Sometimes It Is Okay to Get Personal: Individualizing Targets in Critical Care

"Personalized medicine" is defined as treatment informed by a patient's genetic or biochemical makeup (1, 2). Although the most robust evidence for this approach lies in cancer care, rigorous analyses of patients with sepsis (3) and acute respiratory distress syndrome (4–6) suggest that individualized biomarker-based therapeutic strategies may benefit critically ill patients. Such detailed information is often not clinically available, however. Yet, more readily attainable potentially useful patient data abound, which can allow us to begin personalizing critical care delivery (Figure 1).

In this issue of the *Journal*, Panwar and colleagues (pp. 1407–1418) evaluated the association of a personalized exposure, "relative hypotension," with acute kidney-related outcomes in a cohort of adults with shock and respiratory failure in Australia (7). Meant to capture both the magnitude and duration of time spent below premorbid blood pressure, "relative hypotension" was defined, primarily, as the time-weighted average of the "mean perfusion pressure deficit"—the percent difference between each patient's mean perfusion pressure (mean arterial pressure [MAP] − central venous pressure) while on vasopressors and their premorbid mean perfusion pressure (Figure 2). Additional exposures consisted of a similarly calculated "MAP deficit" and time with a MAP <65 mm Hg. Co–primary outcomes included significant acute kidney injury (AKI: a peak serum creatinine ⩾2 × preillness creatinine) and major adverse kidney events (death, new renal replacement therapy, or significant AKI) within 14 days of vasopressor initiation. To be included, patients had to receive vasopressors for ⩾4 hours; those with end-stage renal disease or AKI in imminent need of renal replacement therapy were excluded.

Notably, 300 out of 302 patients were exposed to some degree of mean perfusion pressure deficit during their shock episode. Across the cohort, the median time-weighted average mean perfusion pressure deficit was 19% (interquartile range, 13–25%). Similarly, the median time-weighted average MAP deficit was 9% (4–15%). Yet, only 1% (0–9%) of all patient-time points had a MAP <65 mm Hg. Taken together, these data demonstrate that patients experienced near-universal relative hypotension despite near-complete maintenance at target MAP (⩾65 mm Hg).

This disconnect between achieving absolute success while failing on a relative scale is one that may apply to much of critical care. For instance, is it correct to target a partial pressure of carbon dioxide of 40 during mechanical ventilation for a patient with emphysema whose premorbid partial pressure of carbon dioxide is 60? If successful, their compensatory metabolic alkalosis would evaporate, leaving them unprepared for extubation. It is uncomfortable to strive for a person's "normal state" when that state, in the abstract, strikes us as abnormal. We do not treat a marathon runner's bradycardia with dopamine, however; on some level, we know that normal is relative.

Panwar and colleagues also found that relative hypotension, but not the time with MAP <65 mm Hg, was associated with worse outcomes in a dose-dependent manner. Specifically, for each percentage point increase in blood pressure deficit, there was a clinically meaningful increase in the odds of significant AKI (adjusted odds ratio [95% confidence interval]: mean perfusion pressure deficit, 1.056 [1.022–1.091]; MAP deficit, 1.059 [1.021–1.099]) and major adverse kidney events (mean perfusion pressure deficit, 1.059 [1.022–1.098]; MAP deficit, 1.062 [1.021–1.005]); no such association was found with absolute hypotension. Moreover, inclusion of either measure of relative hypotension improved model accuracy in predicting adverse kidney-related outcomes; adding time with MAP <65 mm Hg did not.

These results add to a growing literature suggesting that abandoning a one-size-fits-all approach to shock resuscitation may alter care delivery and, potentially, patient outcomes. Using data from four ICUs in Calgary, we determined that patients' premorbid blood pressure was inversely associated with adjusted median vasopressor duration—1.35 days if premorbid blood pressure was low, 1.04 if normal, and 0.84 if high (8). In a subgroup analysis of patients with chronic hypertension from a randomized controlled trial, Asfar and colleagues found that targeting a MAP of 80–85 mm Hg (vs. 65–70 mm Hg) in septic shock resulted in a lower odds of requiring renal replacement therapy (odds ratio [95% confidence interval]: 0.64 [0.41–0.99]) (9).

In this context, Panwar and colleagues' work compels consideration of two questions:

What Drives the Association of Relative Hypotension with Poor Outcomes?

As the authors note, "patients with shock are commonly exposed to a significant *degree and duration* of relative hypotension." What is less clear, however, is whether the *degree* or the *duration* (or both) may matter. The cleverness of their exposure definition as a time-weighted average of the blood pressure deficit is its ability to combine the magnitude of instantaneous pressure differences with the time spent below premorbid values. This strength is also a weakness, though, as it is impossible to disentangle the effects of one from the other. Understanding the impact of each would allow for improved real-time prognostication and, potentially, more optimal resuscitation management.

