# Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease

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***Background:*** **Pulmonary hypertension is associated with congenital heart lesions with increased pulmonary blood flow. Acute increases in pulmonary vascular resistance (PVR) occur in the postoperative period after repair of these defects. These increases in PVR can be ablated by inducing an alkalosis with hyperventilation (HV) or bicarbonate therapy. Studies have shown that these patients also respond to inhaled nitric oxide (iNO), but uncertainty exists over the relative merits and undesirable effects of HV and iNO.**

***Hypothesis:*** **Alkalosis and iNO are equally effective in reducing PVR and pulmonary artery pressure (PAP) in children with pulmonary hypertension after open heart surgery.**

***Setting:*** **Critical care unit of a tertiary care pediatric hospital.**

***Design:*** **Prospective, randomized, crossover design.**

***Patients:*** **Twelve children with a mean PAP > 25 mm Hg at normal pH after biventricular repair of congenital heart disease.**

***Interventions:*** **Patients were assigned to receive iNO or HV (pH > 7.5) in random order, and the effect on hemodynamics was measured. Each treatment was administered for 30 mins with a 30-min washout period between treatments. Finally, both treatments were administered together to look for a possible additive effect.**

***Measurements and Main Results:*** **Cardiac output and derived hemodynamic parameters using the dye dilution technique. Hyperventilation, achieved by an increase in ventilator rate without a change in mean airway pressure, decreased $Paco_2$ from a mean (SD) of 43.7 ± 5.3 to 32.3 ± 5.4 mm Hg and increased pH from 7.40 ± 0.04 to 7.50 ± 0.03. This significantly altered both pulmonary and systemic hemodynamics with a reduction in PAP, PVR, central venous pressure, and cardiac output and an increase in systemic vascular resistance. In comparison, iNO selectively reduced PAP and PVR only. The reduction in PVR was comparable between treatments, although addition of iNO to HV resulted in a small additional reduction in PVR. An additional decrease in PAP was seen when HV was added to iNO, attributable to a reduction in cardiac output rather than a further decrease in PVR.**

***Conclusions:*** **Inhaled NO and HV are both effective at lowering PAP and PVR in children with pulmonary hypertension after repair of congenital heart disease. The selective action of iNO on the pulmonary circulation offers advantages over HV because a decrease in cardiac output and an increase in SVR are undesirable in the postoperative period. (Crit Care Med 2000; 28:2974–2978)**

**KEY WORDS: nitric oxide; congenital heart disease; alkalosis; hyperventilation; pulmonary hypertension; pulmonary vascular resistance**

Congenital heart lesions associated with high pulmonary blood flow may result in increased pulmonary artery pressure and pulmonary vascular resistance (PVR) caused by structural alterations in the intima and excessive muscularization of the small pulmonary vessels (1). Abrupt increases in PVR in the postoperative period after repair of these defects result in increased right ventricular afterload and may compromise cardiac output. These changes can manifest as a life-threatening pulmonary hypertensive crisis (2, 3) with acute right heart failure and dramatic increases in airway resistance (4). Although various vasodilator drugs such as tolazoline, phenoxybenzamine, and nitrodilators (2, 5, 6) have been used to reduce pulmonary artery pressure (PAP), none is selective for the pulmonary vascular bed. Other strategies for minimizing increases in PVR after repair of congenital heart disease have included hyperventilation (HV) to induce a respiratory alkalosis (3, 5, 7) and the use of sedation and paralysis (8). The discovery of the selective pulmonary vasodilator actions of nitric oxide (NO) has led to widespread use of inhaled NO (iNO) to reduce PAP and PVR in infants with persistent pulmonary hypertension of the newborn (9, 10) and to reduce pulmonary artery pressure in infants and children with increased PVR after repair of congenital heart disease (11–20). Although this therapy can be remarkably effective, there are concerns about methemoglobinemia and rebound pulmonary hypertension after discontinuation of the therapy (21, 22). Despite this, iNO has replaced alkalosis as first-line therapy for postoperative pulmonary hypertension in many centers, although no direct comparisons of the two treatments have been reported.

The purpose of this study was to compare the hemodynamic effects of mild alkalosis (pH 7.5), induced by HV, with iNO in a group of children with increased pulmonary vascular resistance after surgical repair of congenital heart disease.

