

# Permissive Approach and Relationship to Outcomes of Infants <27 Weeks Gestation

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## Abstract

**Purpose:** To determine profiles of carbon dioxide (PaCO<sub>2</sub>), pH and blood pressure (BP) in preterm infants (<27 weeks gestational age) in relation to mortality or any of three severe morbidities: (a) severe neurological injury, (b) severe retinopathy or (c) chronic lung disease. **Methods:** Profiles of pH, PaCO<sub>2</sub> and BP in the first week and outcomes were analysed by dividing infants in three groups: (1) no morbidities (n=73); (2) with one/two morbidities (n=125), and (3) death or all three morbidities (n=56). **Results:** Mean pH were higher for Groups 1 and 2 compared to Group 3. Mean PaCO<sub>2</sub> values were normal and lower for Group 1 compared to Groups 2 and 3. Mean BP was not different between three groups. **Conclusion:** Preterm infants with no morbidities had pH and PaCO<sub>2</sub> values near normal range whereas infants with significant morbidities or mortality had values in the so-called "permissive" range.

## Key words

Acidosis; Hypotension; Infant-premature; Outcome; Permissive hypercapnia

## Introduction

Neonatologists have adopted a practice of permissive hypercapnia (PHC),<sup>1</sup> permissive respiratory acidosis,<sup>1</sup> permissive hypotension,<sup>2</sup> and acceptance of lower oxygen saturations<sup>3</sup> (permissive hypoxemia) in the treatment of critically ill preterm neonates. Many of these practices have been adopted in clinical care either to avoid treatment-

induced changes or to avoid fluctuations in these parameters. However, these practices are not based on robust evidence.

Cochrane review of two randomised controlled trials concluded no benefit of hypercapnia over routine ventilator management strategy and asked for further trials.<sup>4</sup> Thome and Ambalavanan<sup>1</sup> in a recent review highlighted that hypocapnia can reduce cerebral perfusion and may lead to periventricular leukomalacia (PVL), whereas hypercapnia can predispose to intraventricular haemorrhage (IVH). Kaiser et al<sup>5</sup> reported maximum partial pressure of carbon dioxide (PaCO<sub>2</sub>) during the first 3 days as a dose-dependent predictor of severe IVH. Narrative reviews<sup>6,7</sup> of permissive hypercapnia have suggested beneficial effects of mild to moderate hypercapnia in preventing lung damage; however, all studies have reported that a safe range of CO<sub>2</sub> for neonates is not established and further studies were needed. Practitioners have adopted practice of PHC that allows PaCO<sub>2</sub> to be in the range of 45-65 (highly variable and practitioner dependent) and pH to drift lower in the range of 7.25 or 7.20 (variable and practitioner dependent). Similarly, for mean blood pressure (BP), the acceptable range for normal is elusive. In a retrospective cohort study, Dempsey et al<sup>2</sup> investigated the effects of permissive hypotension in extremely low birth weight infants with good

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Received December 14, 2011

signs of perfusion on neonatal outcomes and reported that treating blood pressure was associated with adverse outcomes. Concept of "permissive hypotension" was suggested; however, no safe level could be identified and impact on long-term outcome of untreated hypotension is unknown. Impact of low target oxygen saturation is currently subject to rigorous randomised trials; however, a retrospective study reported no harmful effects.<sup>3</sup>

The benefits of permissive approach need to be weighed against the risks involved. With higher levels of CO<sub>2</sub> and lower blood pressures, oxygen delivery to tissues is likely to be affected. Fluctuation in tissue oxygen extraction is implicated in the development of retinopathy of prematurity (ROP) and chronic lung disease (CLD).<sup>1</sup> We hypothesise that infants managed with permissive approach (for CO<sub>2</sub>, pH and BP) will have better outcomes than patients managed using aggressive approach.

## Materials and Methods

**Objective:** To determine the profiles of pH, PaCO<sub>2</sub> and BP in extremely preterm infants (<27 weeks gestational age (GA) ) in the first 7 days of postnatal age in relation to their neonatal outcomes.

**Design and setting:** A retrospective chart review was conducted at tertiary referral Neonatal Intensive Care Unit (NICU).

