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Hyperventilation versus standard ventilation for infants in postoperative care for congenital heart defects with pulmonary hypertension

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Abstract
Purpose. In infants undergoing surgery for cardiac defects with left-to-right shunt, a hyperventilation strategy has been applied to prevent pulmonary hypertensive crisis (PHC). Hyperventilation with a large tidal volume and/or higher airway pressure, however, may be detrimental to the lung. This randomized study compared the effects of hyperventilation versus standard ventilation.
Methods. We enrolled 22 infants with a preoperative pulmonary-to-systemic blood pressure ratio of more than 0.7. Hyperventilation, with a tidal volume of 10–12 ml·kg^{-1} to keep Pa_{CO_2}between 30 and 35 mmHg, was randomly applied in 11 patients for 16 h or more. The other 11 patients were randomly assigned to standard ventilation, with a 6- to 8-ml·kg^{-1} tidal volume.
Results. The peak inspiratory pressure was higher (20 ± 3 vs 18 ± 2 cmH_2O; $P = 0.018$), and Pa_{CO_2} (34 ± 5 vs 42 ± 7 mmHg; $P = 0.003$) and positive end-expiratory pressure (3 ± 0 vs 5 ± 0; $P < 0.0001$) were significantly lower in the hyperventilation than in the standard ventilation group. The Pa_{O_2}/inspiratory fraction of oxygen ($F_{I_{O_2}}$) ratio decreased from 244 ± 160 mmHg at the onset of postoperative ventilation, to 177 ± 96 mmHg at 24 h ($P = 0.038$) in the hyperventilation group, versus a decrease from 240 ± 89 to 220 ± 97 mmHg in the standard ventilation group not significant (NS). Serum interleukin (IL)-6 level, measured at 24 h postoperatively, was significantly lower ($P = 0.02$) in the standard ventilation than in the hyperventilation group, suggesting an attenuated postoperative systemic inflammatory response. A single patient in each group developed PHC.
Conclusion. Hyperventilation may cause lung injury and systemic inflammation in infants with pulmonary hypertension undergoing corrective heart surgery.

Key words Mechanical ventilation · Congenital heart defects · Infants · Pulmonary hypertension

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Introduction

The sudden onset of right ventricular failure and arterial hypotension and hypoxemia caused by an increase in pulmonary vascular resistance, also known as pulmonary hypertensive crisis (PHC), is a complication that occurs in patients who have undergone surgical repair of congenital heart defects with left-to-right shunt [1]. Hyperventilation-induced hyperoxia and alkalosis was first advocated as primary prophylaxis or treatment to relieve pulmonary vasoconstriction and alleviate pulmonary hypertension [2]. Hyperventilation was induced manually or mechanically by ventilating the lungs with a larger tidal volume, higher peak airway pressure, lower positive end-expiratory pressure, and/or rapid rates. However, alveolar overdistention and/or collapse-reopening associated with the hyperventilation may be invasive for the alveoli. Recent studies suggest detrimental effects of large tidal volume ventilation, and protective effects conferred by smaller tidal volumes, particularly in patients suffering from acute lung injury [3–5]. Infants or children who undergo surgery for congenital heart disease may have suffered preoperative lung injury from a high pulmonary blood flow [6], as well as intraoperative damage from cardiopulmonary bypass [7], and they therefore represent a population that might be at particularly high risk from invasive ventilation. To the best of our knowledge, no study has scrutinized the efficacy and safety of hyperventilation in patients at risk of PHC. This randomized pilot trial examined the role of mechanical hyperventilation versus standard ventilation on outcomes in infants with perioperative pulmonary hypertension.

