Is Permissive Hypercarbia Pneumoprotective?

To the Editor:

In their review of how to improve pulmonary care, Futier *et al.*[1] emphasize the pneumoprotective strategies of limiting tidal volume and positive inspiratory pressure and the use of moderate positive end-expiratory pressure and recruitment maneuvers. In theory, and there is some evidence (discussed below), another pneumoprotective strategy that can be used is permissive hypercapnia. Further studies will be needed to verify its effectiveness, but it may be reasonable to aim for, or at least tolerate, hypercarbia, assuming no contraindications (*e.g.*, increased intracranial pressure, right heat failure, hyperkalemia).

Fundamentally, unlike spontaneous ventilation where inspired gases enter alveoli where increased space has been created, positive pressure ventilation forces air into spaces and may cause regional overdistention, resulting in trauma.[2] Every breath is potentially, and likely, traumatic, and the accumulation of these "micro"-traumatic events can eventually lead to clinically significant "macro"-trauma, that is, pulmonary dysfunction. In theory, reducing the number and/or severity of these micro-traumatic insults may reduce the clinically evident pulmonary dysfunction. To achieve normocarbia, one must achieve sufficient minute ventilation. Minute ventilation is achieved by an adequate tidal volume and respiratory rate. Aiming for a lower minute ventilation allows for a lower tidal volume (as well as peak and mean inspiratory pressures) and/or a lower respiratory rate. Futier *et al.*[1] nicely review how excessive tidal volume and inspiratory pressure are damaging. In humans, less attention has been paid to the role of respiratory rate. In animals, it has been shown that an increased respiratory rate increases pulmonary dysfunction.[3] There are at least two potential mechanisms. First, with a higher respiratory rate, there are simply more breaths delivered and hence more cumulative trauma over time. Second, gas flow velocity must be higher to achieve a given tidal volume in a shorter inspiratory time as would typically be the case with a higher respiratory rate. Further studies will be needed to determine whether this excess shear is damaging. A lower respiratory rate may also result in lower peak inspiratory pressures and less auto-positive end-expiratory pressure.

Hypercarbia is common during modern anesthesia practice and seems to be well tolerated. Many patients who breathe spontaneously throughout the course of an anesthetic are hypercarbic, which commonly occurs when a laryngeal mask airway is used or during monitored anesthetic care. Evidence suggests that hypercarbia may be pneumoprotective.[4,5]

Increasing clinical evidence supports the use of permissive hypercapnia in respiratory disease states. Although there are reasons to routinely use permissive hypercarbia as a preventive strategy, conclusive outcome studies that demonstrate its benefits and/or hurtfulness are limited. However, there is stronger rationale to more readily tolerate hypercarbia in the more difficult to ventilate patients. These may be the higher risk patients where pneumoprotection may be most important. It may not be worth the pulmonary risk to increase the respiratory rate and/or tidal volume to normalize a mild-to-moderate high $Paco_2$ level that is not causing any significant problems. A more complete discussion of the non-pulmonary benefits and disadvantages of hypercarbia is beyond the scope of this communication. It is worth noting that low volume ventilation was initially found to be of benefit in diseased patients and then found to be of benefit in patients without preexisting pulmonary disease. It is possible that the role of permissive hypercapnia may evolve in the same manner.

I would be interested in the opinion of Futier *et al.*[1] on the current and/or potential role of permissive hypercarbia in a lung protection strategy and whether we should be limiting respiratory rates.

Competing Interests

The author declares no competing interests.

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References

1. Futier E, Marret E, Jaber S: Perioperative positive pressure ventilation: An integrated approach to improve pulmonary care. Anesthesiology 2014; 121:400–8
2. Mead J, Takishima T, Leith D: Stress distribution in lungs: A model of pulmonary elasticity. J Appl Physiol 1970; 28:596–608
3. Hotchkiss JR Jr, Blanch L, Murias G, Adams AB, Olson DA, Wangensteen OD, Leo PH, Marini JJ: Effects of decreased respiratory frequency on ventilator-induced lung injury. Am J Respir Crit Care Med 2000; 161(2 pt 1):463–8
4. Curley G, Contreras M, Nichol AD, Higgins BD, Laffey JG: Hypercapnia and acidosis in sepsis. 2010; 112:462–72
5. Hedenstierna G: Respiratory physiology, Miller's Anesthesia, 7th edition. Edited by Miller RD. Philadelphia, Churchill Livingston, 2010, pp 361–91

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In Reply:

We sincerely thank Dr. Roth for his interest and positive comments on our recent article[1] on prophylactic perioperative positive pressure ventilation ("P.O.P. ventilation" bundle) to prevent postoperative pulmonary complications, and we are happy to propose the following responses to his letter.

As for patients experiencing acute respiratory distress syndrome (ARDS), evidence is accumulating that lung-protective ventilation, including but not limited to the use of lower tidal

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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References

1. Futier E, Marret E, Jaber S: Perioperative positive pressure ventilation: An integrated approach to improve pulmonary care. Anesthesiology 2014; 121:400–8
2. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci Mde O, Damasceno MC, Schultz MJ: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. JAMA 2012; 308:1651–9
3. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369:428–37
4. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ: High *versus* low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. Lancet 2014; 384:495–503
5. Akça O, Doufas AG, Morioka N, Iscoe S, Fisher J, Sessler DI: Hypercapnia improves tissue oxygenation. Anesthesiology 2002; 97:801–6
6. Domino KB, Emery MJ, Swenson ER, Hlastala MP: Ventilation heterogeneity is increased in hypocapnic dogs but not pigs. Respir Physiol 1998; 111:89–100
7. Komori M, Takada K, Tomizawa Y, Nishiyama K, Kawamata M, Ozaki M: Permissive range of hypercapnia for improved peripheral microcirculation and cardiac output in rabbits. Crit Care Med 2007; 35:2171–5

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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