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CORRESPONDENCE

'Permissive' hypercapnia in ARDS: is it passé?

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Initial correspondence from Drs. Muthu, Agarwal and Sehgal

Recently, Nin et al. demonstrated that hypercapnia was associated with a higher likelihood of intensive care unit (ICU) mortality in subjects with acute respiratory distress syndrome (ARDS) [1]. In order to investigate the effect of $PaCO_2$ in our ICU population, we collected the demographic and clinical information of 415 subjects with ARDS admitted between 1 January 2001 and 31 December 2016. On a multivariate logistic regression analysis, baseline APACHE II, baseline pH and severity of ARDS were predictors of mortality, but the worst $PaCO_2$ values during the initial 48 h were not (Table 1).

Contrary to Nin et al., $PaCO_2$ levels did not predict mortality in our cohort. Most importantly, Nin et al. did not adjust for severity of ARDS in their study population. There is increase in the odds of death with increasing severity of ARDS (also highlighted in our study). Also, if $PaCO_2$ was associated with a higher mortality, the authors should have also adjusted for the baseline $PaCO_2$ levels rather than the values during 48 h after ventilation as a covariate. A high $PaCO_2$ level after ventilation could merely be a reflection of severe ARDS, as those with severe lung injury are more likely to be ventilated with lower tidal volume (less than 6 mL/kg body weight). Moreover, it is the pH and not the $PaCO_2$ that is mechanistically associated with poorer outcomes as seen in our study cohort [2]. Finally, Nin et al. have not adjusted for lung compliance that reflects severity of lung damage, which also could affect the overall survival [3].

In conclusion, it is the severity of ARDS and pH values rather than the $PaCO_2$ levels alone that predicts mortality.

Reply from Drs. Peñuelas, Nin, Muriel and Esteban

Muthu et al. investigated the factors that may be associated with an increased risk of mortality in 415 ARDS patients fulfilling the Berlin criteria of acute respiratory distress syndrome (ARDS), in a retrospective cohort of patients admitted in the ICU. They performed a multivariate logistic regression analysis and found that baseline APACHE II, baseline pH and severity of ARDS were predictors of mortality, but the baseline or the worst $PaCO_2$ values during initial 48 h were not.

The authors have tried to compare these results with previous findings published by Nin et al. [1] that showed a deleterious effect of severe hypercapnia in 1899 patients with moderate or severe ARDS, adjusted by the severity of the lung injury.

This finding from a observational, prospective and multicentre study calls into question the concept of "permissive hypercapnia" for patients with lung injury which has been applied traditionally in routine clinical practice. However, the evidence for this paradigm relies mainly on results of experimental studies [4], and therefore more clinical studies were needed to figure out the effect of acute hypercapnia in ARDS patients.

Muthu et al. have presented their data and apparently found results contrary to those of Nin et al. However, these studies are not comparable for several reasons. First of all, mortality rates between both studies are dramatically different. Whereas Muthu et al. showed a mortality rate of 29%, we reported a mortality rate of 62.5% in hypercapnic patients with ARDS, and 49.6% in non-hypercapnic patients with ARDS. Our results are more

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Table 1 Baseline parameters amongst ICU survivors and non-survivors with ARDS

Parameter	Survivors ($n = 295$)	Non-survivors ($n = 120$)	Crude OR (95% CI)	Adjusted OR (95% CI)	p value
Baseline APACHE II score	17 (11–24)	23 (17–28)	1.19 (1.06–1.11)**	1.062 (1–1.1)*	<0.0001
Baseline $PaCO_2$, mmHg	37 (31.4–44)	41.2 (32.8–54)	1.03 (1.01–1.04)**	1 (0.97–1)	<0.0001
Worst $PaCO_2$ in first 48 h, mmHg	39 (34–46)	43.5 (36–58)	1.03 (1.01–1.04)**	0.9 (0.9–1)	<0.0001
$PaCO_2 > 45$ mmHg at 48 h	88 (29.8)	57 (47.5)			<0.001
Baseline pH	7.37 (7.31–7.41)	7.28 (7.19–7.37)	0.00 (0.00–0.01)**	0.01 (0.0–0.1)**	<0.0001
Severity of ARDS			0.59 (0.44–0.79)**	0.59 (0.35–0.99)*	0.001
Mild, *n* (%)	119 (40.3)	27 (22.5)			
Moderate, *n* (%)	124 (42)	59 (49.2)			
Severe, *n* (%)	52 (17.6)	34 (28.3)			
Baseline PaO_2/FIO_2 ratio	157.3 (57.5)	168.5 (72.7)			0.52
Baseline plateau pressure (cmH_2O)	24.6 (5.6)	27.3 (6.8)			0.001
Baseline PEEP (cmH_2O)	8.7 (4.4)	9.5 (4.4)			0.14
Respiratory rate/min	22.6 ± 14.5	24.3 ± 16.1			0.21
Duration of MV, days	7.5 (6.3)	7.5 (7.1)			0.96
Ventilator-free days	3.2 (4.0)	0.8 (2.5)			<0.0001
ICU length of stay, days	10.7 (8.9)	8.3 (8.3)			0.01
Hospital length of stay, days	17.2 (13.4)	13 (11)			0.002

All values are specified as median (interquartile range), unless specified otherwise

* $p \leq 0.05$; ** $p < 0.0001$

similar to those published by Bellani et al. in the largest observational study of ARDS patients [5].

Secondly, Muthu et al. used the variable $PaCO_2$ as continuous and did not get an independent association between $PaCO_2$ levels and mortality among the entire retrospective cohort. Our aim was to evaluate the effect of hypercapnia (based on predefined statistical criteria using $PaCO_2$ levels as categorical variable), and a multivariate model found that severe hypercapnia was markedly and independently associated with a higher risk of ICU mortality. Finally, we performed a cautious analysis of possible confounders that may affect the finding, and after multiple adjustments and propensity analysis, the authors still found that severe hypercapnia was independently associated with ICU mortality. Unfortunately there is a lack of this type of approach in Muthu's study.

For all of the above, the two studies are not comparable, but doubts remain about the possible deleterious effect of permissive hypercapnia in patients with ARDS. The results obtained by Nin et al. may require an external validation to confirm them, but probably we are witnessing the end of a period of uncertainty of the effect of hypercapnia, and a new momentum starts to raise the safety of hypercapnia from a clinical perspective.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no competing interests.

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