Methods

This study was approved by the Institutional Committee for Clinical Investigation of Kyoto Prefectural

School of Medicine. All parents or persons responsible for the patients included in the study had granted their written consent. Between May 2002 and October 2003, we enrolled 29 infants who were admitted to the pediatric intensive care unit (PICU) of the University Hospital after corrective surgery for congenital cardiac defects with high pulmonary arterial pressure due to left-to-right shunt, such as nonrestrictive ventricular or complete atrioventricular septal defects. The patients included in this study had severe pulmonary hypertension, defined as a pulmonary-to-systemic blood pressure ratio of more than 0.7 at preoperative cardiac catheterization. All patients were exposed to hyperoxia and were found to respond to the high oxygen concentrations. Patients were randomly assigned to a hyperventilation group (n = 14) or a standard ventilation group (n = 15), using a table of random numbers. The bedside physicians could be aware of the random assignment. At the time of this study, the standard policy of our PICU was to keep patients at risk of PHC at least overnight on controlled mechanical ventilation, with continuous intravenous sedation and paralyzed.

Intraoperative remarks

A single board-certified pediatric cardiac surgeon completed the surgeries. Anesthesia was maintained with fentanyl, vecuronium, and midazolam, and sevoflurane as needed. Cardiopulmonary bypass was performed under conditions of moderate hypothermia at 25–30°C. In the bypass priming solution, methylprednisolone, 1 g, was added. Continuous hemodiafiltration was performed during the bypass and immediate postbypass period. Pulmonary arterial pressure was measured by a direct puncture, immediately after the weaning from the cardiopulmonary bypass, as a single measurement. Mechanical ventilation was controlled by each anesthesiologist independently. In the usual manner, tidal volume was set at around 10 $ml \cdot kg^{-1}$. Inhaled nitric oxide (iNO) was administered via the inspiratory limb of a continuous-flow ventilator, in doses between 5 and 20 ppm, starting during the weaning from the cardiopulmonary bypass. The indication for the use of iNO was decided upon by individual decisions (without any protocols) in consideration of preoperative or postbypass pulmonary arterial pressure, postbypass arterial pressure, or arterial oxygenation.

Mechanical ventilation settings

A V.I.P. Bird, time-cycle, pressure-limited, continuous-flow ventilator (Viasys Respiratory Care, Yorba Linda, CA, USA) was used for postoperative mechanical ventilation. The ventilator was set in time-cycle, pressure-limited, assist-control mode, with continuous flow of 10–15 $l \cdot min^{-1}$, for a period of 16 h postoperatively. In the standard ventilation group, the peak inspiratory pressure was controlled to keep tidal volume at 6–8 $ml \cdot kg^{-1}$ body weight, positive end-expiratory pressure (PEEP) at 5 cmH_2O or more, and the target Pa_{CO_2} at 40–45 mmHg. In the hyperventilation group, the peak inspiratory pressure was set to keep tidal volume at 10–12 $ml \cdot kg^{-1}$, PEEP at less than 5 cmH_2O, and the target Pa_{CO_2} at 30–35 mmHg. The ventilator setting in the hyperventilation group was identical to the traditional setting applied for patients with pulmonary hypertension, and the setting in the standard ventilation group was identical to the setting applied universally for infants in our PICU. The inspiratory fraction of oxygen ($F_{I_{O_2}}$) and respiratory rate were adjusted freely by each bedside physician. If the arterial pH decreased to less than 7.35, the respiratory rate was increased, or 7% $NaHCO_3$ was administered, as indicated. iNO was discontinued upon individual decisions by each bedside physician, without any weaning protocol. Midazolam, 0.06–0.12 $mg \cdot kg^{-1} \cdot h^{-1}$; fentanyl, 3–6 $\mu g \cdot kg^{-1} \cdot h^{-1}$; and vecuronium, 0.02–0.04 $mg \cdot kg^{-1} \cdot h^{-1}$, were continuously infused, singly or in combination, to ensure deep sedation at Ramsay's scale 5 to 6 level.

