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Reintroduction of Continuous Negative Pressure Ventilation in Neonates: Two-Year Experience

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Summary. Continuous negative pressure ventilation utilizes subatmospheric pressure around the thorax to improve oxygenation. It has not been routinely used since the mid-1970s. We treated 37 infants with the combination of continuous negative pressure (CNP) and intermittent mandatory ventilation (IMV), after failing to attain a Pa_{O_2} of ≥50 torr on IMV alone. Lung diseases included pulmonary interstitial emphysema (PIE), respiratory distress syndrome (RDS), and pulmonary artery hypertension (PAH) due either to meconium aspiration syndrome (MAS) or other causes (non-MAS). All infants had evidence of severe parenchymal pulmonary disease, or pulmonary artery hypertension resulting in persistent hypoxemia and hypotension. In the PIE group, CNP was started later in the course of the disease, and both positive pressure and oxygen were maintained for a longer period. The group of infants with non-MAS PAH required CNP and positive pressure ventilation for the shortest period of time. The infants with PIE also had a greater incidence of bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). In addition, three patients with PIE died. In the non-MAS patients with PAH, no complications and no deaths occurred. The response to CNP was a rapid improvement in oxygenation in all groups with the greatest increase of Pa_{O_2} in the non-MAS PAH infants: from 30 torr prior to the initiation of CNP to 140 torr within 30 minutes. No significant changes in pH or Pa_{CO_2} occurred in any group. Significant decreases in ventilator rate, mean airway pressure ($\overline{Paw}$) and FI_{O_2} in peak inspiratory pressure were possible by 12 hours of CNP. CNP and Paw were decreased from −5 cm H_2O and 12.8 cm H_2O prior to initiation of CNP to −1 cm H_2O and 5.0 cm H_2O at 72 hours of treatment. FI_{O_2} at 72 hours was decreased to a mean of 0.57. Combined CNP and IMV ventilator therapy improved oxygenation with lessened $\overline{Paw}$ in infants with refractory hypoxemia due to MAS and PAH and in larger infants with RDS. While we cannot advocate the routine use of CNP, it would appear to have a role in the management of infants who have failed conventional ventilator therapy. **Pediatr Pulmonol 1990; 8:245–253.**

Key words: Intermittent mandatory ventilation, combination with; blood gases, peak inspiratory, mean airway pressure, ventilator rate, effects on; respiratory distress syndrome, pulmonary hypertension, meconium aspiration syndrome.

INTRODUCTION

Negative pressure assisted ventilation was introduced for use with neonates in the early 1960s.[1] The Air Shields Company of Hatboro, PA produced the Isolette Respirator® which was used extensively for the treatment of infants with respiratory distress syndrome (RDS).[2–4] Initially, it functioned as a time-cycled ventilator allowing the application of negative pressure to the body for a preset length of time and a period during which the negative pressure was released. The advantage of this system was the avoidance of using an endotracheal tube.[5,6]

In 1971, Gregory et al. reported that constant positive airway pressure (CPAP) was effective in improving oxygenation of infants with RDS.[7] This led Vidyasagar and Chernick in 1971 to modify the negative pressure ventilator so that a constant negative pressure could be applied about the chest and abdomen without cycling. They reported that this method was also a useful adjunct to the treatment of RDS.[8] For infants who were apneic or hypercarbic, continuous negative pressure (CNP) was used in conjunction with endotracheal intubation and intermittent positive pressure breathing, using adult ventilators that were adapted for the newborn.[9,10] Following the introduction of continuous flow ventilators and intermittent mandatory ventilation (IMV) in the mid-1970s, negative pressure ventilation was for the most part abandoned.

We have reintroduced the use of CNP in tandem with

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IMV in our neonatal intensive care unit. Our previously reported preliminary experience with two groups of patients revealed that infants with severe pulmonary interstitial emphysema (PIE) and infants with pulmonary artery hypertension (PAH) appeared to benefit from CNP + IMV.[11,12] We have extended the use of CNP in conjunction with IMV to infants with several forms of respiratory failure who, despite maximal conventional ventilation, have remained hypoxic. This report is a retrospective analysis of our use of CNP for 2 years. Its purpose is to describe observed differences in clinical response of infants undergoing CNP + IMV and the relationship of outcome to specific diagnoses.

