

# Permissive hypercapnia in ventilated preterm infants: when is it safe to perform?

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## Abstract

**Introduction:** In spite of measures to avoid invasive mechanical ventilation, many preterm infants are still artificially ventilated. The need for intubation and positive pressure ventilation is associated with so-called ventilator-induced lung injury (VILI) and bronchopulmonary dysplasia (BPD). A lot of strategies are made in order to minimise VILI. One of these strategies is the use of permissive hypercapnia, in which clinicians use more gentle ventilatory strategies and accept higher than “normal” alveolar partial pressure of carbon dioxide (PaCO<sub>2</sub>) values. Although there are promising studies about the use of permissive hypercapnia in preterm infants, we are still not sure if and when this mode of treatment is safe.

**Aim:** The aim of this study is to investigate conditions in which permissive hypercapnia is safe to prematurely born infants regarding their survival.

**Methods:** The present study was conducted in a tertiary research and educational hospital, NICU, Pediatric Clinic, Clinical Center University of Sarajevo (Sarajevo, Bosnia and Herzegovina). All infants had chest X-ray at admission, and were treated for respiratory distress syndrome (RDS) with nasal continuous positive airway pressure (nCPAP), conventional mechanical ventilation (CMV), or high frequency oscillatory ventilation (HFOV). At admission we registered data regarding birth weight (BW), gestational age in weeks (GW), Apgar score and prenatally given steroids. Inclusion criteria were fulfilled by 200 infants. According to their mean PaCO<sub>2</sub>, patients were divided into hypercapnia and normocapnia groups. We analyzed the outcome (survival) of these two groups.

**Results:** The two groups didn't differ regarding GW, prenatally given steroids, RDS severity, surfactant use, 1- and 5-minute Apgar score, nor according to their CRIB score. Groups had also similar survival. After performing ROC analysis we have found that infants born  $\leq 27$  GW and  $\leq 1,000$  g treated with permissive hypercapnia, and infants with normocapnia born  $\leq 26$  GW and  $\leq 980$  g, have a prediction of negative outcome regarding survival, with a high level of accuracy.

**Conclusions:** This study shows that ventilation with permissive hypercapnia of preterm infants with RDS is not safe, considering survival in children with GW  $\leq 27$  and BW  $\leq 1,000$  g.

## Keywords

Preterm infant, respiratory distress syndrome, permissive hypercapnia.

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## Introduction

Importance of prematurity is reflected not only in a significantly higher rate of mortality, but also in a number of other complications arising from functional immaturity of different organs and organ systems. Respiratory distress syndrome (RDS) is the most common pathological condition of preterm infants born before 32 GW (gestational age in weeks). Its clinical course can be severe, with a mortality rate up to 5% [1, 2]. The most effective prophylactic measures are prevention of preterm birth and antenatal steroid use, and treatment is based on surfactant administration and on use of ventilatory strategies that minimise ventilator-induced lung injury (VILI). Though lifesaving, invasive mechanical ventilation carries a high risk of development of chronic lung disease/bronchopulmonary dysplasia (CLD/BPD), and avoidance of invasive mechanical ventilation is the best BPD prevention strategy in theory [3]. The incidence of CLD has been increasing over the past two decades in parallel with an improvement in the survival of the population of very premature infants [4]. Population studies show incidence of BPD of 13-35% between preterm infants still hospitalized at the age of 36 weeks [5], while the overall incidence is around 20% of all ventilated preterm, with obvious variations among different centers [6]. One of the potential practical measures that can lead to a reduction of the incidence of BPD in premature babies with very low birth weight is a permissive hypercapnia. It is a strategy of respiratory treatment that tolerates levels of PaCO<sub>2</sub> above normal values, thus providing less aggressive respiratory treatment, resulting in less pulmonary damage [7, 8]. Permissive hypercapnia allows values of PaCO<sub>2</sub> up to 50-60 torr or 6.6-8 kPa. According

to the *European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update* [9], during mechanical ventilation with hypercapnia it is necessary to tolerate pH value up to 7.22 during the first 5 days and up to 7.20 after this period of time. A multicenter trial on preterm infants with birth weight (BW) of 501-1,000 g reports a trend towards a lower incidence of BPD or death in the group randomized to minimal ventilation (63 versus 68%) [10]. Despite suggested influence of permissive hypercapnia on lower risk for BPD, it is still not clear whether it is safe for preterm born infants, because of its many effects like cellular acidosis, increase in sympathetic activity [11], dilatation of cerebral arterioles, increase of pulmonary vascular resistance, etc. The aim of this study is to investigate conditions in which permissive hypercapnia is safe to prematurely born babies regarding their survival.