**Inclusion and exclusion criteria:** Inborn preterm infants <27 weeks GA admitted from July 1, 2004 through June 30, 2009, were included. Infants with acutely life-threatening congenital anomalies, infants admitted after 7 days of age, and infants missing data for the first 3 days and infants who died in the first 3 days were excluded as their outcomes were most likely associated with their extreme prematurity and complications associated with pregnancy as opposed to their respiratory and hemodynamic profiles or management practices. Infants included in the study were to have a minimum of three measurements in their profile with at least two of the measurements of exposures of interest in the first 72 hours of life. Readmissions were combined into one profile.

**Usual practice during the period:** The management practices during the study years were consistent. We target pH to be >7.25, PaCO<sub>2</sub> between 45-55 mm of Hg in the first 3 days and 45-65 mm of Hg in days 4-7 of postnatal age, and mean arterial blood pressure > the number of completed gestational age in weeks. Any deviation from these values warranted clinical exploration for reasons and

appropriate response based on these findings. Target preductal saturations were 88-94. Routine head ultrasounds were performed between 2-4 days, 7-10 days, weekly for next 2 weeks and then bi-weekly for the remaining stay. Add-on ultrasounds were performed when clinically indicated. Eye examinations were performed at regular intervals starting from week 6 of postnatal age and followed up as suggested by an ophthalmologist.

**Exposures of interest:** Profiles for blood pH, PaCO<sub>2</sub> measured in an arterial or capillary sample (capillary sample values were only considered after 24 hours of age), and mean arterial blood pressure (measured via cuff or an indwelling catheter) were retrieved from patient charts over first seven postnatal days. We included capillary samples as they are shown to have good correlation with arterial sample for measurements of pH and pO<sub>2</sub>. Data were collected from charts during five pre-defined times: (a) birth to 6 hours, (b) 6-24 hours, (c) day 2, (d) day 3, and (e) day 4 to day 7. If more than one value were available for the time interval, an average was taken to establish values for the period of interest. We undertook this approach as primary aim of the study was to determine validity of cut-offs and we recognise that this may not be the best approach as fluctuations in values are as important.

**Outcome groups:** Data on neonatal outcomes were retrieved from charts. These included mortality, or any of the three severe morbidities: (a) severe neurological injury was defined as IVH grade 3 or 4<sup>8</sup> or periventricular leukomalacia diagnosed at any time prior to discharge or death, (b) severe ROP was defined as stage 3 or higher ROP<sup>9</sup> diagnosed at any time prior to discharge or death and (c) CLD was defined as oxygen or respiratory support dependency at 36 weeks postmenstrual age.<sup>10</sup> Patients were divided in 3 groups:

- Group 1: patients with no morbidities or mortality
- Group 2: patients with one or two morbidities but no mortality
- Group 3: patients who had either all three morbidities or who died before discharge.

**Statistical analysis:** Descriptive statistical methods were used to describe the study population. The characteristics of infants were compared among the three outcome groups using chi-square test for categorical variables and analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables. Data points were missing for 3.9% of the sample. These were imputed using both mean and last value carry forward methods. The univariate analyses were performed to identify the risk factors and confounders. We then compared the exposure profiles among the three outcome

groups using fixed-effect linear models for repeated measures, adjusting for the gestational age, sex and Transport Risk Index for Preterm infants (TRIPS) score. The analyses were performed using S v. 9.2 and R v. 2.8.1 without adjusting for multiple comparisons.

## Results

**Patient flow and baseline characteristics:** A total of 326 preterm infants <27 weeks GA were admitted to the Mount Sinai NICU during the study period. Seven infants with congenital anomalies, seven infants who were late admissions, nine infants with missing data in first three days and 49 infants who died during the first three days after birth were excluded. Therefore, 254 infants in total were included in this study: there were 73 neonates in Group 1, 125 infants in Group 2, and 56 neonates in the Group 3. Baseline comparison revealed significant differences between groups in terms of GA, BW, and TRIPS score on admission (Table 1). On average neonates in Group 1 had higher birth weight, higher GA, and lower severity of illness.