Weaning from the ventilator was attempted after 16 h by discontinuing vecuronium and slowing the infusion of sedatives, in accordance with normal PICU care practice. The extubation criteria included: (1) appropriate spontaneous breathing without tachypnea or bradypnea under around 10 cmH_2O of pressure assist, (2) a $Pa_{O_2}/F_{I_{O_2}}$ (P/F) ratio of more than 200 mmHg, (3) absence of hemodynamic instability or signs of PHC, and (4) the decision by the primary physician that the patient was ready to be extubated. iNO was decreased gradually when the patient was considered ready for weaning from the ventilator, and was discontinued before extubation.

Study measurements

PHC was defined as the sudden onset of overt signs of right ventricular failure, elevated central venous pressure, echocardiographically confirmed decreases in right ventricular ejection fraction, a more than 25% decrease in arterial pressure from baseline, and a decrease in $S_{P_{O_2}}$ to less than 90% with supplemental oxygen via a nasal cannula.

Serum C-reactive protein (CRP) and interleukin (IL)-6 concentrations were measured to assess the postoperative inflammatory status. We selected IL-6 as a single representative of proinflammatory cytokines due to limited blood withdrawal. The postoperative IL-6 concentration was measured by enzyme-linked immunosorbent assay at 24 h. Routine blood chemistry, serum CRP concentration, and blood cell counts were mea-

sured daily. Arterial blood gases were obtained every 4 h as part of standard care.

The inotropic score was calculated as the dose of dopamine, in $\mu g \cdot kg^{-1} \cdot min^{-1}$, plus dobutamine, in $\mu g \cdot kg^{-1} \cdot min^{-1}$, plus 100 × epinephrine, in $\mu g \cdot kg^{-1} \cdot min^{-1}$ [8]. Days on the ventilator, days of inotropic support, and days spent in the PICU were recorded.

Statistical analyses

The data values are expressed as medians and interquartile ranges (IQR) or as means ± SD for continuous variables. Student's *t*-test or the Mann-Whitney test were used to examine the statistical significance of between-group differences. Fisher's exact test was used to examine differences between categorical variables. A *P* value of less than 0.05 was deemed significant.

Results

Baseline characteristics

Of the 29 patients initially enrolled in the study, 7 were excluded because they were extubated within less than 16 h upon the decision of the bedside physician. Ultimately, data from 11 patients in each study group were analyzable.

No significant difference between the study groups was found in age, sex distribution, or body weight, or in the duration of the operation, cardiopulmonary bypass, or aortic cross-clamp (Table 1). Likewise, the mean pulmonary arterial pressure, pulmonary-to-systemic blood pressure ratio, and pulmonary vascular resistance were similar in both groups, preoperatively as well as after surgical repair (Table 2), measured immediately after the bypass by direct pulmonary arterial puncture. The dose of fentanyl (63 ± 26 vs 58 ± 25 $\mu g \cdot kg^{-1}$) and the amount of blood products transfused (45 ± 23 vs 48 ± 21 $ml \cdot kg^{-1}$) during surgery in the hyperventilation group and standard ventilation group were also similar in the two groups.

Ventilator settings and gas exchange

The ventilator settings at 2 h after admission to the PICU are shown in Table 3. The targeted tidal volumes and Pa_{CO_2} concentrations were successfully applied and maintained throughout the study period in both groups. Peak inspiratory pressure was significantly lower and PEEP was significantly higher in the standard ventila-

Table 1. Characteristics of the study groups

	Hyperventilation (n = 11)	Standard ventilation (n = 11)
Male/female, *n*	4/7	4/7
Median (interquartile range)		
Age, months	5 (2–9)	3 (1–5)
Weight, kg	4.7 (3.8–7.2)	4.3 (2.5–5.9)
Procedural duration, min (mean ± SD)		
Overall operation	289 ± 51	275 ± 54
Cardiopulmonary bypass	126 ± 38	124 ± 30
Aortic cross-clamp	69 ± 21	71 ± 24
Congenital defects, *n*		
Ventricular septal	5	4
Ventricular septal + atrial septal or patent foramen ovale	3	6
Atrioventricular septal	3	1