## Patients and methods

This study was conducted at Neonatal Intensive Care Unit, Pediatric Clinic, Clinical Center University of Sarajevo (Sarajevo, Bosnia and Herzegovina). It included 200 prematurely born infants with RDS, treated from April 1, 2013, to July 1, 2015. During the treatment of RDS we have performed blood gas analyses at least twice a day, or more frequently if necessary. Capillary samples were interpreted as arterial, and in the case of venous samples the calculated difference was equal to 5 mmHg. Patients were divided in two groups, according to their mean PaCO<sub>2</sub>: 1) patients whose PaCO<sub>2</sub> in > 60% of the blood gases was 6.6-8.0 kPa were classified into permissive hypercapnia (PH) group; 2) patients whose PaCO<sub>2</sub> in > 60% of the blood gases was 4.6-6.6 kPa were classified into normocapnia (NC) group. PH group had 69 (43.7%) patients, and NC group 89 (56.3%) patients. The rest of 42 patients could not be classified into neither of the groups due to their extreme fluctuations of PaCO<sub>2</sub>. At admission we registered data regarding BW, gestational age, Apgar score, CRIB score, and prenatally given steroids. Chest X-ray was performed in all infants at admission. RDS was treated according to the European guidelines for management of RDS (2013 update) using continuous positive airway pressure (CPAP), conventional mechanical ventilation (CMV) or high frequency oscillatory ventilation (HFOV) [9].

When indicated, bovine surfactant (Survanta®) was used. RDS was graded as severe when patients

needed surfactant and/or mechanical ventilation, or mild without it. Kolmogorov-Smirnov test has been used for estimation of possible sample deviation from normal distribution. Independent samples t-test was calculated to compare observed clinical parameters between PH and NC groups. When samples have deviated statistical significant values from normal distribution, Mann-Whitney (MW) test was additionally applied. Chi square test was used for comparing frequency data. In order to estimate the validity of criteria of GW and BW values as predictors of survival, ROC (Receiver Operating Characteristic) was applied. AUC (Area Under the Curve) was estimated to assess their survival differentiation reliability. All statistical analyses were implemented within MedCalc® software ver. 17.2.0 (MedCalc Software, Mariakerke, Belgium).

## Results

Mean PaCO<sub>2</sub> in PH group was 7.46 kPa (range: 6.3-10.6 kPa). In NC group, mean PaCO<sub>2</sub> was 5.9 kPa (range: 4.6-7.3 kPa). The two groups did not differ regarding GW (29.2 ± 3.08 in PH vs. 28.29 ± 3.01 in NC group). BW was statistically significantly higher in PH group comparing to NC (1,539 ± 584 vs. 1,348 ± 504). There was no statistically significant difference between groups regarding antenatal steroid use, condition at birth (CRIB score, and Apgar score), surfactant use or the severity of RDS. Observed groups had also similar survival rate (**Tab. 1**).

ROC analysis was performed in order to show if there was a value of GW, within PH and NC groups, that was predicting in terms of outcomes. In case of GW for PH group, results showed very good differentiation accuracy (AUC = 0.879, SE = 0.0462,

95% CI = 0.778-0.945, p < 0.0001). Estimated cut-off value was GW ≤ 27, with maximal sensitivity of 75% and specificity of 89.8% (**Fig. 1**). When we considered NC group, we had similar results (AUC = 0.872, SE = 0.0479, 95% CI = 0.784-0.933, p < 0.0001). Estimated cut-off value was GW ≤ 26 with maximal sensitivity of 72% and specificity of 92.2% (**Fig. 2**). These results indicate that a GW ≤ 27 in PH group, or ≤ 26 in NC group, is predictive of negative outcome regarding survival, with a high accuracy.

We also performed ROC analysis in order to show if the value of BW within PH and NC groups of patients can be predicting in terms of outcomes. We found a cut-off value ≤ 1,000 g with maximal sensitivity of 75% and specificity 98.0% (AUC = 0.908 SE = 0.0407, 95% CI = 0.814-0.964, p < 0.0001) for PH group (**Fig. 3**). We had similar results for NC group: estimated cut-off value was ≤ 980 g with maximal sensitivity of 76% and specificity of 95.3% (AUC = 0.911 SE = 0.0388, 95% CI = 0.831-0.961, p < 0.0001) (**Fig. 4**). Results showed that a BW ≤ 1,000 g in PH group, and ≤ 980 g in NC group, can be informative with a high sensitivity and specificity in prediction of negative outcome regarding survival.