**Outcomes:** The overall rates of outcomes in the entire cohort were: Severe neurological injury – 20.1%, severe ROP 32.7%, CLD 36.6% and mortality 19.7% (some infants had more than one morbidities).

## Effects of Exposures on Outcomes

Profile analyses results using linear fixed-effect models for repeated measures, controlled for gestational age, sex and TRIPS score are reported in Table 2.

**pH profile comparison:** There was a statistically significant difference in the mean pH values when Groups 1 and 2 were compared with Group 3, for first 3 days (Table 2). The average pH of Group 1 was higher than both Groups 2 and 3 (Figure 1). Although insignificant, Group 2 exhibited similar trends of higher pH compared to Group 3.

**Partial pressure of carbon dioxide profile comparison:** There was a statistically significant difference in the mean PaCO<sub>2</sub> values between Groups 1 and 2 at all time points after first day. Group 3 was only significantly different from group 1 at day 2 and days 4-7 (Table 2). The mean PaCO<sub>2</sub> for Group 1 was lower than both Groups 2 and 3 at all time points. The PaCO<sub>2</sub> values were within normal range of 35-45 mm of Hg in Group 1 as opposed to higher than this range in Group 2 and Group 3 (Figure 2).

**Mean arterial blood pressure profile comparison:** There was no significant difference in the mean BP profiles between outcome groups (Table 2). The mean BP was higher than usually acceptable range of BP for preterm infants in all three groups.

## Discussion

In this exploratory study to investigate the respiratory and hemodynamic profiles of extremely preterm infants of <27 weeks GA in relation to their neonatal outcomes, we identified significant differences between groups in relation to pH and PaCO<sub>2</sub> profiles during the initial days after birth in both adjusted and unadjusted comparisons. There was no significant difference in mean BP profile between groups. The mean pH values of the group with no

**Table 1** Comparison of infant characteristics among groups

Characteristic	Outcome Group 1 n=73	Outcome Group 2 n=125	Outcome Group 3 n=56	P-value
Gestational age weeks (Mean + SD)	25.4±0.8	25.1±0.8	24.3±1.0	<0.01
Birth weight grams (Mean + SD)	856±169	785±151	685±131	<0.01
SGA n (%)	3 (4)	7 (6)	8 (14)	0.07*
Apgar at 5 minutes n (%)				
≥7	56 (77)	83 (67)	32 (57)	0.06
<7	17 (23)	41 (16)	24 (43)	
Male sex n (%)	37 (50)	62 (50)	32 (57)	0.63
TRIPS score <sup>†</sup> (Mean + SD)	21±8	20±8	23±10	0.04

\*Fisher exact test; <sup>†</sup>TRIPS=Transport risk index for preterms

SGA=small gestational age

morbidities were around 7.30 as compared to around 7.25 in group with the highest adverse outcomes. Similarly, mean PaCO<sub>2</sub> values were in upper range of normal for the group with no morbidity (<45) as compared to 48-50 mm of Hg for the group with the highest rates of adverse outcomes. We acknowledge that this may be due to baseline patient characteristics (lower GA, lower BW, and higher severity of illness scores) rather than approach of care; however, this study warrants caution with deliberate use of

"permissive" approaches and highlights uncertainty in this area and persistence of differences after controlling for confounders.

Permissive hypercapnia has been evaluated in both randomised trials and cohort studies. Mariani et al<sup>11</sup> reported on short term outcomes of 49 infants randomised to PHC (PaCO<sub>2</sub> 45-55 mm of Hg) and normocapnia (PaCO<sub>2</sub> 35-45 mm of Hg). There was reduction in the number of days on assisted ventilation, oxygen support; however, none of the