## METHODS

*Patient Population.* We obtained Institutional Research Ethics Board approval for the study, and after obtaining informed parental consent, we enrolled 12 children with postoperative pulmonary hypertension (mean PAP > 25 mm Hg at a normal pH) in the study. Patient details are given in Table 1. All patients

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underwent a biventricular repair, and at the end of the procedure catheters were placed into the left atrium and pulmonary artery as part of routine postoperative monitoring. Residual intracardiac shunts were excluded by cardiac echo, dye dilution, and the measurement of pulmonary artery and superior vena cava oxygen saturations. Two patients were paced for heart block with the rate held constant throughout the study. Patients were studied a median 8.5 hrs (range 4–40 hrs) after arrival in the intensive care unit. Inotropic and vasodilator infusions were not altered during the study period, and no fluid boluses were given. All patients were sedated with a continuous morphine sulfate infusion at 40 μg/kg/hr and received muscle relaxants. Core body temperature was maintained at 36.0–37.8°C throughout the study.

*Study Protocol.* The design was a crossover study with the order of the treatments randomized. Measurements were made before and 30 mins after commencing mild HV with the aim of increasing arterial pH to 7.50. This was achieved by increasing the ventilator rate without changing the tidal volume. All patients were ventilated by using a Servo 900C (Siemens, Solna, Sweden) in pressure control mode with positive end-expiratory pressure 5 cm $H_2O$ and peak inspiratory pressure set to deliver 10–15 mL/kg tidal volume. To avoid alterations in PVR by changing lung volume, we reduced $Paco_2$ by increasing the ventilator rate while holding tidal volume constant. Inspiratory to expiratory time ratio and mean airway pressure also remained constant during HV. Inhaled NO was administered sequentially at two concentrations to examine a possible dose effect: 5 parts per million (ppm) for 15 mins followed by 40 ppm for a further 15 mins. The inhaled NO concentration was monitored by using an electrochemical monitor (Sensor-Stik EIT, Exton, PA). Methemoglobin concentration was measured and remained <2% in all patients. A period of at least 30 mins was permitted between the end of the first treatment and the start of the second treatment to allow hemodynamic variables to return to baseline. At the end of the second treatment, both treatments were given in combination for a further 30 mins so we could look for possible additive effects of HV and iNO. Measurements recorded at the start and end of each treatment period were heart rate, systemic arterial pressure (BP), PAP, left atrial pressure (LAP), central venous pressure, dye dilution (indocyanine green) cardiac output (mean of three values), arterial pH, $Pao_2$, $Paco_2$, and mixed venous oxygen saturation. Cardiac index (CI), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI) were calculated using standard formulae. Arterial oxygen saturation minus mixed venous oxygen saturation was calculated.

*Statistical Analysis.* Changes within each treatment period were analyzed by using a paired Student's *t*-test with statistical significance defined as $p < .05$, whereas differences between the three treatments (NO, HV, NO+HV) were analyzed by comparing the values recorded at the end of each treatment period by using analysis of variance for repeated measures and the Fisher least significant difference multiple comparison procedure. The Bonferroni correction for the *p* value, adjusted for multiple comparisons, was set at <.01. Values are given as mean ± SD.

## RESULTS

Hyperventilation was achieved by increasing ventilator rate from a mean (SD) of 18.6 ± 3.1 to 31.5 ± 2.1. $Paco_2$ decreased from 43.7 ± 5.3 mm Hg to 32.3 ± 5.4 mm Hg and arterial pH increased from 7.40 ± 0.04 to 7.50 ± 0.03. This was associated with significant changes in both systemic and pulmonary hemodynamics (Table 2). PAP, PVRI, central venous pressure, and CI decreased, whereas SVRI increased. Median reduction in PVRI was 19.9% (range −2–43.2). A small increase in oxygen extraction was seen (mean 29.8 ± 8.9% to 33.0 ± 8.6%, $p < .05$), in keeping with the observed reduction in cardiac index. Inhaled NO resulted in selective pulmonary vasodilatation with no effect on SVRI (Table 3). Cardiac index remained unchanged. Median reduction in PVRI was 23.7% (range 3.8–41.2). No difference in response was seen between 5 and 40 ppm. No rebound pulmonary hypertension was associated with the discontinuation of iNO. Inhaled NO and HV resulted in a comparable lowering of PVRI (Fig. 1). The differences between the three treatments (HV, iNO, both) are shown in Table 4. Compared with iNO alone, the combination of HV with iNO increased SVRI. A further reduction in PAP was seen without a change in PVRI.

