COVID-19 Pathophysiology: An Opportunity to Start Appreciating Time-Dependent Variation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains pandemic more than 2 years after its first occurrence in Wuhan, China. To date, coronavirus disease (COVID-19) has resulted in substantial morbidity and caused more than 5 million deaths worldwide (1). In this relatively short period of time, which may feel like an eternity, major advances have been made in understanding the pathophysiology of this new virus (2). Much attention has been drawn to the endothelial injury provoked by the virus and how this differs from other common respiratory pathogens.

In this issue of the *Journal*, Leisman and colleagues (pp. 507–519) present novel and exciting data on dynamic changes in biomarker levels representative of alveolar injury, endothelial activation, and organ injury (3). In a cohort of 225 patients, included in the first wave of COVID-19, before effective treatment became available, patients were sampled on admission and, if still hospitalized, on Day 3 and Day 7. A wide array of biomarkers was measured using Olink proximity extension assay, and the authors selected biomarkers reflective of the pathophysiological processes of interest. Using this serial approach, the authors meticulously showed that levels of alveolar injury markers decreased over time in both mechanically ventilated and spontaneously breathing patients. Patients with more severe respiratory failure had higher biomarker concentrations of alveolar injury markers at baseline (Figure 1A). Interestingly, alveolar injury marker concentrations dropped markedly during invasive mechanical ventilation. When analyzing markers representative of more systemic disease, endothelial markers and nonpulmonary organ injury markers were somewhat delayed and showed an increase in critically ill patients from Day 3 onward (Figure 1B). In addition, these endothelial markers better predicted 28-day outcomes. In this nicely executed work, the authors show that alveolar injury happens early in the disease process, followed by endothelial injury and activation.

The article by Leisman and colleagues provides relevant insight into the pathophysiological order of events in patients admitted with COVID-19. From early in the pandemic, much has been speculated on the primary disease process in this disease. Many have argued that endothelial dysfunction and injury are the driving force behind the occurrence of respiratory failure (4, 5). This could explain severe hypoxemia in the presence of a relatively well-aerated lung, may cause pulmonary embolism via *in situ* thrombosis, and might provide a therapeutic target. Yet, the data provided by Leisman and colleagues suggest a reverse order of events: patients developing respiratory failure requiring invasive ventilation first show signs of alveolar injury, followed by endothelial injury and systemic inflammation.

As mentioned by the authors, a limitation is the observational study of the systemic compartment alone. Using protein levels in plasma, we cannot draw any conclusions on how alveolar injury is initiated and why it would initiate such a cascade of endothelial dysfunction and systemic inflammation. Clearly, the alveolar side of the equation is of particular interest. An uncontrolled host response in the alveolus is difficult to assess but would result in the observed injury and could explain the positive effect of corticosteroids. A slowly unfolding alveolitis driven by macrophages has indeed been described (6).

The biological heterogeneity in patients with COVID-19 brings to mind similarities with the variation observed in patients with acute respiratory distress syndrome due to other causes (7). Indeed, Sinha and colleagues recently showed that the hyperinflammatory and hypoinflammatory subphenotypes derived from non–COVID-19–related acute respiratory distress syndrome populations can be identified in patients with COVID-19 as well and that biological subphenotypes might drive response to immunomodulation with steroids (8).

The data presented by Leisman and colleagues suggest that time could influence subphenotype membership, as indicated by IL-6 and TNFRI dynamics, and should be considered in future studies of systemic host response. Therefore, studies such as this one provide an opportunity to start appreciating time-dependent variation. For example, this paper and another large study using serial biomarker systemic measurements consistently show angiopoietin 2, a marker of endothelial dysfunction, is found in higher concentrations in the plasma of patients requiring ICU treatment and that the temporal change in this biomarker is prognostic in this population (9). Ventilatory ratio trajectories have also been identified in this patient group (10), and dynamic changes in this surrogate of dead space ventilation are confirmed in the study by Leisman and colleagues. However, no relation with endothelial dysfunction markers and ventilatory ratio change was found, which may suggest that these two phenomena do not share the same pathophysiology as microvascular thrombosis.

