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Postextubation Respiratory Support: Of Clinical Trials and Clinical Decisions

Hardly a day goes by in the ICU without the lament arising at some point on rounds that “there are no data” to inform some challenging clinical decision. Daily rounds in the ICU occasion hundreds, if not thousands, of clinical decisions by the interdisciplinary team. Very few of these decisions can be made with explicit reference to a specific clinical trial; too often we can only acknowledge that “we need a trial.” Yet clinical trials are costly, time-consuming, and burdensome affairs. It is easy to say that we need a trial; it is quite another thing to actually make the trial happen. Thus, clinicians are left to make most of their decisions using judgment informed by experience and mechanistic understanding, giving rise to considerable variation in practice (and outcomes) between centers and countries (1).

One approach to address this pressing need for trials is “learning while doing” (2). Advocates of this pragmatic research philosophy envision a “learning health system” that incorporates randomization to various treatments as part of routine clinical care (3), reflecting the genuine clinical equipoise and uncertainty that clinicians have over specific clinical decisions. It is a compelling and lofty vision but one that has, to date, achieved only limited implementation.

In this issue of the *Journal*, Casey and colleagues (pp. 294–302) report a pragmatic clinical trial (PROPER [Protocolized Post-Extubation Respiratory Support]) that provides an important and instructive exemplar of the learning health system concept in critical care medicine (4). They studied postextubation respiratory support, inquiring whether a strategy of routine postextubation respiratory support by either high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV) was superior in terms of reintubation rate in comparison to usual care (which, in their ICU, meant NIV for high-risk

patient groups). These forms of postextubation respiratory support have some proven efficacy to reduce the risk of reintubation (5). The PROPER trial compared a pragmatic strategy of postextubation respiratory support in “all-comers” as compared with the usual strategy of selectively applying postextubation respiratory support according to clinical judgment. The main effect of the routine postextubation respiratory support strategy was to dramatically increase the use of HFNC after extubation (75% vs. 3%); the use of NIV was similar under both strategies (18% vs. 14%). The trial demonstrated a small and “nonsignificant” difference in the risk of reintubation between strategies (16% vs. 13%), with a low posterior probability of any benefit under varying priors.

These findings are of considerable interest to the clinical community. The data suggest that, in a similar medical ICU population, routine use of postextubation respiratory support (especially HFNC) does not improve outcome in comparison to selective application of postextubation respiratory support based on established risk categories (chronic hypercapnia, etc.). But we suggest that clinicians should sit up and especially take notice of the almost breathtakingly simple and cost-effective manner in which the trial was conducted. The investigators divided their ICU in half, treating the individual beds in each half as a cluster. The two strategies under investigation were applied alternately between clusters over time. The strategies were pragmatic and respiratory therapist led. The primary outcome (reintubation) was rapid and easily ascertained. And the success of the approach—more than 700 patients randomized at a single center in less than 2 years to achieve a definitive answer to an important pragmatic clinical question—is undeniable. The PROPER trial convincingly demonstrates the potential of the learning health system concept to resolve simple, pragmatic research questions in a timely fashion. For this the investigators must be congratulated.

In view of the results of the PROPER trial, work remains to be done to improve our understanding of the mechanisms leading to postextubation respiratory distress and need for reintubation—on this point, methods to assess and enhance expiratory muscle function deserve greater attention (6), as also noted by the PROPER investigators. A mechanistic understanding is especially important to accurately