## DISCUSSION

In this study we demonstrated that iNO and alkalosis, induced by HV, are equally effective in reducing PVR in children after open heart surgery but that the latter resulted in an adverse effect on cardiac output and an increase in SVR mediated through a reduction in $Paco_2$ and an increase in pH that was independent of a change in intrathoracic pressure. Although the effect of HV on venous return has been known for many years, animal and human studies have documented a decrease in cardiac output associated with HV that was not induced by increased tidal volume and raised intrathoracic pressure. These experiments were done by altering the $Fico_2$ (23–25)

**Table 1.** Patient details on enrollment in the study

| Patient | Age (Yrs) | Diagnosis | Mean PAP (mm Hg) | PVRI (Wood Units/m$^2$) | Mean PAP/BP | Infusions (μg/kg/min) |
|---|---|---|---|---|---|---|
| 1 | 0.2 | Hemitruncus | 51 | 10.7 | 0.91 | Dop 10, SNP 2, Iso 0.05, Amri 10 |
| 2 | 0.5 | AVSD | 30 | 4.7 | 0.49 | Dop 10, SNP 3 |
| 3 | 0.7 | AVSD | 41 | 6.5 | 0.59 | Dop 5, SNP 2 |
| 4 | 17.7 | TGA mustard baffle obstruction | 34 | 5.5 | 0.43 | Dop 7.5 |
| 5 | 0.2 | TAPVC | 55 | 14.8 | 1.21 | Dop 5, Amri 15 |
| 6 | 0.3 | TAPVC | 32 | 11.3 | 0.43 | Dop 10, SNP 4 |
| 7 | 0.3 | TAPVC | 27 | 4.1 | 0.42 | Dop 7.5, Iso 0.2, Amri 10 |
| 8 | 0.1 | Hemitruncus | 30 | 8.9 | 0.56 | Dop 7.5, SNP 1, Amri 15 |
| 9 | 0.7 | VSD | 36 | 7.3 | 0.56 | Dop 5 |
| 10 | 13.3 | MS, SAS | 35 | 11.3 | 0.47 | Dop 7.5, SNP 1.5 |
| 11 | 0.7 | AVSD | 29 | 8.6 | 0.55 | Dop 5, SNP 1 |
| 12 | 2.9 | MVR | 34 | 6 | 0.52 | Dop 5, SNP 2, Iso 0.01 |

PAP, pulmonary artery pressure; PVRI, pulmonary vascular resistance index; BP, blood pressure; Dop, dopamine; SNP, sodium nitroprusside; Iso, isoprenaline; Amri, amrinone; AVSD, atrioventricular septal defect; TGA, transposition of the great vessels; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect; MS, mitral stenosis; SAS, subaortic stenosis; MVR, mitral valve replacement.

Table 2. Hemodynamic effects of hyperventilation (HV)

| | Heart Rate | | Cardiac Index | | Stroke Index | | CVP | | LAP | | Mean PAP | | Mean BP | | PVRI | | SVRI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Pre | HV | Pre | HV | Pre | HV | Pre | HV | Pre | HV | Pre | HV | Pre | HV | Pre | HV | Pre | HV |
| 1 | 169 | 160 | 4.41 | 3.84 | 26.1 | 24 | 13 | 14 | 7 | 8 | 56 | 37 | 54 | 71 | 11.1 | 7.6 | 9.3 | 14.8 |
| 2 | 147 | 124 | 3.21 | 2.63 | 21.8 | 21.2 | 13 | 11 | 15 | 12 | 30 | 22 | 61 | 52 | 4.7 | 3.8 | 14.9 | 15.6 |
| 3 | 132 | 113 | 3.56 | 2.73 | 27.1 | 24.2 | 13 | 10 | 18 | 9 | 41 | 24 | 70 | 65 | 6.5 | 3.7 | 15.7 | 20.2 |
| 4 | 113 | 110 | 4.84 | 4.81 | 42.9 | 43.7 | 21 | 19 | 10 | 9 | 36 | 34 | 75 | 71 | 5.4 | 5.2 | 11.2 | 10.6 |
| 5 | 139 | 142 | 2.32 | 2.28 | 16.7 | 16.1 | 13 | 10 | 13 | 11 | 56 | 38 | 50 | 56 | 18.6 | 11.8 | 16.1 | 20.2 |
| 6 | 131 | 116 | 1.51 | 1.45 | 11.6 | 12.5 | 14 | 12 | 19 | 17 | 35 | 27 | 95 | 90 | 10.6 | 6.9 | 52.8 | 53.7 |
| 7 | 147 | 149 | 3.45 | 3.24 | 23.5 | 21.8 | 14 | 10 | 13 | 11 | 27 | 23 | 64 | 66 | 4.1 | 3.7 | 14.8 | 16.9 |
| 8 | 170 | 180 | 2.15 | 2.33 | 12.7 | 12.9 | 10 | 11 | 9 | 12 | 28 | 29 | 43 | 67 | 8.8 | 7.3 | 15.3 | 24.1 |
| 9 | 155 | 145 | 4.14 | 3.07 | 26.7 | 21.2 | 13 | 11 | 6 | 6 | 36 | 27 | 64 | 58 | 7.3 | 6.9 | 12.3 | 15.1 |
| 10 | 123 | 119 | 1.59 | 1.51 | 13.1 | 12.7 | 14 | 12 | 17 | 15 | 35 | 28 | 75 | 72 | 11.3 | 8.6 | 37.6 | 39.6 |
| 11 | 142 | 139 | 2.21 | 2.04 | 15.5 | 14.7 | 11 | 10 | 10 | 10 | 29 | 24 | 53 | 61 | 8.6 | 6.9 | 19.1 | 24.9 |
| 12 | 108 | 100 | 3.61 | 3.16 | 33.4 | 31.6 | 11 | 10 | 14 | 12 | 32 | 28 | 65 | 63 | 5.1 | 5.1 | 15.1 | 16.8 |
| Mean | 139.7 | 133.1 | 3.08 | 2.76[a] | 22.6 | 21.4[a] | 13.3 | 11.7[b] | 12.6 | 11.0 | 36.8 | 28.4[c] | 64 | 66 | 8.5 | 6.4[b] | 19.5 | 22.7[b] |
| SD | 19.7 | 23.4 | 1.11 | 0.96 | 9.4 | 9.1 | 2.7 | 2.6 | 4.3 | 3.0 | 9.8 | 5.3 | 13.7 | 9.8 | 4.1 | 2.4 | 12.7 | 12.3 |