MATERIALS AND METHODS

Patient Selection

From July 1, 1986 to June 30, 1988, 50 newborns in the Infant Special Care Unit at the University of California Irvine Medical Center were treated with CNP in tandem with IMV. These represent infants not previously reported. Eleven infants, all weighing less than 1,250 g, could not be maintained on negative pressure continually for more than 2 hours and were excluded, because it was felt that they could not be given an adequate therapeutic trial. Of these 11 infants 4 had severe PIE with pneumothoraces that were incompletely evacuated upon placement into CNP. These pneumothoraces enlarged with the inception of CNP, and oxygenation and ventilation deteriorated. This necessitated immediate removal from the negative pressure chamber. Two infants had been in septic shock and were not hemodynamically stable when placed into CNP. Because of further decrease in blood pressure, they were removed from negative pressure. Four patients had a patent ductus arteriosus (PDA) as their primary abnormality with a significant left-to-right shunt. Negative pressure caused further deterioration with worsening ventilatory and hemodynamic status. They were therefore removed for emergency surgical ligation. One infant who weighed only 780 g acutely deteriorated secondary to a large grade IV intraventricular hemorrhage (IVH) shortly after starting CNP. Two patients were given an adequate therapeutic trial of CNP but are not included in the statistical analysis since they do not contribute any information to this analysis. One of these had non-immune hydrops and survived, and the other was treated at 6 weeks of age with severe bronchopulmonary dysplasia (BPD) and expired. The 37 remaining infants, who were maintained in CNP, were compared by diagnosis, duration of treatment, complications, changes in ventilatory requirements, and changes in hemodynamics. These infants were placed into one of four diagnostic categories: PIE, RDS, pulmonary artery hypertension secondary to meconium aspiration syndrome (MAS-PAH) or PAH secondary to other cause (non-MAS PAH).

Management Prior to CNP

All infants were ventilated by one of several positive pressure ventilators (Healthdyne 200 Transport Vent., Healthdyne, Marrieta, GA; Sechrist IV-100B, Sechrist Industries, Inc., Anaheim, CA; Baby Bird Mark VII, Bird Corp., Palm Springs, CA) prior to placement in the negative pressure chamber. Ventilator settings and mean airway pressure ($\overline{Paw}$) were monitored with the use of a Pneumogard® (Novametrics Medical Systems, Inc., Wallingford, CN). Infants remained hypoxic ($Pa_{O_2} < 50$ torr) for at least 2 hours while on an FI_{O_2} of 1.0 and various IMV strategies (increased peak inspiratory pressure, increased rate, increased positive end expiratory pressure). Infants with PAH were hyperventilated to produce a pH of 7.50–7.60, given a constant infusion of sodium bicarbonate, and a trial of tolazoline (1 mg/kg I.V.).

Heart rate, blood pressure, temperature, transcutaneous Pa_{O_2}, P_{CO_2} and oxygen saturation were continuously monitored. Intravenous fluids were adjusted to maintain euglycemia, electrolyte balance, and adequate urine output (1–3 mL/kg/min). Vasopressor agents were used (dopamine 5–20 μg/kg/min and dobutamine 5–10 μg/kg/min) to correct hypotension (mean systemic blood pressure < 35 mm Hg in preterm infants and < 40 mm Hg in term infants).

Chest X-rays were obtained at least every 12 hours, or as needed because of acute changes in the clinical status of the patient, and just prior to placement in the negative pressure chamber. A cranial ultrasound was also performed prior to placement in CNP.

Echocardiography was performed shortly after birth to examine for the presence of a PDA and to rule out other forms of congenital heart disease. Premature infants with hemodynamically significant PDA received indomethacin, beginning within the first 4 hours of life. If an infant did not respond to indomethacin (worsening hypercarbia, metabolic acidosis, pulmonary edema, persistent hypotension on vasopressor agents), surgical ligation was performed. A two-dimensional and M-mode echocardiogram was repeated, prior to entry into CNP, on any infant suspected of PAH. The latter was diagnosed by echocardiographic criteria,[13,14] visualizing a right to left shunt of peripherally injected saline across the foramen ovale, and by a greater than 20 torr gradient of Pa_{O_2} between simultaneously drawn right radial and umbilical arterial blood samples. Echocardiograms were not routinely repeated, therefore the diagnosis or exclusion of PAH was made at the onset of treatment with CNP.