So how should we incorporate time in future biological studies? We should start appreciating individual patient trajectories rather than solid state alone by repeated sampling and appropriate statistical testing (such as linear mixed-model analysis, joint models, or time-dependent latent class analysis, depending on the question at hand). Using these methodologies, we will learn that longitudinal data

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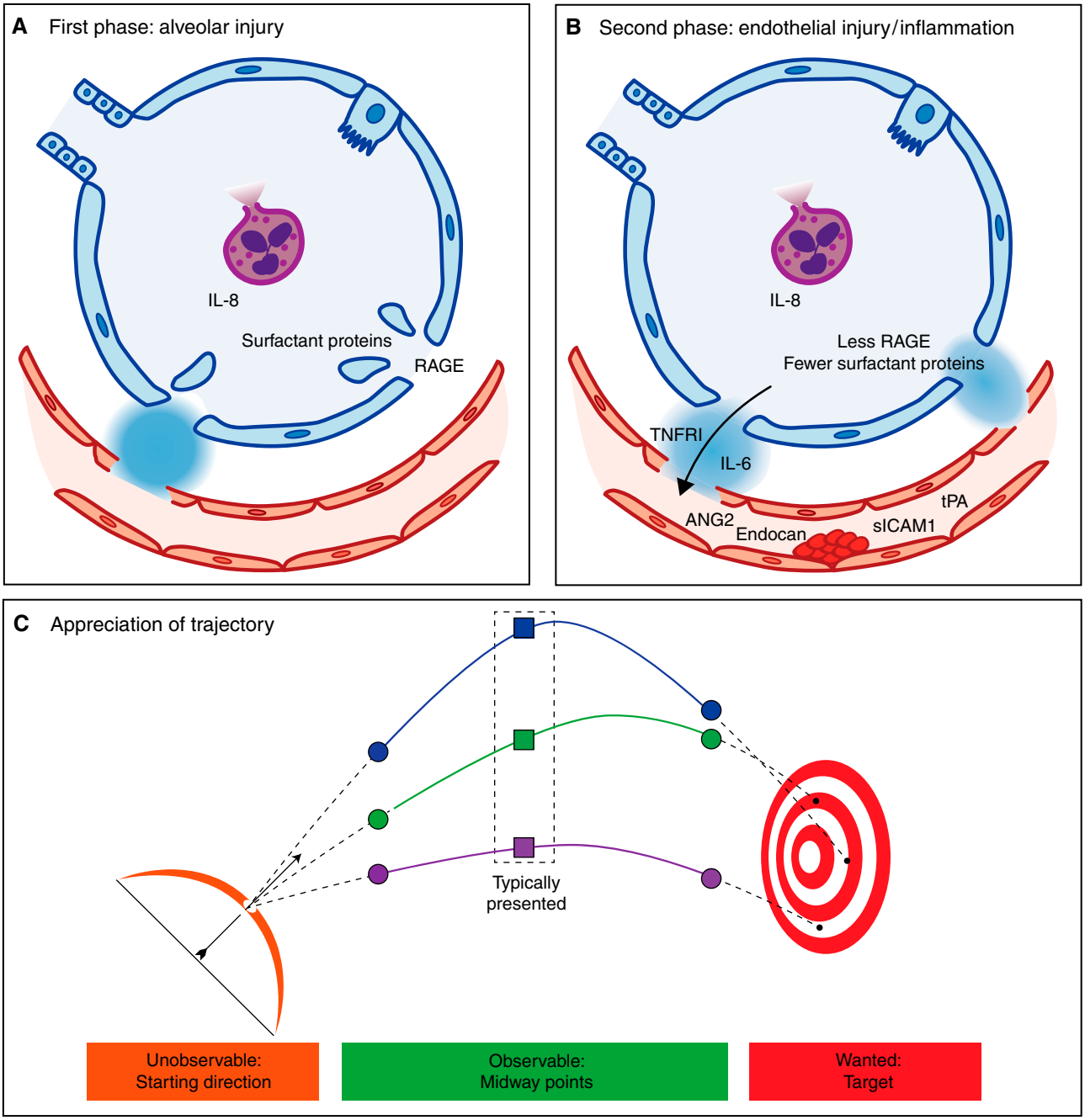