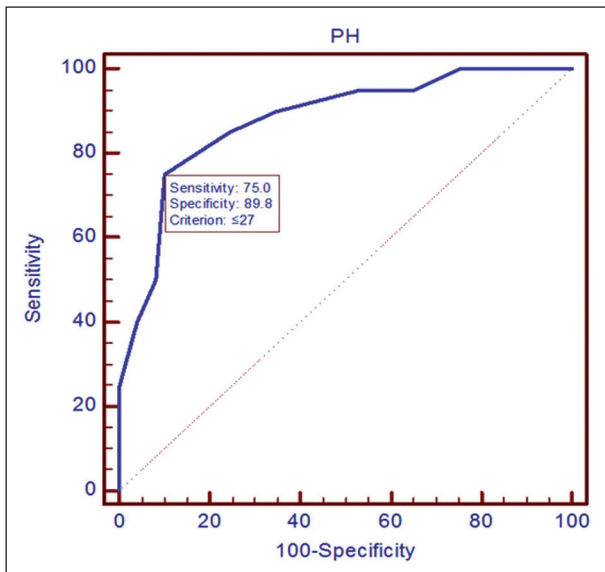
## Discussion

Worldwide, preterm birth is a major cause of mortality and a significant cause of long-term disability among survivors. Complications of premature birth are the most common direct cause of neonatal death, responsible for 35% of the 3.1 million deaths in the neonatal period on annual basis, and the second most common cause of death up to the age of 5 years, after pneumonia [12]. Thanks to interventions such as antenatal corticosteroid

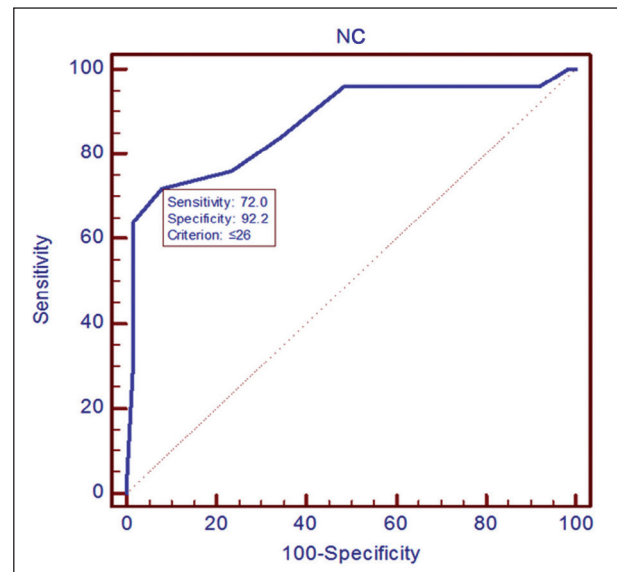
**Table 1.** The comparisons of observed clinical parameters.

Parameters	PH group		NC group		Difference
GW, mean ± SD	29.2 ± 3.08		28.29 ± 3.01		t = 1.864, p = 0.064
BW, mean ± SD	1,538.55 ± 584.0		1,347.47 ± 504.39		t = 2.204, p = 0.029
Antenatal steroid use, n (%)	25/69 (36.23%)		28/89 (31.46%)		χ <sup>2</sup> = 0.383, p = 0.536
CRIB score, mean ± SD (range)	2.66 ± 3.69 (0-17)		3.29 ± 3.95 (0-23)		t = 1.022, p = 0.308; MW = 2,521.0, p = 0.082
Apgar 1, mean ± SD (range)	5.40 ± 2.39 (0-9)		4.96 ± 2.43 (0-10)		t = 1.122, p = 0.264; MW = 2,533.5, p = 0.253
Apgar 5, mean ± SD (range)	6.40 ± 2.26 (1-10)		6.02 ± 2.11 (1-10)		t = 1.055, p = 0.293; MW = 2,269.0, p = 0.173
Surfactant use, n (%)	26/69 (37.7%)		35/89 (39.3%)		χ <sup>2</sup> = 0.005, p = 0.940
RDS, n	Mild	Severe	Mild	Severe	χ <sup>2</sup> = 0.456, p = 0.499
	41/69	28/69	53/89	36/89	
Death, n (%)	20/69 (28.99%)		25/89 (28.09%)		χ <sup>2</sup> = 0.0154, p = 0.901