TABLE I—Patient Characteristics by Diagnosis

Diagnosis	n (% total)	BWT ($\bar{X}$ ± 1 SD) (g)	G.A. ($\bar{X}$ ± 1 SD) (weeks)	Delivery (% C/S)	Sex (% M)	Median 1/5 min APGAR
PIE	10 (27.1)	1,426 ± 368	30.5 ± 1.9	60	60	5/7
RDS	12 (32.4)	1,677 ± 733	31.6 ± 3.1	66.7	50	6.5/8
MAS-PAH	8 (21.6)	3,328 ± 567	39.4 ± 1.9	87.5	50	5/7
Non-MAS-PAH	7 (18.9)	2,607 ± 306	36.7 ± 2.6	85.7	71	8/9

BWT, birthweight; G.A., gestational age; % C/S, % cesarean section; % M, % males. For diagnosis abbreviation see Text.

Criteria for Beginning CNP

Infants were placed in the negative pressure chamber (Air Shields Isolette Respirator®, Hatboro, PA) after failing to attain a Pa_{O_2} of ≥50 torr on conventional positive pressure ventilation and FI_{O_2} of 1.0 for at least 2 hours, and when further increases in $\overline{Paw}$ (to a mean of 13 cm H_2O pressure) resulted in a decrease of the mean systemic blood pressure, by at least 10% of the previous level. Infants were also evaluated for endotracheal tube-leak by comparing inspiratory and expiratory tidal volumes using a neonatal volume monitor (NVM-1®, Bear Medical Systems, Inc., Riverside, CA). In case of evidence of a leak, a larger endotracheal tube was inserted, if possible.

Management During CNP

After warming the negative pressure chamber the infant's torso was placed inside, the head was rested outside of the chamber, and the neck fitted with a soft vinyl iris diaphragm. All lines, wires, and tubings were passed through side portholes. Following stabilization and reconnection of the lines and monitors, the neck diaphragm, side portholes, and end door were closed thus isolating the infant's torso within an airtight chamber. Using a vacuum pump, a constant negative pressure was gradually generated within the chamber over a 2–5 minute period.

All infants remained intubated and continued on IMV, in tandem with CNP, at the same settings as they were immediately prior to initiation of CNP, with the exception of PEEP. Prior to CNP, PEEP ranged from 0 to 9 cm H_2O depending on the diagnosis (patients with PIE were treated with 0 PEEP). A negative pressure of −5 cm H_2O was substituted for PEEP. This amount of CNP was chosen by previous experience, being about the average necessary to increase oxygenation. When the transcutaneous oximeter and pulse oximeter indicated that oxygenation was improving, arterial blood gasses (ABG) were obtained and repeated every 4 hours. If Pa_{O_2} did not improve, CNP was increased by −1 cm H_2O increments to a maximum of −10 cm H_2O, until there was an initial improvement in all patients. When the Pa_{O_2} remained stable at >50 torr, the $\overline{Paw}$ of the IMV settings was lowered by decreasing the ventilator rate and the peak inspiratory pressure (PIP). FI_{O_2} was then gradually decreased in response to a Pa_{O_2} greater than 50 torr, but only after a 40% reduction of $\overline{Paw}$. CNP was decreased in −0.5 to −1.0 cm H_2O decrements after FI_{O_2} was less than 0.8.

Removal from CNP

The infant was removed from the negative pressure chamber when values of −1 cm H_2O CNP, <6 cm H_2O $\overline{Paw}$, and <0.55 FI_{O_2} were reached. PEEP of 1–2 cmH_2O was then reinstituted in order to preserve acceptable levels of Pa_{O_2}. The last ventilator settings while in CNP were maintained. The infant was returned to a radiant warming bed, and ABG, chest X-ray, and cranial ultrasound were repeated.