CVP, central venous pressure; LAP, left atrial pressure; PAP, pulmonary artery pressure; BP, blood pressure; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.

[a] $p < .05$; [b] $p < .01$; [c] $p < .001$ vs. prevalue.

Table 3. Hemodynamic effects of nitric oxide (NO) at 40 ppm

| | Heart Rate | | Cardiac Index | | Stroke Index | | CVP | | LAP | | Mean PAP | | Mean BP | | PVRI | | SVRI | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Pre | NO | Pre | NO | Pre | NO | Pre | NO | Pre | NO | Pre | NO | Pre | NO | Pre | NO | Pre | NO |
| 1 | 174 | 165 | 4.12 | 4.41 | 23.7 | 26.7 | 13 | 13 | 7 | 8 | 51 | 37 | 56 | 61 | 10.7 | 6.6 | 10.5 | 10.9 |
| 2 | 145 | 134 | 3.24 | 3.24 | 22.3 | 24.2 | 11 | 12 | 13 | 14 | 29 | 26 | 64 | 61 | 4.9 | 3.7 | 16.4 | 15.1 |
| 3 | 102 | 102 | 2.64 | 2.27 | 24 | 22 | 10 | 11 | 14 | 15 | 27 | 25 | 60 | 63 | 4.9 | 4.4 | 18.9 | 22.5 |
| 4 | 104 | 103 | 4.33 | 5.16 | 41.6 | 50.1 | 19 | 20 | 10 | 10 | 34 | 32 | 79 | 76 | 5.5 | 4.3 | 13.9 | 10.9 |
| 5 | 140 | 139 | 2.84 | 2.33 | 20.3 | 16.7 | 12 | 12 | 13 | 13 | 55 | 39 | 46 | 53 | 14.8 | 11.2 | 12 | 10.9 |
| 6 | 142 | 137 | 1.68 | 1.95 | 11.8 | 14.2 | 11 | 13 | 13 | 18 | 32 | 31 | 74 | 89 | 11.3 | 6.7 | 38.2 | 39 |
| 7 | 151 | 150 | 3.9 | 3.78 | 25.9 | 25.2 | 14 | 14 | 14 | 14 | 29 | 26 | 76 | 74 | 3.8 | 3.2 | 16.1 | 15.9 |
| 8 | 172 | 173 | 2.37 | 2 | 13.8 | 11 | 9 | 9 | 9 | 9 | 30 | 26 | 54 | 46 | 8.8 | 8.5 | 18.9 | 18.5 |
| 9 | 146 | 143 | 3.25 | 3.4 | 22.3 | 23.8 | 13 | 12 | 5 | 7 | 34 | 27 | 55 | 58 | 8.9 | 5.9 | 12.9 | 13.2 |
| 10 | 125 | 122 | 1.74 | 1.79 | 13.9 | 14.7 | 13 | 13 | 17 | 17 | 34 | 30 | 76 | 75 | 9.8 | 7.2 | 36.2 | 34.6 |
| 11 | 134 | 131 | 2.08 | 2.27 | 15.5 | 17.3 | 10 | 10 | 10 | 10 | 25 | 24 | 55 | 56 | 7.2 | 6.2 | 21.6 | 20.3 |
| 12 | 118 | 112 | 3.66 | 3.53 | 31.1 | 31.5 | 9 | 11 | 12 | 12 | 34 | 30 | 65 | 66 | 6 | 5.1 | 15.3 | 15.6 |
| Mean | 137.8 | 134.3[a] | 2.99 | 3.01 | 22.2 | 23.1 | 12 | 12.5 | 11.4 | 12.3 | 34.5 | 29.4[a] | 63.3 | 64.6 | 8.1 | 6.1[b] | 19.2 | 19.5 |
| SD | 22.9 | 22.3 | 0.91 | 1.08 | 8.4 | 10.4 | 9.2 | 4.8 | 10.9 | 12 | 2.8 | 2.7 | 3.3 | 3.5 | 3.3 | 2.2 | 8.9 | 8.8 |

