volume (VT),[2] should be considered in patients receiving mechanical ventilation for shorter duration in the operating room. The rationale behind the use of low VT is that surgery and anesthesia do place even normal lungs at risk of injury by cyclic recruitment and derecruitment of unstable units and that the lung parenchyma should not be strained up to an unphysiologic level. There is a widespread opinion that hypercapnia is the almost inevitable consequence of the decrease in the required minute ventilation induced by lower VT ventilation. The mechanical and physical constraints associated with mechanical ventilation that can lead to a tolerant approach to moderate elevations in arterial carbon dioxide ("permissive hypercapnia") in the context of ARDS should however be distinguished from the perioperative setting in patients with healthy lungs for whom normocapnia is achieved without the need for sophisticated ventilator settings. In most clinical situations, arterial carbon dioxide is maintained within physiological ranges during lower VT ventilation through a moderate increase in respiratory rate (in the absence of intrinsic positive end-expiratory pressure) combined, where appropriate, with a longer expiratory time. For example, a recent randomized trial highlighted that, compared with standard ventilation, a lung-protective ventilation composed of lower VT ventilation, positive end-expiratory pressure, and recruitment maneuver was associated with a statistically, although clinically not relevant, difference in the respiratory rate (11.0 ± 1.0 *vs.* 12.8 ± 2.2 breath/min, respectively, $P < 0.0001$) to maintain the end-tidal carbon dioxide below 40 mmHg. It must be emphasized that, in the two recent *IMPROVE* and *PROVHILO* randomized trials,[3,4] the study protocol stressed that arterial carbon dioxide had to be maintained within normal ranges throughout the surgical procedure.

We fully concur with the author that both preclinical and clinical studies have documented beneficial effects of hypercapnia beyond the scope of ARDS. The benefits of hypercapnia are often related to the decrease in airway pressure and VT leading to less baro-volutrauma and atelectrauma. Hypercapnia was also found to improve arterial and tissue oxygenation,[5] to increase local alveolar ventilation,[6] and to induce microvascular vasodilation, thus promoting oxygen delivery and tissue perfusion.[7] However, as mentioned by the author, hypercapnic acidosis is not without risks and whether there is or not added benefit to provide hypercapnia in lung-protective ventilation in the perioperative setting needs to be elucidated before being implemented in routine clinical practice. It is our opinion that a physiological approach to mechanical ventilation must remain the objective, which certainly involves to keep a close eye on the respiratory rate.

Competing Interests

The authors declare no competing interests.

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Technique and Time Range Used for Early Detection of Inflammation after Volutrauma

To the Editor:

Fernandez-Bustamante *et al.*,[1] in their study evaluating the early effects of tidal volume on lung injury biomarkers in surgical patients with healthy lungs, showed that tidal volume (V_T) of 6 *versus* 10 ml/kg did not have any significant effect on inflammatory biomarkers after 60 min of ventilation.

The effect of V_T on healthy lungs has always been controversial. Some of the studies having addressed this issue in surgical patients have found no differences in either the lung inflammatory response or outcome between low *versus* high V_T with short ventilatory durations (1 to 3 h)[2,3]; yet, those having suggested that high V_T increases proinflammatory mediators have focused on longer ventilatory times.[4–6] Furthermore, bronchoalveolar lavage concentrations of proinflammatory biomarkers have been introduced as a more reliable marker of lung injury than plasma levels of these markers.[7] Hence, using plasma levels of lung injury biomarkers within 60 min of volutrauma is not an appropriate method for comparing the inflammatory biomarkers concentration. Yet, administration of other techniques rather than plasma levels of biomarkers with longer periods following

volutrauma are required to obtain a solid method for the early detection of inflammation following volutrauma.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Mahmoodpoor and Dr. Golzari for their interest in our work[1] on the early detection of lung injury related to volutrauma during mechanical ventilation. They highlight the limitations of the short time course of ventilation in our study and the analysis of volutrauma-related biomarkers in blood. Although 60 min of mechanical ventilation is certainly a short period of time, this time frame is supported by previously reported significant increases in blood of interleukin (IL)-1 receptor antagonist, IL-6, IL-10, and tumor necrosis factor within 60 min of initiation of large tidal volume ventilation in adults[2] and of tumor necrosis factor-α, IL-1β, and IL-6 within 15 min after recruitment maneuvers in children.[3] Prior studies have also shown changes in neutrophil elastase and Clara Cell protein 16 plasma levels within 1 to 3 h of ventilation in animal models[4,5] and humans.[6] Blood measurements of the latter biomarkers have been extensively used in the literature of lung injury because of their reliable lung source.[7–9] In our healthy surgical patients, we have shown that tidal volume differentially affects plasma levels of neutrophil elastase and Clara Cell 16. We believe that these data can be used as a reference for future studies. Similarly, although bronchoalveolar lavage fluid may better reflect lung inflammation, its serial collection is not devoid of risks and interpretation challenges that make it suboptimal for healthy surgical patients. We pursued these analyses in exhaled breath condensate samples, a technique that poses its specific challenges but is noninvasive, repeatable, and safe. Our understanding of the early development of ventilation-mediated lung injury in patients is incomplete, and developing safe and clinically relevant plasma and exhaled breath condensate surrogates is a rational strategy.

Competing Interests

The authors declare no competing interests.

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