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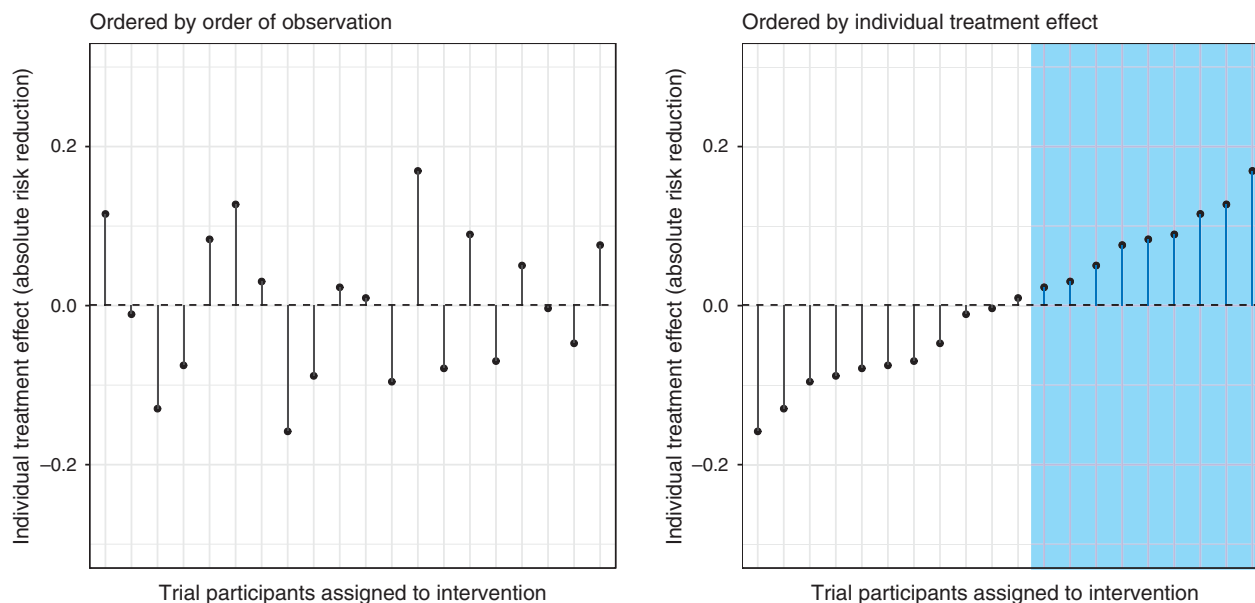


Figure 1. Average treatment effect (dashed line) and individual treatment effect (points) in a theoretical population of patients enrolled in a trial. Treatment is appropriate in patients with a favorable individual treatment effect (blue shaded region). Designing trials with the goal of learning individual treatment effect will maximize the relevance of clinical trials to clinical decisions.

identify individual patients who are most likely to benefit from postextubation respiratory support. Just because there was, on average, no improvement in outcome between groups does not entail that none of the individual patients accrued benefit from the intervention.

And here we must address the more general issue of moving from clinical trials to clinical decisions. The reported treatment effect in a trial represents an “average treatment effect” (ATE), the mean of many values for “individual treatment effect” (ITE) for each patient included in the trial (Figure 1). Depending on the heterogeneity of the population, the ITE may differ considerably from the ATE in some patients. Clinical decisions for individual patients are ideally based on an informed estimate of the ITE for the patient at the center of the clinical encounter, not the ATE for the heterogeneous population that happens to include the patient. In the PROPER trial, there were signals of possible variation in treatment effect among patient subgroups, especially based on duration of ventilation before randomization. The possibility that some patients can benefit from routine use of postextubation respiratory support cannot therefore be ruled out. Trials can be designed to adapt sample size requirements as the trial progresses to ensure sufficient information to definitively rule in or rule out treatment benefit in homogeneous subgroups of patients, and advances in analysis of data from trials can move us closer to estimates of ITE for each patient (7, 8). The learning health system approach could facilitate accrual to feasibly achieve the larger sample sizes needed for such designs. Combining the learning health system concept with adaptive designs that account for heterogeneity of treatment effect could substantially inform and improve clinical decision-making for individual patients.