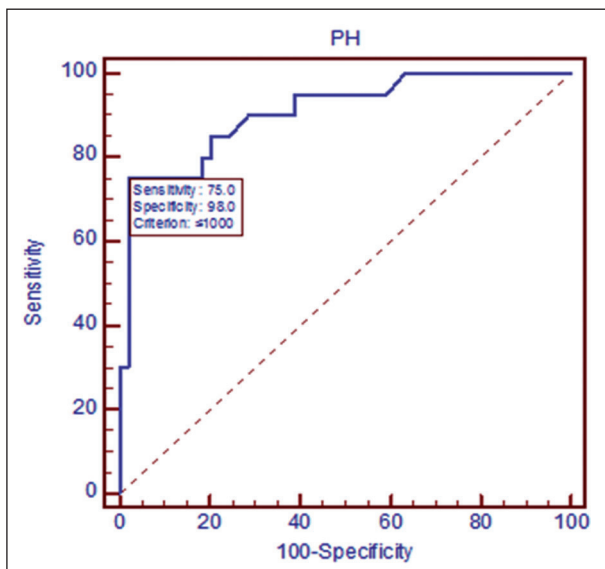
PH: permissive hypercapnia; NC: normocapnia; GW: gestational age in weeks; BW: birth weight; RDS: respiratory distress syndrome.



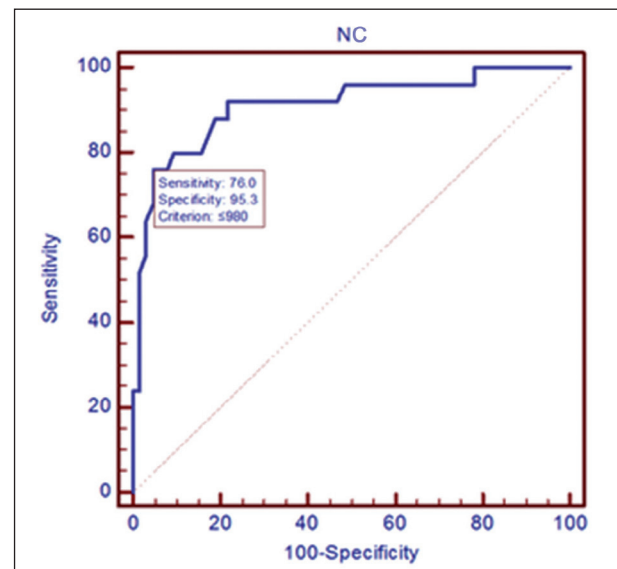
**Figure 1.** ROC – values of gestational age (gestational weeks, GW) in permissive hypercapnia (PH) group.



**Figure 2.** ROC – values of gestational age (gestational weeks, GW) in normocapnia (NC) group.



**Figure 3.** ROC – values of birth weight (BW) in permissive hypercapnia (PH) group.



**Figure 4.** ROC – values of birth weight (BW) in normocapnia (NC) group.

use, surfactant application, non-invasive ventilation and many others, the survival of preterm infants has dramatically increased in recent decades. Statistics are diverse and depend primarily on the level of development of the country, ranging from a survival rate of 93.8% in Japan, 90.2% in Canada, 92.2% in Australia and New Zealand, and 89.4% in the European Union [13]. Data from developing countries are limited, but a study by Macedonian authors shows survival rates of RDS in infants requiring invasive mechanical ventilation ranged from 25% in those newborns with BW < 1,000 grams up to 53% in those with BW > 2,500 grams

[14]. Overall mortality in this study was 28.48% (45 patients). In PH group there were 20/69 (28.99%) deaths, and in NC group 25/89 (28.09%). No association between mode of treatment and outcome was noticed ( $\chi^2 = 0.0154$ ;  $p = 0.901$ ). In a study on adults, Amato et al. [15] showed that protective ventilation was not associated with a higher rate of survival to hospital discharge. There is an obvious and expected correlation between GW and outcome. After performing ROC analysis (95% CI) in the total number of subjects, it can be said that preterm infants have significantly higher risk for death when  $GW \leq 27$  weeks, with test sensitivity of 76% and

specificity of 82.3%. PH group has cut-off value of  $\leq 27$  weeks (sensitivity 75%, specificity 89.8%), and in NC group cut-off is  $\leq 26$  weeks (sensitivity 72%, specificity 92.2%). The conclusion is that, considering survival of preterm infants, ventilation strategy of permissive hypercapnia is safer when gestational age is  $> 27$  weeks. We have also analyzed correlation between BW and death. In all subjects ROC analysis reveals cut-off value for survival  $\leq 1,000$  g (sensitivity 78%, specificity 93.8%). In PH group cut-off value was also  $\leq 1,000$  g (sensitivity 75%, specificity 98.0%), and in NC group cut-off is  $\leq 980$  g (sensitivity 76%, specificity 95.3%). The conclusion is that, considering survival of preterm infants, ventilation strategy of permissive hypercapnia is safer when BW is  $> 1,000$  g.

## Conclusion

This study shows that ventilation with permissive hypercapnia of preterm infants with RDS is safer, considering survival, in children with GW above 27 and BW above 1,000 g.

## Declaration of interest

The Authors declare no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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