Figure 1. Appreciation for time-dependent changes in coronavirus disease (COVID-19)–related severe acute respiratory failure. (*A*) Schematic of the biological situation as studied by Leisman and colleagues (3) in patients with COVID-19–related acute respiratory failure requiring ICU admission; these patients are characterized by alveolar epithelial injury, likely secondary to alveolar inflammation rather than systemic inflammation. (*B*) Illustration of the situation in these same patients after 3 days in the ICU; they have endothelial activation and injury, systemic inflammation, and thrombosis. (*C*) Schematic representation of the difference in information that can be obtained from one observation (squares) rather than multiple observations. The latter can be used to evaluate the dynamic changes over time and predict the future trajectory. Of note, the situation of biological signals is much more complex than for arrows (even though arrows have more complex trajectories than might be expected because of oscillations of the arrow itself, known as the archer's paradox), and the provided cartoon should therefore not be interpreted such that precise prediction can be made with longitudinal measurements but just that accounting for time-related changes will likely better reflect reality than cross-sectional analyses.

contain more information than the sum of several snapshots analyzed cross-sectionally, a lesson that archery could have taught us some time ago (Figure 1C). If precision is our target, we need to know the trajectory, not only the situation at one specific point in time. If the arrow is observed midflight (as is the situation for our patients), we need multiple observations to calculate the trajectory (the subsequent states) and therefore the target (the prediction). ■

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Hospital Capacity Strain as a Window into the Value of ICU Admission

Some Answers, More Questions

Millions of patients are admitted to ICUs every year in the United States (1). ICU admission is costly, because ICU patients receive more expensive care, and building and staffing ICUs imposes high fixed costs (2). At the same time, ICU admission may not always provide value—there is wide variation in ICU admission practices across hospitals that is not tightly linked with better outcomes (3–6). We therefore urgently need to understand which patients benefit most from ICU care, and which aspects of ICU care drive this benefit, so we can use ICU and hospital resources more efficiently.

In this issue of the *Journal*, Anesi and colleagues (pp. 520–528) work to address these questions by analyzing the association between ICU triage and patient outcomes (7), using a previously validated instrumental variable in the form of hospital capacity strain (8). Their two cohorts included patients in 27 emergency departments—90,150 patients with sepsis and 45,339 with acute respiratory failure—who did not require life support (vasopressors or invasive mechanical ventilation) before ICU triage. These cohorts were chosen as archetypical patients whose need for and likely benefit from ICU admission were uncertain. The study's primary endpoint was hospital length of stay (LOS), using a "placement of death" approach in which in-hospital deaths or hospice discharges were assigned a LOS value equal to the 99th percentile of hospital LOS for the cohort. This primary outcome attempts to capture the fact that ICU care may modify LOS independent of mortality, while accounting for the effects of mortality censoring on LOS. The authors then analyzed the association between ICU admission and hospital LOS, using hospital capacity strain at the time of triage as an instrumental variable.

The primary finding was that ICU admission was associated with harm in patients with sepsis (1.32 d longer LOS), whereas it was associated with benefit in patients with acute respiratory failure (0.82 d shorter LOS). Secondary analyses suggested that these LOS changes were driven by higher mortality associated with ICU admission in patients with sepsis (odds ratio [OR], 1.48) and lower mortality in patients with acute respiratory failure (OR, 0.75). The results were generally consistent across sensitivity analyses. However, when code status at hospital admission was included as a covariate, the LOS and mortality results were attenuated, and the OR for mortality in patients with sepsis was no longer statistically significant.

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