Christelle Cantrelle, Ph.D.
Richard Dorent, M.D.
Direction Prélèvement Greffe Organes-Tissus
Saint Denis La Plaine, France

Nicolas Carlier, M.D.
Assistance Publique Hôpitaux de Paris
Paris, France
and
ERN-Lung CF Network
Frankfurt, Germany

François Kerbaul, M.D., Ph.D.
Direction Prélèvement Greffe Organes-Tissus
Saint Denis La Plaine, France

Pierre-Régis Burgel, M.D., Ph.D.*
Université de Paris
Paris, France

Assistance Publique Hôpitaux de Paris
Paris, France
and
ERN-Lung CF Network
Frankfurt, Germany

ORCID ID: 0000-0001-7752-1144 (C.L.).

*Corresponding author (e-mail: pierre-regis.burgel@aphp.fr).

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Addition of 5% CO$_2$ to Inspiratory Gas in Preventing Lung Injury Due to Pulmonary Artery Ligation

To the Editor:

The article by Marongiu and colleagues in the recent issue of the *Journal* unravels several interesting effects of 5% CO_2 on lung pathophysiology in a porcine model of unilateral pulmonary artery (PA) ligation (1). Pathological changes in the lung due to unilateral PA ligation and the effects of 5% CO_2 are noticeable. Nevertheless, the corresponding physiological changes do not reflect the extent of injury due to left PA ligation. Despite a substantial increase in wasted or dead space ventilation due to left PA ligation, the Pa_{CO_2}–end-tidal CO_2 (ET_{CO_2}) gradient remained constant. Surprisingly, Pa_{CO_2} did not rise significantly in the isolated PA ligation group at all time points from 2 hours to 48 hours despite worsening lung pathology, declining lung compliance, and constant ventilator settings. Moreover, Pa_{CO_2} decreased from 39 mm Hg at baseline to 33 mm Hg at 48 hours in the isolated PA ligation group. Notably, in the 5% CO_2 group, Pa_{CO_2} rose significantly to 67 mm Hg at 2 hours after ligation from the baseline value of 36 mm Hg. Additionally, the magnitude of increase in ET_{CO_2} was similar to Pa_{CO_2}, and the Pa_{CO_2}–ET_{CO_2} gradient became negative. Intuitively, CO_2 rebreathing cannot be solely responsible for a substantial increase in Pa_{CO_2} in the 5% CO_2 group.

Main branch PA closure during Blalock-Taussig shunt and cavopulmonary anastomosis has been associated with a significant rise in Pa_{CO_2} and Pa_{CO_2}–ET_{CO_2} gradient (2). In cyanotic congenital heart disease, oxygenation and CO_2 elimination are critically dependent on pulmonary blood flow, and the rise in Pa_{CO_2} and Pa_{CO_2}–ET_{CO_2} gradient during transient PA branch occlusion is obvious (3). The Pa_{CO_2}–ET_{CO_2} gradient has also been noted to increase in patients with acute pulmonary thromboembolism, pulmonary artery banding, or single-lung ventilation despite normal or excessive preoperative pulmonary blood flow (4). Therefore, readers may be curious to hear from the authors why Pa_{CO_2} did not rise after PA ligation in isolated ligation groups and the 5% CO_2 inhalation group whether Pa_{CO_2} increased due to rebreathing or PA ligation.

The authors asserted that lung injury is a major determinant of PA pressure that does not correspond to hourly hemodynamic data. Pulmonary vascular resistance (PVR) in the 5% CO_2 group nearly doubled at the 12th hour from the baseline (360 dyne/s/cm^{-5} versus

189 dyne/s/cm^{-5}). A higher trend in PVR was maintained through 48 hours compared with the ligation group alone. However, the rise in mean arterial pressure after double insults of hypercarbia and PA ligation appears clinically insignificant. This finding is indeed clinically promising for anesthesiologists and critical care physicians managing various cardiac surgeries, noncardiac surgeries, and acute respiratory distress syndrome. Considering the extent of the rise in PA pressure after ligation and hypercarbia in the 5% CO_2 group in this study, a ventilator strategy involving permissive hypercapnia and hypercarbia to avoid volutrauma in acute respiratory distress syndrome appears safe. Furthermore, 5% CO_2 may offer protection from lung damage during PA ligation (pneumonectomy or lobectomy), PA banding, and PA occlusion to facilitate Blalock-Taussig shunt and cavopulmonary anastomosis.