The between-group differences are not statistically significant

Table 2. Preoperative and post-bypass pulmonary circulatory measurements

	Hyperventilation (n = 11)	Standard ventilation (n = 11)
Mean pulmonary artery pressure, mmHg		
Preoperative	45 ± 9	52 ± 11
Post-bypass	23 ± 7	23 ± 5
Pulmonary-to-systemic blood pressure ratio		
Preoperative	0.8 ± 0.1	0.8 ± 0.1
Post-bypass	0.4 ± 0.1	0.4 ± 0.1
Pulmonary-to-systemic vascular resistance ratio		
Preoperative	0.4 ± 0.2	0.3 ± 0.2

The between-group differences are not statistically significant
Values are means ± SD
Post-bypass, immediately after cardiopulmonary bypass

Table 3. Ventilator settings

	Hyperventilation ($n = 11$)	Standard ventilation ($n = 11$)	P
Tidal volume, ml·body weight·kg^{-1}	10.4 ± 0.9	7.7 ± 1.4	0.0004
Peak inspiratory pressure, cmH_2O	20 ± 3	18 ± 2	0.018
Positive end-expiratory pressure, cmH_2O	3 ± 0	5 ± 0	<0.0001
$F_{I_{O_2}}$	0.8 ± 0.2	0.7 ± 0.2	0.09
Arterial pH	7.49 ± 0.05	7.43 ± 0.05	0.026
Pa_{CO_2}, mmHg	34 ± 5	42 ± 7	0.003

Values are means ± SD, 2 h after PICU admission

Table 4. Postoperative hemodynamic profiles

	Hyperventilation ($n = 11$)	Standard ventilation ($n = 11$)
Heart rate, bpm		
0 h	185 ± 23	174 ± 15
24 h	163 ± 15	166 ± 16
Mean arterial pressure, mmHg		
0 h	69 ± 10	68 ± 7
24 h	66 ± 9	72 ± 9
Central venous pressure, mmHg		
0 h	10 ± 3	11 ± 2
24 h	10 ± 1	9 ± 1
Inotropic score, μg·kg^{-1}·min^{-1}		
0 h	16 ± 11	13 ± 7
24 h	15 ± 10	11 ± 6

Values are means ± SD
The between-group differences are not statistically significant
0 h, on PICU admission; 24 h, 24 h after PICU admission

tion group, consistent with the use of smaller tidal volumes.

The P/F ratio decreased significantly in the hyperventilation group, from 244 ± 160 mmHg at the onset of postoperative ventilation, to 177 ± 96 mmHg at 24 h ($P = 0.038$), whereas no significant change was observed in the standard ventilation group (240 ± 89 mmHg to 220 ± 97 mmHg). The decrease in the P/F ratio tended to be greater in the hyperventilation group ($P = 0.19$). The $F_{I_{O_2}}$ showed no statistically significant changes during the 24-h period in either group.

Pulmonary and systemic hemodynamic measurements

The heart rate, mean arterial pressure, central venous pressure, and inotropic score were similar in both groups on admission to the PICU, and at 24 h after surgery (Table 4).

Inflammatory response

The mean postoperative concentrations of CRP were 8.8 ± 7.2 and 7.6 ± 3.8 mg·dl^{-1} at 24 h, and peaks of 13.5 ± 9.9 and 11.2 ± 6.7 mg·dl^{-1} were reached in the hyperventilation and the standard ventilation groups, respectively. However, the period when the CRP concentration was more than 5 mg·dl^{-1} was 5 ± 4 days in the hyperventilation group, versus 3 ± 2 days in the standard ventilation group ($P = 0.12$). After 24 h of mechanical ventilation, the mean serum IL-6 concentration was significantly higher ($P = 0.02$) in the hyperventilation than in the standard ventilation group (Fig. 1).

