and thoughtful challenges like those of Suisse are needed to ensure that those advocating a treatment have not made significant errors. On balance, that does not seem to have happened in these new analyses. Clinicians can be confident that in appropriately selected patients with COPD with a history of exacerbations despite taking long-acting inhaled bronchodilators, and especially in those with blood eosinophilia, regular ICS treatment can reduce the risk of further moderate and severe events. They should note that many doctors had worked this out before their patients entered the IMPACT study and that the results have been very carefully scrutinized. Surely St. Thomas would have approved. ■

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A central challenge in clinical studies of acute respiratory distress syndrome (ARDS) is its inherent heterogeneity (1). As documented in the landmark LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) (2) trial, patients with ARDS present with a spectrum of abnormalities in gas exchange and respiratory mechanics, a spectrum of clinical severity, and a spectrum of outcomes. Indeed, for this reason the Berlin (3) definition of ARDS has been criticized as being overly broad. A major focus of ARDS clinical research has therefore been identification of subphenotypes or endotypes within ARDS that can be used to design trials and tailor treatment. To date, however, no subphenotype has been demonstrated to predict treatment response or improve outcomes in a prospective trial. Crucially, despite its limitations, the Berlin definition does identify populations of patients that benefit from particular treatments. Volume- and pressure-limited ventilation, when applied to the broad population who meet the Berlin definition, reduces mortality (4). This is likely true even in the setting of relatively normal respiratory system mechanics. For example, a reanalysis of ARMA (Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome) trial data by Hager and colleagues (5) showed that reduced VT is associated with reduced mortality even when plateau pressures (Pplats) are not high. In the two decades since the publication of that landmark trial, initial suspicion (6) of low VT ventilation has therefore given way to widespread consensus that most patients with ARDS by the Berlin definition benefit from a lung-protective approach.

However, we are reminded in the book of Ecclesiastes (Eccles 1:9) that what has been will be again. The global pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has brought renewed attention to the phenomenon of respiratory failure with relatively preserved mechanics and has led some to suggest that coronavirus disease (COVID-19) respiratory failure, despite nearly always meeting the Berlin definition (7, 8), is characterized by novel subtypes of ARDS. Furthermore, it has been asserted that for some patients with COVID-19 ARDS, deviation from standard lung-protective settings (in particular, by the use of larger VTs) is potentially beneficial (9). Advocates point to observations of preserved respiratory system compliance (Crs) in the setting of severely impaired gas exchange in COVID-19 as suggestive of a novel pathophysiology, perhaps related to endothelial dysfunction and impaired hypoxic vasoconstriction (10). In this issue of the Journal, however, Panwar and colleagues (pp. 1244–1252) point out that such phenotypes were easily identifiable the pre–COVID-19 era (11).

The authors undertake reanalysis of data from LUNG SAFE. They define several categories of Crs impairment and attempt to

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identify a relationship between Crs and gas exchange abnormalities, as well as between Crs and mortality. Like others, they find a similar mean Crs in this non–COVID-19 ARDS cohort as in published COVID-19 ARDS cohorts. They also find, in their words, “a near complete dissociation between Crs and the PaO2/FiO2 ratio.” In patients with Crs >50 cm H2O, 43% had a ratio of PaO2 to FiO2 <150 mm Hg, making it clear that the combination of preserved compliance and severely impaired gas exchange is neither a novel finding nor specific to COVID-19. Interestingly, the authors also find an inverse relationship between mortality and Crs. Previous reports (12, 13) have differed on the prognostic significance of Crs, but none have included as many patients as the current one. Finally, the authors report no clear breakpoint in the relationship between Crs and mortality—lower Crs is associated with higher mortality but continuously so. Any choice of a Crs cutoff to define a subgroup will necessarily be arbitrary, and Crs is therefore a poor candidate marker for selecting patients for whom it is safe to deviate from established practice. In the present study, clinicians were less likely to recognize ARDS in patients with higher compliance, and accordingly, these patients were more likely to receive higher VTs. It may seem paradoxical that despite that, as noted above, patients with higher Crs also had lower mortality. It is reasonable to suppose, however, that these patients may still have benefited from lower VTs had it been provided. Hager and colleagues, for example, identified a group of patients in the original ARMA trial who had low Pplat on standard low VTs (i.e., 6–8 cc/kg predicted body weight) and therefore relatively preserved Crs. Even these patients, who were in the best quartile of Pplat, had improved outcomes compared with patients in the best quartile of Pplat on higher VTs, suggesting that assigning higher VTs to patients with preserved compliance might cause harm.

This impressive report joins a growing body of literature that confirms the substantial clinical and physiologic similarity between COVID-19 ARDS and non–COVID-19 ARDS. As such, it should provide additional reassurance that applying evidence-based therapies developed in the pre–COVID-19 era to patients with COVID-19 remains standard of care. Panwar and colleagues also confirm the substantial heterogeneity that is subsumed within the Berlin definition and that has motivated efforts (14) to identify meaningful subphenotypes. As pointed out by Bos and colleagues (15), however, only solid evidence of improved outcomes from personalized treatment can recommend clinical use of such categorizations—the observation of clusters of distinguishing clinical features by itself is an insufficient basis on which to alter clinical approach. Therefore, even as Panwar and colleagues add to the literature demonstrating that significant heterogeneity exists in ARDS, we must be mindful that the clinical trials that established current evidence-based protocols applied those protocols irrespective of subtyping. In sum, Panwar and colleagues have nicely illustrated that for COVID-19, as with ARDS of other etiologies, it is as the song says—same as it ever was (16).

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