Physiology Is Vital to Precision Medicine in Acute Respiratory Distress Syndrome and Sepsis

The American Thoracic Society recently released a thoughtful and forward-thinking statement outlining a research agenda for precision medicine in sepsis and acute respiratory distress syndrome (ARDS). The statement draws attention to the problem of highly variable treatment responsiveness in these heterogeneous syndromes and proposes a range of promising solutions to address this problem, with a focus on enhanced molecular phenotyping and novel trial designs (1). This approach is predicated on an overarching hypothesis that the molecular contents of biospecimens contain the key to unlocking patient heterogeneity for precision-guided therapy for sepsis and ARDS. Although this hypothesis is very attractive and will undoubtedly yield exciting discoveries and therapies in the future, we suggest that the focus on molecular measurements is too narrow and overlooks critical readouts of systems biology, yielding an incomplete data set for precision medicine. We contend that physiology remains an important and feasible means to understand and predict heterogeneity of treatment effect. It has a proven record of success and can be used in real time to monitor and tailor treatment.

The concept of precision medicine can carry multiple meanings. Applied to individual patients, it connotes the tailoring of treatments to some optimal dose or setting according to a patient's individual characteristics. Physiology, including the information obtained from laboratory tests (e.g., blood gases), vital signs and hemodynamics (e.g., blood pressure), point-of-care ultrasound, and echocardiography, is routinely used to this end in the ICU (e.g., titration of ventilator settings, vasopressors, and inotropes). This tailoring relies on the individual patient's physiological response, (often) in real time to the specific intervention, and how that intervention interacts with the patient's host response to the particular insult (e.g., infection or trauma). The tailoring is also dependent on some understanding of the relationship between physiological parameters and the benefit or harm of the therapy, an understanding often derived from experimental physiology (e.g., plateau pressure and the risk of barotrauma).

Applied to populations of patients, precision medicine connotes the selection of subgroups of patients for treatment on the basis of characteristics that suggest a higher probability of benefit. In discussions of this type of precision, increasing attention has focused on treatment responsiveness defined by molecular biological phenotypes (2), but here we also contend that physiology has an important role to play. For example, phenotypes based on molecular biomarkers may predict whether a broadly "liberal" or "conservative" fluid strategy is more likely to be of benefit in ARDS (3), but it is targeting fluid therapy to physiological parameters such as change in capillary refill time that may result in lower mortality and faster resolution of organ dysfunction in patients with septic shock (4).

As a discipline studying the mechanisms of living organisms, physiology aims to assess and understand the integrated function of organ systems. There is compelling evidence that systematic assessment of whole-organ function can be used to identify treatment-responsive subpopulations across a range of interventions in ARDS and sepsis. Distinct clinical phenotypes of ARDS have been detected using physiological markers as well as molecular characteristics (5). Physiological parameters can predict not only prognosis but also treatment effect and can do so dynamically over time. For example, higher positive end-expiratory pressure probably benefits only patients with significant potential for lung recruitment as measured by lung mechanics and imaging (6). Dead space and respiratory system elastance identify patients with a greater clinical response to extracorporeal CO_2 removal (7). Respiratory system elastance appears to identify patients who will (and who will not) benefit from lowering V_T from 10–12 ml/kg to 4–8 ml/kg (8). Physiological markers of fluid responsiveness may be useful to determine whether patients are likely to benefit from further volume resuscitation (9, 10). Clinical physiology remains relevant and relatively easy to implement at the bedside to identify patients who are potentially more or less likely to benefit from a specific therapy.

Of course, as with molecular markers, trials are required to confirm clinically relevant treatment benefits in subsets of patients defined by these physiological markers. Only those physiological characteristics that reflect the mechanisms that drive injury and outcomes will be relevant to personalizing care. Many physiological markers do not predict the relative benefit or harm of treatment, even those that usefully stratify the risk of death. For example, the benefit of lung-protective ventilation is unrelated to the severity of hypoxemia, as lung-protective ventilation in any given patient may be associated with worsened oxygenation but improved mortality (11), and the effect of lowering V_T on mortality is independent of the severity of hypoxemia (8). In contrast, elastance and driving pressure, which reflect mechanistically relevant lung stress and strain, provide more appropriate targets for personalizing V_T (8).

The uses of physiology and physiological responsiveness for precision medicine in a prospective trial design have already been described (6, 7). The recent multiplatform trial of therapeutic anticoagulation with heparin in coronavirus disease (COVID-19) provides an instructive example of using both physiology and biomarkers in trial design for precision medicine (12). At the outset, the investigators hypothesized that treatment effect may vary according to both the patient's physiological state (severely ill, requiring ICU-level organ support, vs. moderately ill, not requiring organ support) and by baseline D-dimer (a biomarker hypothesized to reflect hypercoagulation from COVID-19). Implementing some of

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the trial design principles outlined by Shah and colleagues (1), the trial was designed to reach conclusions about treatment effect within each of these states. States with similar treatment effects could be functionally combined in a hierarchical model to increase effective sample size and statistical precision (thereby minimizing the potential statistical costs of splitting the population to test precision medicine hypotheses). In this trial, physiology, rather than a molecular marker, proved to be the more relevant predictor of treatment effect. The probability of harm was high in patients with severely deranged physiology requiring ICU-level organ support, and the probability of benefit was high in patients without severe organ dysfunction. On the other hand, the difference in treatment effect according to baseline D-dimer concentration among patients not critically ill was comparatively smaller. Of course, other biomarkers or other cut points for D-dimer than were chosen for the trial may have more clearly stratified relative benefit, but the major conclusion remains the same: physiology has an important potential role to play in determining (or at least predicting) treatment effect, and it would be a mistake to disregard it.

Admittedly, we must be careful to avoid the "seduction" of physiology (13). Our field has learned repeatedly that targeting "normal physiology" can cause patients more harm than benefit. Yet predicting treatment effects on the basis of physiological parameters does not require us to assume that "normal physiology" is always better. In any case, molecular biology can be seductive too. The molecular marker or phenotype that will transform care for patients with ARDS and sepsis always seems to be just around the corner. We should also acknowledge that to date, biomarker-based precision medicine has yielded limited benefits at a substantial increase in financial cost (14). Physiology-based precision medicine is likely to be more useful in monitoring moment to moment therapeutic efficacy, which is particularly important in the critical care setting, as well as being more feasible and cost-effective than molecular biomarkers.

Ultimately, we would argue that the most promising way forward is to deploy both approaches, integrating a continually evolving mechanistic understanding with agnostic big-data techniques in the search for seemingly ever-elusive therapies for individual critically ill patients. ■

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