CVP, central venous pressure; LAP, left atrial pressure; PAP, pulmonary artery pressure; BP, blood pressure; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.

[a] $p < .01$; [b] $p < .001$ vs. prevalue.

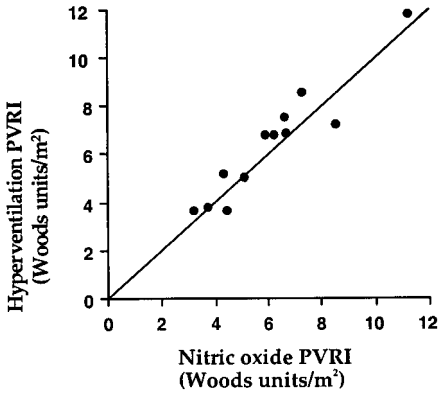


Figure 1. A comparison of pulmonary vascular resistance index (*PVRI*) after hyperventilation and nitric oxide. A *line of unity* is shown.

Further studies suggested that this was predominantly a pH effect that could be reversed by increasing left ventricular preload (26, 27). The reduction in preload that occurs during HV is probably the result of an increase in vascular capacitance. Previous studies have shown that SVR either increases (7, 23, 24, 27) or remains unchanged (26) during hypocarbic alkalosis, making the arterial circuit unlikely as the site of increased capacitance. Others have suggested that systemic venous dilation could explain the reduction in preload (28), although a study in spontaneously breathing subjects who became alkalotic by hyperventilating demonstrated constriction of forearm veins rather than dilation (29). It is conceivable that the pulmonary vascular bed, which is known to dilate in response to hypocarbic alkalosis, is the site of increased capacitance.

In a study of children with pulmonary hypertension after cardiac surgery, Morray et al. (7) examined the cardiovascular response to a respiratory alkalosis. They found a very similar hemodynamic response to that seen in the present study, including a reduction in central venous pressure (and LAP), a decrease in cardiac output, and an increase in SVRI. They altered pH by adding and withdrawing

Table 4. Hemodynamic comparison of hyperventilation (HV), nitric oxide (NO), and combined therapy (Mean ± SD)

| | HV | NO | HV + NO |
|---|---|---|---|
| Heart rate | 133.1 ± 23.4 | 134.3 ± 22.3 | 131.3 ± 25.2 |
| Cardiac index | 2.76 ± 0.96 | 3.01 ± 1.08 | 2.62 ± 0.89[a] |
| Stroke index | 21.4 ± 9.1 | 23.1 ± 10.4 | 20.7 ± 8.9[b] |
| CVP | 11.7 ± 2.6 | 12.5 ± 2.7 | 11.5 ± 2.7 |
| LAP | 11.8 ± 3.7 | 12.3 ± 3.5 | 11.8 ± 3.9 |
| Mean PAP | 28.4 ± 5.3 | 29.4 ± 4.8 | 26.8 ± 3.5[b] |
| Mean BP | 66.0 ± 9.8 | 64.6 ± 12.0 | 66.9 ± 12.3 |
| PVRI | 6.4 ± 2.4 | 6.1 ± 2.2 | 6 ± 2.0 |
| SVRI | 22.7 ± 12.3 | 19.5 ± 8.8 | 29.2 ± 15.9[b] |
| PVRI/SVRI | 0.33 ± 0.15 | 0.35 ± 0.16 | 0.29 ± 0.13[b] |

CVP, central venous pressure; LAP, left atrial pressure; PAP, pulmonary artery pressure; BP, blood pressure; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.
[a]$p < .001$ NO vs. HV + NO; [b]$p < .01$ NO vs. HV + NO.