Other outcome measures

The postoperative adverse events and other outcome measures are listed in Table 5. PHC occurred in one patient in each group—at 0 and 2 days postoperatively (twice) in the hyperventilation group and at 1 day postoperatively in the standard ventilation group. In the hyperventilation group, six patients (55%) required iNO therapy for more than 24 h, versus two patients (18%) in the standard ventilation group ($P = 0.09$). No differences in rates of postoperative pulmonary complications, including atelectasis and reintubation, were observed between the two groups. Similarly, the between-group differences in the number of days spent on the ventilator, on inotropic support, or in the PICU, were not significant. No death occurred in either group.

Table 5. Outcome measures

	Hyperventilation (n = 11)	Standard ventilation (n = 11)
Pulmonary hypertensive crisis, n	1	1
Atelectasis, n	1	1
Reintubation, n	1	2
Days of		
Inhaled nitric oxide	2.7 ± 2.6[a]	1.1 ± 1.6[b]
Inotropic support	7 ± 3	7 ± 3
Ventilator support	7 ± 4	6 ± 3
Stay in PICU	11 ± 4	10 ± 4

Unless specified otherwise, values are means ± SD
The between-group differences are not statistically significant
PICU, pediatric intensive care unit
[a] n = 7; [b] n = 4

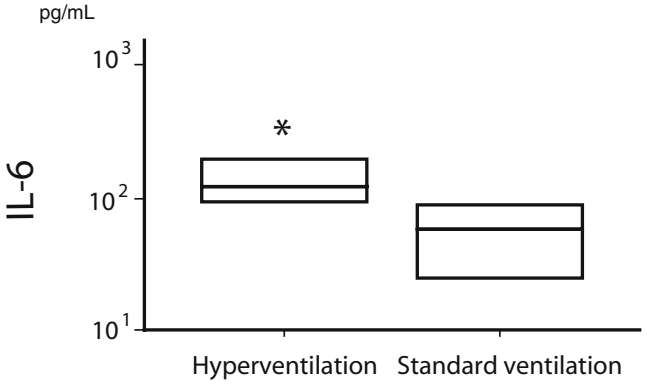

Fig. 1. Serum concentrations of interleukin-6 (*IL-6*). The serum concentration of IL-6 was significantly lower (*P = 0.02) in the standard ventilation group than in the hyperventilation group after 24 h of mechanical ventilation. Data values are medians (*horizontal lines in boxes*), with interquartile ranges shown as box

Discussion

This study examined the effects of hyperventilation versus standard ventilation strategies applied during the immediate postoperative period in patients at risk of PHC. Increases in postoperative systemic inflammatory mediators, along with the poor arterial oxygenation in the hyperventilation group, suggest that vascular or parenchymal injury, or both, was caused by hyperventilation, and that standard ventilation may have mitigated these adverse lung changes.

Hyperventilation has traditionally been accepted for the postoperative management of patients presenting with pulmonary hypertension, to increase the arterial pH and decrease the pulmonary vascular resistance [2], and is being used in current intensive care practice as prophylaxis or treatment of PHC [9]. This practice, however, has been lacking controlled clinical trials supporting its efficacy. Morris et al. [10] directly compared the effects of hyperventilation with those of iNO therapy, and found a comparable decrease in pulmonary vascular resistance, though a considerably higher systemic vascular resistance, associated with hyperventilation, which may be harmful for infants with poor myocardial reserve undergoing cardiac surgery. Other experimental and clinical studies have suggested adverse effects on lung function caused by hyperventilation-induced hypocapnia [11,12]. These observations suggest that the clinical evidence supporting the benefit of hyperventilation in patients suffering from pulmonary hypertension is weak.

