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Tidal Volume, Positive End-expiratory Pressure, and Postoperative Hypoxemia: Comment

To the Editor:

We read the article by Turan *et al.*[1] with great interest and would like to congratulate the authors on conducting this large, important, factorial trial. The authors found that neither a "high" (8 cm H_2O) positive end-expiratory pressure (PEEP), nor a low (6 ml/kg) tidal volume strategy or a combination impacted postextubation hypoxemia or postoperative pulmonary complications. As such, the trial confirms findings of previous studies[2] that nonindividualized PEEP levels do not improve patient outcomes. It corroborates findings from a large study by Karalapillai *et al.*[3] that simply randomizing to high *versus* low tidal volumes does not seem to confer benefit for patients undergoing mechanical ventilation for general anesthesia.

We would like to add two important observations based on recent literature to the discussion of the study by Turan *et al.*[1] First, Neto *et al.*[4] and others have shown that it is not tidal volume *per se* that is the critical component of lung protection, but rather the resulting driving pressure, *i.e.,* the interaction of the applied tidal volume with the individual patient's respiratory system compliance, which is a more accurate determinant of perioperative lung injury and postoperative pulmonary complications. Our group recently corroborated these findings in a cohort of 197,474 surgical patients where higher intraoperative tidal volumes (greater than 8 ml/kg) were associated with increased risk of postoperative respiratory failure only in patients with a low compliance, and this effect was completely mediated by the resulting driving pressure.[5] In addition to lowering the applied tidal volume, modification of PEEP, which was the second factor in the trial by Turan *et al.,*[1] can reduce driving pressure through shifting tidal ventilation toward the high-compliance part of the pressure or volume loop. However, even in patients with "healthy" lungs undergoing general anesthesia, PEEP requirements are heterogeneous, and a "standard" PEEP is often inadequate.[6,7] To better understand the effect of the study intervention, it would be helpful if the driving pressure per group could be provided by Turan *et al.* to understand group differentiation regarding this crucial factor. Based on previous literature,[5,6] it may be hypothesized that the interventions in the present study[1] were effective when they resulted in a reduction in driving pressure, which might be tested in a *post hoc* analysis. In addition, it would be informative to analyze the effects of lowering tidal volume in patients with a lower respiratory system compliance.[6] It is highly likely that lung-protective ventilation in the operating room is effective only in patients with impaired compliance. A study that lumps those patients with a mass of healthy patients is bound to show a "negative" result.

Second, it is a classic phenomenon that physicians increase the respiratory rate when lowering tidal volume to maintain minute ventilation and end-tidal carbon dioxide.[8] This is relevant because it has been shown that increasing repetition of stress and strain might be equally damaging and therefore negates the effect of lowering tidal volume (and, subsequently, driving pressure).[9] Indeed, in the study by Turan *et al.*, the respiratory rate in the low tidal volume groups was more than 30% higher. Therefore, randomly assigning patients on the basis of factorial clusters with low *versus* high tidal volumes omitted the weight of impactful components like respiratory rate. Measures have been proposed to quantify this interaction of PEEP, tidal volume, and respiratory rate by estimating the intensity of ventilation. In a cohort of 230,767 surgical patients, we recently observed that an increased intraoperative ventilation intensity quantified by mechanical power was associated with higher odds of postoperative respiratory failure.[10] This was corroborated by a secondary analysis of the study by Karalapillai *et al.,*[3] who found that not tidal volume, but ventilation intensity, measured as mechanical power, incorporating the respiratory rate explained the variance in the risk of postoperative pulmonary outcomes.[11]

There is an impressive success in completing such a large trial in a 2-yr period. Based on the findings from Turan *et al.* and recent literature, we should move away from studies focusing on single, "standard" ventilator parameters, and we propose that the era of trials of mechanical ventilation in unselected patients in the operating room is over.