How Can We Best Operationalize Personalized Medicine in Critical Care?

One of the challenges of personalized medicine is the difficulty obtaining needed data (e.g., biomarker panels). Panwar and colleagues

Originally Published in Press as DOI: 10.1164/rccm.202007-2728ED on July 30, 2020

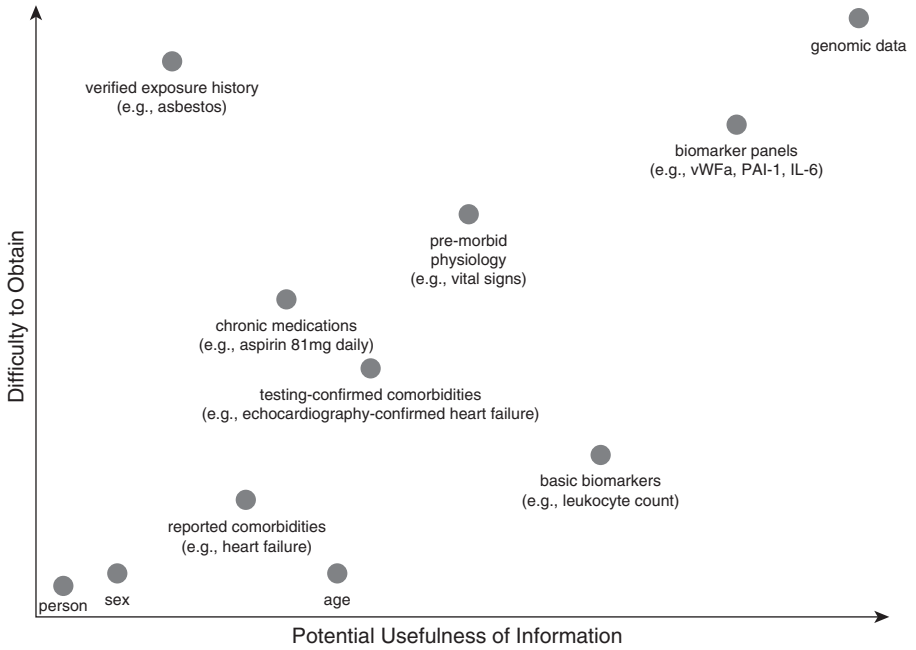

Figure 1. Theoretical model balancing challenges obtaining personalized patient data and the data's value for clinical decision making. PAI-1 = plasminogen activator inhibitor-1; vWFa = von Willebrand factor antigen.

force us to reconceptualize "needed data," however—premorbid vital signs rather than blood tests or genes. This is not to say that such personalization is easy. Barriers to real-world use of mean perfusion pressure deficit as defined by Panwar and colleagues exist.

Specifically, patients required at least two premorbid blood pressures (preferably from outpatient, overnight recordings) and, ideally, a right-heart catheterization to determine baseline central venous pressure. Only 78 out of 1,283 screened patients (6%) had missing