Recent clinical studies have revealed a possible beneficial effect conferred by protective ventilation, specifically in patients with an injured lung. The use of PEEP during mechanical ventilation is also recommended for the avoidance of alveolar collapse and reopening. Established lung damage has been alleviated by using smaller tidal volumes, or by limiting the inspiratory plateau pressure, or by both methods [4,13–19]. Avoidance of shear stress or overstretching of the alveoli in protective ventilation may attenuate the local production of pro-inflammatory cytokines, represented by IL-6 [20]. The significant difference in IL-6 concentrations between the two ventilatory strategies in the present study, supported by the persistent postoperative elevation of C-reactive protein (CRP) in the hyperventilation group, is consistent with previous observations. Because patients who undergo cardiac surgery suffer from lung endothelial or parenchymal injury, and from an accentuated systemic inflammatory response associated with cardiopulmonary bypass [21], the attenuation of that response by a lung-protective strategy appears important.

Despite being statistically insignificant, the trend toward a greater impairment of arterial oxygenation capacity in the hyperventilation group than in the standard ventilation group in our study is noteworthy. Experimental data suggest that only 4 h of hyperventilation contribute markedly to a decrease in arterial oxygenation [22]. Hyperventilation applied for approximately 16 h may suffice to cause lung injury in infantile

vulnerable lung [23], although no apparent signs of lung injury were noted in the chest X-ray findings in our study. Postoperative alveolar collapse during mechanical ventilation with lower PEEP may also have affected the poor oxygenation in our hyperventilation group. Although the present study did not address the long-term effects of the two ventilator modes, our results at least suggest that hyperventilation with lower PEEP levels is not an appropriate mode for the prevention of pulmonary hypertension or PHC. Concordant with previous clinical studies supporting the clinical efficacy of gentle ventilation, instead of hyperventilation, for the management of neonatal pulmonary hypertension [24,25], it appears that abstaining from using hyperventilation in pediatric patients undergoing cardiac surgery might be the preferred option.

The benefits of standard ventilation compared with hyperventilation barely reached statistical significance in the present study. The 7.7 $ml \cdot kg^{-1}$ versus 10.4 $ml \cdot kg^{-1}$ difference in tidal volume, and 5 cmH_2O versus 3 cmH_2O difference in PEEP, on average, between the two groups, may explain the borderline significance of our results. In a previous study showing a benefit conferred by small tidal volume ventilation and high PEEP, the differences were 6 $ml \cdot kg^{-1}$ versus 12 $ml \cdot kg^{-1}$ [4] and 14.8 cmH_2O versus 6.5 cmH_2O, respectively [5]. Further trials comparing mechanical ventilation with greater differences in tidal volume or plateau pressure, or in both settings, might be warranted.

Study limitations

We did not directly measure the pulmonary arterial pressure. This may have prevented the precise monitoring and detection of pulmonary hypertension and PHC, a major outcome measure of the ventilatory procedures. Insertion of a pulmonary arterial catheter, however, is a complicated procedure, associated with risks of potentially fatal postoperative hemorrhage and arrhythmias. Our standard practice, therefore, does not include the use of a pulmonary arterial catheter.

This study was underpowered to ascertain the impact of the two ventilation modes on the incidence of PHC. Given the 14% rate of postoperative PHC observed in repairs of common atrioventricular septal defects [1], more than 100 patients would have been needed to detect significant differences between patients assigned to one ventilator mode versus the other. The numbers of patients were limited by our selection of patients with severe preoperative pulmonary hypertension in a single institution. This limitation needs to be addressed in a larger multicenter study.

Finally, the broader issue of which is the best means of respiratory care in patients at risk of PHC remains unsettled. A recent study has suggested the safety of early extubation in patients with pulmonary hypertension [26], which may be a less-invasive, more lung-protective, and more cost-effective option. Studies are needed to further define the best postoperative respiratory care for infants undergoing cardiac surgery.

Conclusions

This study was the first to compare the effects and risks of hyperventilation versus standard ventilation on postoperative outcome, including lung injury, in infants undergoing corrective surgery for congenital cardiac defects. It suggests a benefit conferred by standard ventilation in the postoperative care of patients presenting with pulmonary hypertension.

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