our understanding of respiratory muscle dysfunction induced by sepsis has advanced markedly in the last 20 years: different mechanisms have been proposed (alterations in calcium homeostasis, mitochondrial dysfunction, and sarcolemal injury) and the role of several mediators (proinflammatory cytokines, reactive oxygen species, and nitric oxide) has been characterized (1). Despite these advances, however, several unresolved questions remain.

In this issue of the *Journal* (pp. 679–686), Divangahi and coworkers show, for the first time, that *Pseudomonas aeruginosa* lung infection lasting for 7 days induces significant diaphragmatic weakness without change in the strength of hindlimb muscles (2). Because respiratory mechanics were unchanged during the entire experimental period, diaphragmatic fatigue seems an unlikely cause of the muscle weakness. This study sets the stage to discuss two clinically relevant features of respiratory muscle pathophysiology that are still relatively underinvestigated: the effects of infections arising in thoracic or abdominal organs; and the effects of chronic infections.

Respiratory failure is a common complication of severe infectious or inflammatory processes originating in organs or tissues of the abdominal and thoracic cavities, such as peritonitis, pancreatitis, or pneumonia. These pathological conditions can theoretically affect the diaphragm directly by contiguity. Relatively few investigators have examined the effects of acute peritonitis and pancreatitis on the diaphragm in animals (3–6); they showed a significant reduction in diaphragmatic strength, as observed by Divangahi and coworkers (2) with lung infection. Preferential weakness of the respiratory muscle was also observed with necrotizing pancreatitis in rats (5), the only study investigating the effects of abdominal processes that compared the diaphragm

and hindlimb muscles. In contrast with these data, systemic inoculation of two boluses of *Escherichia coli* endotoxin in hamsters produced equivalent decreases in the strength of the diaphragm and a fast-twitch peripheral muscle (7). Divangahi and coworkers (2) hypothesize that both muscle activity (sustained in the case of the diaphragm) and topographic proximity between the respiratory muscle and the inflamed lung could be responsible for its selective weakness. This is also probably true in the case of abdominal disorders. Diaphragmatic histology was normal and muscular levels of myeloperoxidase, a marker of neutrophil infiltration, did not increase in either the muscle of the *Pseudomonas*-infected animals (2) or in animals with pancreatitis and peritonitis (3, 5), thus excluding direct extension of the infectious/inflammatory process to the muscle. Anatomical proximity to the infectious site could, however, be responsible for direct exposure of the diaphragm to bacteria and/or inflammatory mediators synthesized in the infected organ via direct lymphatic spread (8). Another pathway might involve mediators synthesized by activated macrophages and/or mesothelial cells of the pleural or peritoneal surfaces of the muscle. These mediators could, in turn, act on the underlying diaphragm, as seen in the heart, where mediators released by the cardiac endothelium act on the underlying myocardium (9).

The results of Divangahi and coworkers (2), showing diaphragmatic impairment 7 days after the bacterial inoculum, are of clinical importance because long-lasting infections are common. Few investigators have examined the effects of chronic or semichronic infections on the respiratory muscles. Drew and associates (10) studied the effects of chronic visceral leishmaniasis on the diaphragm and hindlimb muscles of hamsters. They noted atrophy of all muscles and a selective loss in force of a