Competing Interests

Dr. Baedorf-Kassis has received lecturing fees from Hamilton Medical, Inc. (Reno, Nevada), outside the submitted work and has received a KL2 award from Harvard Catalyst, The Harvard Clinical and Translational Science Center (Boston, Massachusetts; National Center for Advancing Translational Sciences [Bethesda, Maryland], National Institutes of Health award No. KL2 TR002542 [Bethesda, Maryland]). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health. Dr. Talmor received speaking fees and grant funds from Hamilton Medical, Inc. (Bonaduz, Switzerland), outside the submitted work. Dr. Schaefer has received a grant for investigator-initiated trials not related to this article from Merck & Co (Rahway, New Jersey). The other authors declare no competing interests.

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Tidal Volume, Positive End-expiratory Pressure, and Postoperative Hypoxemia: Reply

In Reply:

Suleiman *et al.*[1] assert that driving pressure and mechanical power (because of increased respiratory rate in low tidal volume groups) may be more important determinants of perioperative lung injury and postoperative pulmonary complications than tidal volume and positive end-expiratory pressure (PEEP). We used a factorial cluster design to assign 2,860 patients to four combinations of tidal volume and PEEP. There were no differences in oxygenation during recovery or in pulmonary complications among the groups. We therefore concluded that any combinations of tidal volume between 6 and 10 ml/kg and PEEP between 5 and 8 cm H_2O are comparably safe in relatively healthy patients having general anesthesia for orthopedic surgery.[2]

As expected, both driving pressure and mechanical power differed among our four treatment groups (table 1). For example, mechanical power increased approximately 1.2 J/min with each increase in tidal volume and/or PEEP, ranging from 10.7 to 14.4 J/min with the biggest intergroup difference being 1.3 J/min. Driving pressure increased 2 to 3 cm H_2O with higher tidal volume (table 1).

Mechanical power is affected by tidal volume and respiratory rate. We therefore evaluated mechanical power as a predictor of our primary outcome, the oxygen saturation measured by pulse oximetry to fraction of inspired oxygen (Sp_{O_2}/F_{IO_2}) ratio. The relationship was significant, with each Joule per minute increase in mechanical power being associated with –2.12 (95% CI, –2.49 to –1.74; $P < 0.0001$) reduction in Sp_{O_2}/F_{IO_2} ratio, an amount that is not remotely clinically meaningful.

At least in healthy lungs, postoperative oxygenation and complications are similar at any combination of tidal volume 6 to 10 ml/kg and PEEP of 5 to 8 cm H_2O, which is roughly twice as high as the threshold for a change in intraoperative mechanical power that is associated with increased risk for postoperative respiratory failure.[3]

Competing Interests

Dr. Gama de Abreu received consultation fees from Ambu (Ballerup, Denmark), Lungpacer (Vancouver, Canada) and Medtronic (Lisbon, Portugal). The other authors declare no competing interests.

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Table 1. Mechanical Power and Driving Pressure per Group

	VT = 6 ml/kg, PEEP = 5 cm H_2O (N = 727)	VT = 6 ml/kg, PEEP = 8 cm H_2O (N = 635)	VT = 10 ml/kg, PEEP = 5 cm H_2O (N = 799)	VT = 10 ml/kg, PEEP = 8 cm H_2O (N = 699)	*P* Value
Time-weighted average intraoperative mechanical power, J/min	10.7 ± 3.6	11.9 ± 3.7	13.1 ± 4.7	14.4 ± 4.9	< 0.001
Time-weighted average Sp_{O_2}/F_{IO_2} in post anesthesia care unit	356 ± 46	355 ± 45	350 ± 46	351 ± 49	
Time-weighted average intraoperative driving pressure, cm H_2O	14 ± 3.4	14 ± 3.2	17 ± 4	16 ± 3.6	

Summary statistics are presented as mean ± SD. Because we were unable to obtain plateau pressure in all patients, mechanical power was estimated as 0.098 · respiratory rate · Vt · peak pressure[3] a surrogate equation for pressure-controlled ventilation. Accordingly, driving pressure was estimated as peak pressure – PEEP. Therefore, both mechanical power and driving pressure were slightly overestimated, but comparably in each group.

F_{IO_2}, fraction of inspired oxygen; PEEP, positive end expiratory pressure; Sp_{O_2}, oxygen saturation measured by pulse oximetry; VT, tidal volume.