PA ligation is akin to acute thromboembolism, which may lead to a rapid rise in right ventricular load, right ventricular dilatation, and reduction in cardiac output (5). Interestingly, cardiac output rose (4.4 L/min to 5.1 L/min) in the 5% CO_2 group, and therefore ligation and hypercarbia did not seem to produce right ventricular dysfunction until the end of the study. Thus, assessing change in systolic or diastolic right ventricular function compared with baseline after pulmonary artery ligation or hypercarbia could have further provided mechanistic insight.

Finally, the authors have stressed that the diversion of minute ventilation instead of blood flow is responsible for pulmonary edema in the nonligated lung (right lung). Nevertheless, hypercarbia in the 5% CO_2 group produced pulmonary vasoconstriction (PVR = 360 and 352 dyne/s/cm^{-5} at 12 and 24 hours) during the initial phases, which could have prevented the development of pulmonary edema in the right lung. Moreover, in addition to excessive ventilation in producing lung injury, the role of toxic or inflammatory mediators from the ligated hypoxic, anoxic, or infarcted lung in inflicting lung damage to the nonligated lung needs to be investigated. ∎

Ajay Kumar Jha, M.D., D.M.*
Jawaharlal Institute of Postgraduate Medical Education and Research
Pondicherry, India

*Corresponding author (e-mail: drajaykjha@rediffmail.com).

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Reply to Jha

From the Authors:

We thank Jha for the insightful comments on our recent experimental study (1). Indeed, the experiment offers food for thought as we are at the very beginning of understanding pathophysiological changes induced by unilateral pulmonary artery ligation (UPAL) and mechanisms of lung protection by inhaled 5% CO_2.

After UPAL, Pa_{CO_2} did not increase, as if the additional experimental dead space did not affect the efficiency of gas exchange. Several pivotal studies on animals (2) and humans (3, 4) already showed that Pa_{CO_2} does not change after unilateral pulmonary artery occlusion, despite little or no increase in minute ventilation. Our and previous findings suggest that a compensatory mechanism, consisting of redistribution of ventilation toward perfused lung regions, maintains the effectiveness of CO_2 clearance, avoiding the increase in wasted ventilation. This might help with understanding the lack of increase in Pa_{CO_2} after UPAL in our experiment. Moreover, decreased total CO_2 production might also have occurred along the course of the experiment and affected the level of Pa_{CO_2} at stable minute ventilation independently from changes in dead space. As inhalation of 5% CO_2 counteracted the compensatory redistribution of ventilation after UPAL, wasted ventilation could have been higher in the ligation + $F_{I_{CO_2}}$ (fractional inspired CO_2) animals and might have contributed to the higher Pa_{CO_2} in this group.

With respect to the comments on the Pa_{CO_2}–end-tidal CO_2 (ET_{CO_2}) gradient, we would like to underline that the latter might have reflected regional alveolar CO_2 rather than the global average level. Indeed, unilateral bronchoconstriction and/or pneumoconstriction might have caused delayed or even incomplete exhalation from the ligated lung, which might have altered ET_{CO_2} values (4, 5), potentially hindering the reliability of the Pa_{CO_2}–ET_{CO_2} gradient to estimate wasted ventilation.

We appreciate the thoughtful comments on changes in pulmonary vascular resistance (PVR). As suggested by Jha, the combination of ligation and hypercapnia induced a relevant increase in PVR in the ligation + $F_{I_{CO_2}}$ group. Nevertheless, this effect tended to be dampened over time, possibly due to renal buffering of respiratory acidosis (6), while the increase in PVR seemed to progress in the ligation group, and we only foresee the development of injury as an underlying mechanism. The effects of inhaled CO_2 on PVR and right heart function in the presence of increased dead space definitely need further assessment before envisioning clinical applications (7).