P_{AO_2}–Pa_{O_2} gradient by using a simplified alveolar gas equation assumes that the respiratory quotient is 0.8 in all patients. This might not be the case in our critically ill patient with ARDS. Particularly, three patients in our study (1) received extracorporeal membrane oxygenation, an intervention that can remarkably alter the respiratory quotient. *2*) For a given F_{IO_2}, titrating PEEP by reaching the lowest P_{AO_2}–Pa_{O_2} gradient is similar to seeking the "best" oxygenation but can be misled by an increase in Pa_{CO_2}. In other words, both an increase in the Pa_{CO2} and an increase in Pa_{O_2} can reduce the calculated P_{AO_2}–Pa_{O_2} gradient. *3*) Although it may be practically preferable to assume the P_{AO_2}–Pa_{O_2} gradient represents the shunt in patients with ARDS, optimizing PEEP by reaching the lowest shunt can be misdirected by a reduction in cardiac output. Indeed, classical studies have shown that higher PEEP often reduces cardiac output and then reduces the intrapulmonary shunt (6). Improved Pa_{O_2} and P_{AO_2}–Pa_{O_2} gradient can then be observed with higher PEEP, but the price may be a lower oxygen delivery to the tissues because of the reduction in cardiac output.

For these multiple reasons, we prefer to rely on the direct assessment of lung recruitability to guide the PEEP setting. Our primary goal is to reduce the risk of ventilator-induced lung injury, such as atelectrauma and overdistension. Our study has demonstrated that the assessment of lung recruitability is feasible at the bedside by only using the ventilator of the patient, even in very constrained situations like COVID-19 (1). ■

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Reply by Xu *et al.* to Haouzi *et al.*

From the Authors:

Globally, numerous patients with coronavirus disease (COVID-19) develop acute respiratory distress syndrome (ARDS) and require mechanical ventilation (1–3). Great attention is paid to the respiratory pathophysiology of COVID-19, which potentially leads to "atypical" ARDS (4). A recent study by Haouzi and colleagues reanalyzed the data from a newly published case series reporting the lung mechanics of COVID-19 (4–6) and found enormous heterogeneity of COVID-19–related ARDS. In our previous study, hypercapnia was common when using low V_T ventilation in such patients with ARDS (5). Elevated pulmonary dead space in these patients was captured by ventilatory ratio and reinforced by Haouzi and colleagues. Reports have indicated that increased dead space is independently associated with an increased risk of death in patients

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with ARDS (7). In addition, optimal positive end-expiratory pressure should be achieved at the highest compliance with the lowest dead space fraction individually; thus, positive end-expiratory pressure titration and lung recruitment can be guided through measuring dead space (8). Moreover, prone positioning was proven to improve oxygenation and CO_2 clearance by the recruitment of dorsal lung units and redistribution of ventilation and perfusion (9, 10), suggesting that dead space may be useful for assessing the benefits of prone positioning. Ziehr and colleagues have reported an improvement in terms of oxygenation and compliance with prone positioning in patients with COVID-19–related ARDS, with an estimated physiologic dead space ratio of 0.45 (11).

Therefore, calculating a simple bedside index of ventilatory ratio to guide the personalized ventilation is highly recommended given the importance of pulmonary dead space in the management of COVID-19–related ARDS. ■

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