*The selective action of inhaled nitric oxide on the pulmonary circulation offers advantages over hyperventilation by maintaining cardiac output without increasing afterload.*

inhaled $CO_2$ without altering ventilator settings; therefore, these effects were independent of changes in intrathoracic pressure. They also demonstrated that the response to alkalosis was directly related to the height of the pulmonary artery pressure. Ryan and Soder (30) also studied the effect of acute changes in $CO_2$ on hemodynamics in children after open heart surgery by adding dead space to the ventilator circuit. They found little effect when pH was changed from normal to 7.5 but an increase in cardiac output and reduction in SVR with hypercarbia (pH 7.3). In the present study, we altered ventilator rate without changing inspiratory: expiratory ratio, peak inspiratory pressure, or positive end-expiratory pressure so that mean airway pressure remained constant. We therefore cannot ascribe the reduction in preload during hypocarbic alkalosis to a direct effect of transmitted intrathoracic pressure reducing venous return.

After repair of congenital heart disease, a reduction in cardiac output is seen that reaches its nadir in the first 8–12 hrs after surgery (31), probably as a result of ischemia-reperfusion injury to the myocardium. A reduction in cardiac output and an increase in SVR during HV, therefore, are likely to be detrimental. An alternative strategy would be to infuse an alkaline solution, such as sodium bicarbonate, to induce a metabolic rather than a respiratory alkalosis. As a hypertonic fluid, sodium bicarbonate also would provide additional intravascular volume and possibly result in a different hemodynamic response. A study by Chang et al. (32) provides supportive evidence. They studied 15 infants after cardiac surgery, although not all had an elevated PAP. After increasing PAP and PVR by inducing a respiratory acidosis, Chang et al. (32) administered 4 mEq/kg of sodium bicarbonate. This returned arterial pH to normal and reduced PAP and PVR but increased cardiac output. In this study, sodium bicarbonate infusion significantly increased preload, which may explain the observed increase in cardiac output. It is possible that increasing preload during HV would restore cardiac output and reduce SVR to previous levels, but we did not test this hypothesis.

In the iNO phase of the present study, we found no demonstrable effect on systemic hemodynamics and no significant rebound effect. However, this was an acute study, and one would expect to see rebound pulmonary hypertension where there has been prolonged use. As shown in previous studies, the magnitude of the reduction in PVR with treatment depends on the initial level, being greatest when PVR is high (7, 15). The optimal concentration of iNO for effect in children with congenital heart disease and increased PVR has been based on the fact that doses of ≤40 ppm are used in persistent pulmonary hypertension of the newborn. Different studies have found differing dose response effects. Miller et al. (15) compared 2, 10, and 20 ppm in a group of ten infants and found a good response to low-dose iNO. Our study supports this finding, with no significant difference in response demonstrated between 5 and 40 ppm. However, Atz et al. (33) showed an increasing vasodilator effect as the dose was increased from 1 to 80 ppm.

Combining iNO with HV further decreased PAP by reducing flow (cardiac output) during HV rather than via any additional decrease in PVR, whereas addition of iNO resulted in a small additional reduction in PVR over HV alone. The other hemodynamic effects of HV were reproduced when HV was added to iNO. The different hemodynamic profiles and additive effects of iNO and HV support existing evidence that suggests different mechanisms of action on the pulmonary vasculature for alkalosis and iNO (34).

Hyperventilation may result in a number of potentially undesirable effects in addition to the hemodynamic changes described. These include a reduction in coronary (35) and cerebral blood flow (36), an increase in ventilation/perfusion mismatch (37), arrhythmias (38), a leftward shift of the oxygen-hemoglobin dissociation curve, an increased risk of barotrauma, and electrolyte derangement. Inhaled NO therapy, on the other hand, results in selective pulmonary vascular effects and appears to be safe and free from serious side effects when administered in the dose range currently employed with appropriate monitoring of inhaled nitrogen dioxide and plasma methemoglobin concentrations. The selective action of iNO on the pulmonary circulation offers advantages over HV by maintaining cardiac output without increasing afterload.

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