Data Analysis

The data were analyzed with respect to each of the pretreatment diagnostic categories versus patient characteristics and outcome variables (complications, length of therapy, change in ventilatory parameters, blood gases over time, and survival). Prevalence data were compared using chi square analysis, and numerical data with the Mann-Whitney U or Kruskal-Wallis tests. Changes in variables over time were analyzed with repeated ANOVA, and multiple comparison analysis was done with the Fisher PLSD. Results were considered to be significant at $P < 0.05$.

RESULTS

The four major categories of patient diagnoses are shown in Table 1. The patients with evidence of PAH by echocardiography had either MAS or underlying lung disease including pneumothorax, pneumonia, or RDS. The infants in the RDS categories were those who did not have evidence of PAH at the onset of CNP and were subsequently not treated as such.

There were no significant differences in the mode of delivery, sex, or median Apgar scores, according to diagnosis (Table 1). However, expected differences were found in birthweight and gestational age, the PIE and RDS groups having lower mean birthweights and gestational ages than the MAS and non-MAS PAH groups.

TABLE 2—Duration of Therapy by Diagnosis

Diagnosis	CNP begun (hrs of age)	Duration CNP (hrs)	Duration positive pressure (days)	Duration O_2 (days)
PIE (n = 10)	93 ± 84	102 ± 103	23 ± 17	36 ± 27
RDS (n = 12)	31 ± 60	44 ± 25	9 ± 5	23 ± 17
MAS-PAH (n = 8)	48 ± 71	73 ± 48	6 ± 4	9 ± 5
NON MAS-PAH (n = 7)	28 ± 16	42 ± 9	5 ± 2	10 ± 6

All values are mean ± 1 S.D. For diagnosis abbreviations see text.

The MAS group represented the largest and most mature infants of the total study population.

Duration of therapy is shown in Table 2. Among the four diagnostic groups, the time in hours when CNP was initiated was not significantly different. There was also no difference among groups in duration of CNP, except for patients with PIE who remained in CNP longer than those with RDS. The PIE group also remained longer on positive pressure than the other categories ($P < 0.01$) and received oxygen for a longer time than infants in the MAS or non-MAS PAH groups ($P < 0.05$).

Table 3 shows the complications of CNP, and survival. Patients with pneumothoraces did not have a recurrence of the pneumothorax while in CNP. Only one patient (with RDS) developed a new pneumothorax in CNP, an incidence of 2.7%. BPD was defined as oxygen requirement at 28 days of life. The total incidence of BPD was 18.9%.

Overall, no significant difference in survival was found between groups. The PIE group, however, had the greatest proportion of deaths (30%), whereas the non-MAS PAH group had the least (no death). Two infants with MAS, both of whom had sepsis and were in shock, expired during the course of treatment with CNP. Four other infants (3 with PIE, 1 with RDS and sepsis) died within 48 hours after removal from CNP. The overall survival was 89%.

Ten infants had IVH prior to placement into CNP: 3 Grade I, 2 Grade II, and 5 Grade III. The grading is by Papile et al. Only the PIE group had significant enlargements in IVH while in CNP ($P < 0.01$). Overall 12.8% of the patients had extended IVH after CNP. The average birthweight and gestational age of infants with extending IVH was 1,510 g and 30.5 weeks, respectively.

Prior to placement into CNP, infants were placed on increasing amounts of PEEP. Table 4 shows the highest PEEP used with the corresponding Pa_{O_2} for all patients other than those with PIE, since PEEP was decreased or eliminated in those infants.

Changes of mean blood gas values and ventilator settings for all 37 patients are shown in Table 5. Pa_{CO_2} and pH remained fairly stable, however Pa_{O_2} increased significantly with the first blood gas, measured at an average of 30 minutes after the start of CNP. The Pa_{O_2} remained elevated over time, compared to the pre-CNP value. The improvement in oxygenation is also shown by the gradual increase in the arterial-to-alveolar ratio (Pa/A_{O_2}). The PIP could not be decreased until 12 hours of CNP, with a further decrease at 60 hours. The ventilatory rate also was decreased at 12 hours and again at 72 hours, when the patients were on less than one-third of the original rate. PEEP was set at zero, but as infants were removed from CNP, PEEP was reapplied at an average of 2 cm H_2O by 72 hours. FI_{O_2} was lowered, averaging 0.85 by 12 hours, and continued to be significantly lowered as Pa_{O_2} was maintained in an acceptable range. By 72 hours, 28 infants (76%) were out of negative pressure, 3 were extubated, 28 (76%) were on a $\overline{Paw}$ of less than 6 cm H_2O, and 20 (54%) were receiving an FI_{O_2} of less than 0.5.