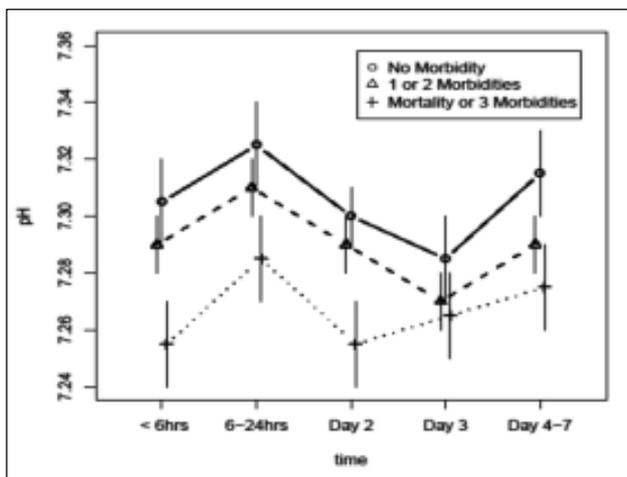
**Table 2** Comparison of exposure of interests among outcome groups

Time	Exposure	Outcome Group 1	Outcome Group 2	Outcome Group 3
<6 hours	pH	7.30 (7.29, 7.32)*	7.29 (7.28, 7.30) ‡	7.25 (7.24, 7.27)* ‡
	PaCO <sub>2</sub>	47 (45, 49)*	49 (48, 51)	52 (50, 54)*
	MAP	33 (31, 34)	32 (31, 33)	32 (31, 34)
6-24 hours	pH	7.32 (7.31, 7.34)*	7.31 (7.30, 7.32) †	7.29 (7.27, 7.30)* †
	PaCO <sub>2</sub>	43 (41, 45)	45 (43, 46)	46 (44, 48)
	MAP	36 (35, 37)	35 (34, 36)	35 (33, 36)
Day 2	pH	7.30 (7.29, 7.31)*	7.29 (7.28, 7.30) †	7.25 (7.24, 7.27)* †
	PaCO <sub>2</sub>	44 (42, 46)* ‡	47 (45, 48) ‡	48 (46, 50)*
	MAP	39 (38, 40)*	38 (37, 39)*	38 (37, 39)
Day 3	pH	7.29 (7.27, 7.30)*	7.27 (7.26, 7.28)	7.26 (7.25, 7.28)*
	PaCO <sub>2</sub>	45 (46, 47)* ‡	47 (46, 49) ‡	47 (45, 50)*
	MAP	40 (39, 41)*	38 (37, 39)	39 (38, 41)
Days 4-7	pH	7.31 (7.30, 7.33)* ‡	7.29 (7.28, 7.30) ‡	7.28 (7.26, 7.29)*
	PaCO <sub>2</sub>	46 (44, 48)* ‡	49 (47, 50) ‡	49 (47, 52)*
	MAP	39 (38, 40)	38 (38, 39)	39 (37, 40)

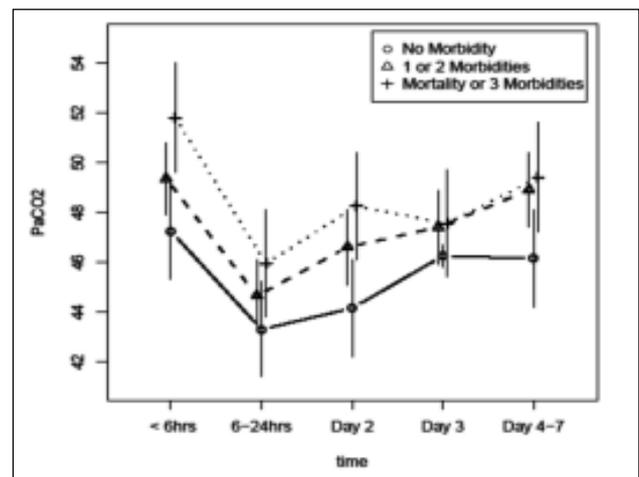
Analyses results using linear fixed-effect models for repeated measures, controlled for gestational age, sex and TRIPS score

\*p<0.05 between Group 1 and Group 3; †p<0.05 between Group 2 and Group 3; ‡p<0.05 between Group 1 and Group 2