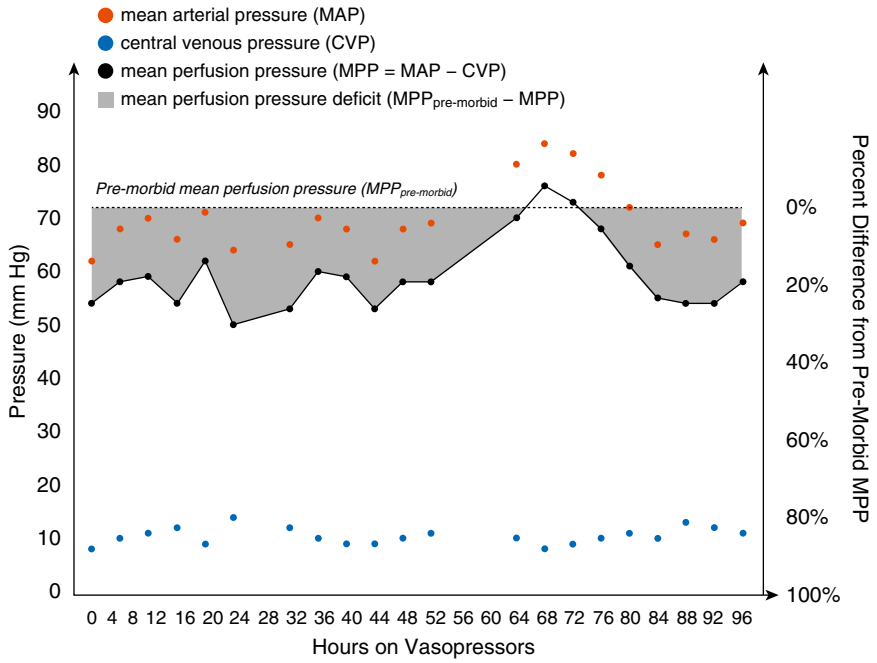

Figure 2. Pictorial depiction of mean perfusion pressure deficit. Depiction of an example patient who received vasopressors for 96 hours, during which three MAP and CVP recordings were missing (at hours 28, 56, and 60). The patient's premorbid MPP (72 mm Hg) was determined from two overnight (105/58 mm Hg and 102/62 mm Hg) and one daytime (118/70 mm Hg) outpatient recordings using the algorithm outlined in Panwar and colleagues' Table E2 (7) assuming no history of heart disease (CVP = 2 mm Hg). The time-weighted average MPP deficit = 17.7%. CVP = central venous pressure; MAP = mean arterial pressure; MPP = mean perfusion pressure.

premorbid blood pressures; however, it is unclear if this rate is generalizable to settings with less interconnected electronic health records (e.g., the United States). Out of the 302 included patients, none had a right-heart catheterization; premorbid central venous pressure was instead estimated from echocardiography (25%) or cardiac disease history (75%). Using MAP deficit may be more pragmatic, therefore, given its relatively similar performance characteristics and reliance on less premorbid data.

Randomized controlled trials to assess the value of individualized blood pressure targets are warranted. Such personalization is not antithetical to protocolization. Rather, protocolized tailoring of vasopressor titration based on individualized targets—akin to protocolized tailoring of ventilator settings based on predicted body weight (10)—may allow us to realize the best of both worlds: standardization with a personal touch. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Hayley B. Gershengorn, M.D.
Division of Pulmonary, Critical Care, and Sleep Medicine
University of Miami Miller School of Medicine
Miami, Florida
and
Division of Critical Care Medicine
Albert Einstein College of Medicine
Bronx, New York

ORCID ID: 0000-0002-7360-2489 (H.B.G.).

References

1. US Food & Drug Administration. Personalized medicine: a biological approach to patient treatment. 2016 [accessed 2020 Jul 7]. Available from: https://www.fda.gov/drugs/news-events-human-drugs/personalized-medicine-biological-approach-patient-treatment.
2. National Cancer Institute. Dictionary of cancer terms: personalized medicine. [accessed 2020 Jul 7]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/personalized-medicine.
3. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, *et al*. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* 2019;321:2003–2017.
4. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, *et al*.; Irish Critical Care Trials Group. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018;6:691–698.
5. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, *et al*.; ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017;195:331–338.
6. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2:611–620.
7. Panwar R, Tarvade S, Lanyon N, Saxena M, Bush D, Hardie M, *et al*.; REACT Shock Study Investigators; ANZICS Clinical Trials Group. Relative hypotension and adverse kidney-related outcomes among critically ill patients with shock: a multicenter prospective cohort study. *Am J Respir Crit Care Med* 2020;202:1407–1418.
8. Gershengorn HB, Stelfox HT, Niven DJ, Wunsch H. Association of premorbid blood pressure with vasopressor infusion duration in patients with shock. *Am J Respir Crit Care Med* 2020;202:91–99.
9. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, *et al*.; SEPSISPAM Investigators. High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014;370:1583–1593.
10. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.

Spelunking in Sputum: Single-Cell RNA Sequencing Sheds New Insights into Cystic Fibrosis

Cystic fibrosis (CF) is autosomal recessive disease caused by mutations in the CFTR (CF transmembrane conductance regulator) gene, which leads to chronic pulmonary disease and gastrointestinal abnormalities through the loss of CFTR-mediated chloride and bicarbonate transport (1, 2). Clinically, the lung disease is characterized by chronic neutrophilic inflammation with bacterial airway infection, especially by *Pseudomonas aeruginosa*, which can lead to progression of CF lung disease, the primary cause of morbidity and mortality in CF (3). Although the dominant inflammatory cells in CF sputum are neutrophils, other cells including macrophages, eosinophils, T cells, and B cells have been reported in sputum and BAL fluid (4). However, much of this analysis has been morphological or based on flow cytometry with prespecified antibody panels, which by definition introduce some bias to the analysis. There have been prior bulk RNA sequencing (RNAseq) studies that found clear evidence of excessive inflammation, dominated by neutrophils, as well as type 1 and type 17 inflammation (5, 6). In this issue of the *Journal*, Schupp and colleagues (pp. 1419–1429) conducted an unbiased analysis by performing single-cell RNAseq analyses in sputum between nine CF subjects and five healthy control subjects (7).

The authors found a cluster of recruited lung mononuclear phagocytes in CF sputum and identified three different archetypes of monocytes: activated monocytes, monocyte-derived macrophages,

Supported by the NHLBI (R35HL139930).

Originally Published in Press as DOI: 10.1164/rccm.202006-2456ED on July 28, 2020