In sum, by making learning and discovery a formal part of patient care, perhaps some decisions on ICU rounds may eventually be a little easier. ■

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⊕ The Staying Power of Pressure- and Volume-limited Ventilation in Acute Respiratory Distress Syndrome

Titration of mechanical ventilator support is a key modifiable determinant of morbidity and mortality in patients with acute respiratory distress syndrome (ARDS). Limiting V_T and plateau pressure (Pplat) attenuates ventilator-induced lung injury (VILI), extrapulmonary organ failure, and risk of death in ARDS (1). However, uncertainty lingers over whether common clinical targets (e.g., V_T 6–8 ml/kg predicted body weight [PBW]; Pplat 30 cm H₂O or less) are ideal for all patients with ARDS, sparking interest in other bedside measures that might help guide V_T selection, including airway driving pressure (ΔP ; $\Delta P = P_{\text{plat}} - \text{positive end-expiratory pressure [PEEP]}$) (2). Experimental data suggest other modifiable characteristics of ventilator support also might modulate mechanical lung injury, including PEEP, respiratory rate, and air flow (3–5).

Mechanical power has been proposed as a unifying metric to quantify total VILI risk (6). Mechanical power, which reflects the energy delivered by the ventilator to the respiratory system per unit time, is computed in J/min as $0.098 \times \text{respiratory rate} \times V_T \times (\text{PEEP} + 0.5\Delta P + [\text{peak pressure} - P_{\text{plat}}])$. This empirical formulation for power is associated with VILI in preclinical models and with mortality in cohort studies (7, 8), but whether it properly weights clinical importance (if any) of each component is uncertain. Moreover, the components of mechanical power often move in competing directions, leaving clinicians who seek to “minimize mechanical power” without a clear bedside strategy. For example, attempts to limit V_T and ΔP will generally reduce V_E , but compensatory increases in respiratory rate can increase power. Increases in PEEP can also cause increases in mechanical power when unaccompanied by adequate reduction in ΔP . Therefore, clinicians using the concepts of mechanical power at the bedside are faced with a challenge: which ventilator parameters are most important to attenuating VILI and improving patient outcomes?

In this issue of the *Journal*, Costa and colleagues (pp. 303–311) explore associations between the often-competing components of

mechanical power and mortality (9). The authors address associations between components of power and mortality using data from 4,549 patients with ARDS undergoing controlled mechanical ventilation. Their retrospective analysis included patients from six randomized trials—ranging from early trials of pressure-volume limitation (1) to more recent trials of PEEP titration (10, 11)—as well as observational data from the Medical Information Mart for Intensive Care III single-center electronic health record database from years 2001–2012. Costa and colleagues performed multiple analyses to evaluate the association of 60-day mortality with total mechanical power and its major subcomponents: elastic static power (differentiated by the PEEP component), elastic dynamic power (the ΔP component), and resistive power (the peak pressure minus Pplat component). The authors then used directed acyclic graphs to demonstrate their assumptions regarding pathways of confounding and to choose covariates for models evaluating the association between mechanical power and mortality. Additional mediation analyses using only the randomized trial data explored whether ΔP and respiratory rate mediated associations between randomly assigned pressure-limited ventilation or higher PEEP strategies with mortality.

Results showed that, of all the components of mechanical power, only ΔP and respiratory rate were significantly associated with mortality in the multivariable-adjusted model. From this model, the authors estimated that each 1-cm H₂O increase in ΔP was associated with a fourfold higher mortality risk as compared with each 1 breath/min increase in respiratory rate, yielding an equation ($4 \times \Delta P + \text{respiratory rate}$) that the authors suggest could be used at the bedside to estimate the relative benefits of changing ΔP or respiratory rate. Only the elastic dynamic component of power (determined by ΔP) was associated with mortality in multivariable models, whereas static and restrictive components were not associated with mortality. In addition, the authors showed that associations between ΔP and respiratory rate with mortality risk were dependent on respiratory system compliance—patients with higher compliance were predicted to benefit slightly more from lower respiratory rates, even at the expense of higher V_T (and higher ΔP), whereas patients with low compliance were predicted to benefit more from a lower V_T (and ΔP) at the expense of high respiratory rates. Results showing ΔP as the primary factor influencing associations between mechanical power and mortality, with a lower contribution from respiratory rate, were supported by a number of sensitivity and

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