MAP=mean arterial pressure



**Figure 1** Comparison of pH among outcome groups.



**Figure 2** Comparison of PaCO<sub>2</sub> among outcome groups.

values was statistically significantly better. The authors cautioned physicians to seek further investigation as their study lacked power. Carlo et al<sup>12</sup> randomised 220 patients in a factorial design trial that was stopped early due to adverse impact noted in steroid arm of the trial. Permissive hypercapnia group had target of PaCO<sub>2</sub> of >52 for 10 days and control group had target of PaCO<sub>2</sub> of <48 for 10 days. There was no reduction in the outcome of death or CLD in PHC group (63% in PHC group vs. 67% in normocapnia group). Fabres et al<sup>13</sup> in an retrospective analysis of infants <1250 g BW in first 2 days revealed that extremes of hypo and hypercapnia in the first two days were associated with risk of IVH. Hagen et al<sup>14</sup> evaluated impact of hypercapnia in very low birth weight infants and reported association between hypercapnia and risk of IVH in infants with low Apgar score at 1 minute. Thus, none of the studies has been able to confirm either superiority of PHC approach or safe levels of CO<sub>2</sub> in preterm neonates and concerns have been raised for both high and low levels. A recently completed trial comparing CPAP (with tolerance for pH of 7.2 and PaCO<sub>2</sub> of 65 mm of Hg) with intubation and surfactant strategy (with tolerance of pH of 7.3 and PaCO<sub>2</sub> of 50 mm of Hg) revealed no difference in primary outcome of death or CLD.<sup>12</sup>

In our study, we observed a potential dose dependent effect during the first week. As evident from figures, pH tended to be higher at all times in Group 1, intermediate in Group 2 and lower in Group 3. Levels of PaCO<sub>2</sub> were lower (within normal range) for Group 1, in intermediate range for Group 2 and higher in the Group 3. These differences were marked in the first 72 hours indicating period of maximum vulnerability. As far as pH is concerned, most of our babies (60% of total) had mild metabolic acidosis in the first 3 days (base deficit of 3-7).

Mean BP values in our patients in all three groups were within normal range. Number of infants who received inotropes in our series was very small indicating high tolerance for blood pressure values in the lower range and unlikely impact on neonatal outcomes. Our findings concur with Dempsey. They reported similar clinical outcomes between patients who were normotensive according to GA based criteria and those who were hypotensive based on GA based criteria but had good perfusion and were not treated.

Strengths of our study include contemporary cohort of extremely preterm neonates from a large perinatal center. There has been no change in the practiced targets during this period regarding PaCO<sub>2</sub>, pH or BP. There has also been

no change in the use of narcotics (the use during the study period had been <5%), muscle relaxants (use <1%), inotropes (use <5%), and postnatal steroids (<5%) which may have impact on exposure or outcomes. However, limitations of our study include impact of unknown confounders that we have not controlled for, and an approximately one week lower GA and 150 g lower BW of patients in the most adverse outcome group. Patients with BW in normal range for GA may have improved homeostasis and had improved gas exchange leading to their CO<sub>2</sub> and pH in normal range compared to smaller and younger infants. We acknowledge limitation of averaging values over time when more than one values were available as this may have affected the results. It will also be useful if more infants in each GA or BW groups that we can stratify to understand differential effects. Despite these limitations, our results do suggest that for small and immature infants permissive approach as employed in the current practice requires further evaluation.

Our purpose in this paper is to highlight the possibility of adverse outcomes in association with high CO<sub>2</sub> and low pH, to warrant careful studies before accepting this as standard of care, and not to suggest causal inference. Recently published results of SUPPORT trial<sup>15</sup> indicated a higher mortality but lower rates of severe ROP in the group of infants randomised to lower saturation targets compared to infants randomised to higher saturation target. This was against the trend observed in cohort studies of no impact of lower target oxygen saturations on mortality and unless practices are scrutinised in proper RCT small but clinically significant differences may remain masked.

## Summary

Extreme preterm infants with no morbidities had pH and PaCO<sub>2</sub> values in normal range during first week whereas infants with significant morbidities and mortality had values of pH and PaCO<sub>2</sub> lower than normal, albeit in the range that many considered acceptable. "Permissive" approach of management of extremely preterm neonates needs careful evaluation.

## Acknowledgement

Maternal Infant Care Research Center is supported by Ministry of Health and Long-term Care, Ontario, Canada.

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