Mean systemic blood pressure did not change over the course of therapy; however, cardiopressors were decreased so that by 36 hours of negative pressure, all infants were off cardiopressor support. Concurrently, there was a significant decrease in heart rate, from a mean of 150 prior to CNP to 135 by 72 hours of treatment.

Figures 1–3 represent the changes in oxygenation and ventilatory measurements for each of the four diagnoses. In Figure 1 the significant increase in Pa_{O_2} is shown for each category, immediately after placement into CNP, except for the RDS group for which Pa_{O_2} increased significantly by 12 hours. The best response was seen in the non-MAS PAH group where Pa_{O_2} increased from a mean of 30 torr before to almost 140 torr within 30 minutes after initiating CNP. Following initial stabilization, Pa_{O_2} was lower at 12 hours, compared to the first ABG in CNP, because FI_{O_2} and $\overline{Paw}$ were decreased to keep the Pa_{O_2} in the 50–70 torr range. The changes of Pa_{O_2} in patients with MAS were somewhat erratic compared to the other groups. These patients were more labile when disturbed for any reason. Improvement in oxygenation, calculated by a Pa/A_{O_2} ratio is also shown in Figure 2. The non-MAS PAH group had the best response at 72 hours, reaching a Pa/A_{O_2} ratio of 0.3.

TABLE 3—Complications by Diagnosis

Diagnosis	Pneumoth. before CNP (%)	Pneumoth. in CNP (%)	BPD (%)	Worsening IVH after CNP (%)	Survival (% survived)
PIE (n = 10)	2 (20)	0 (0)	4 (40)	4 (40)	7 (70)
RDS (n = 12)	4 (33.3)	1 (8.3)	3 (25)	1 (8.3)	11 (91.7)
MAS-PAH (n = 8)	3 (37.5)	0 (0)	0 (0)	0 (0)	6 (75)
Non MAS-PAS (n = 7)	1 (14.3)	0 (0)	0 (0)	0 (0)	7 (100)

Pneumoth., pneumothorax; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage. For diagnosis abbreviations see text.

TABLE 4—Highest PEEP vs. Pa_{O_2} Prior to CNP

Patient No.	PEEP (cm H_2O)	Pa_{O_2} (torr)
1	9	36
2	6	20
3	5	41
4	7	28
5	7	36
6	5	48
7	4	31
8	5	33
9	5	40
10	5	42
11	4	38
12	5	39
13	6	45
14	5	41
15	5	43
16	6	41
17	4	29
18	5	44
19	5	42
20	4	30
21	6	29
22	6	45
23	5	20
24	7	39
25	4	44
26	9	38
27	7	31

Figure 3 shows changes of mean airway pressure made for each group. The change in $\overline{Paw}$, as measured by a Pneumogard®, from pre-CNP to the first ABG during CNP is due to elimination of PEEP, since the Pneumogard® will not show the true $\overline{Paw}$ while on CNP. The more significant value, transpulmonary pressure, could not be measured in these patients. Thereafter, however, the decrease in $\overline{Paw}$ reflects changes in PIP and IMV, since PEEP was held at zero while the infants were in CNP. By 12 hours, the $\overline{Paw}$ of each group was decreased to less than 50% of the pre-CNP values. In the non-MAS PAH group, $\overline{Paw}$ was lowered from a mean of 15 cm H_2O prior to CNP to 4 cm H_2O by 12 hours (73% decrease). There were no significant changes in $\overline{Paw}$ after 12 hours of CNP.

DISCUSSION

We have found CNP to be an important adjunct to positive pressure ventilation in our NICU for those infants who remained hypoxic while their $\overline{Paw}$ was increased by IMV. The use of CNP is not new. Its earlier employment for the treatment of RDS is well documented.[3,9,10] Although its use had been reported in association with IPPB prior to the introduction of neonatal ventilators, there is no information on the use of CNP in tandem with IMV for abnormal conditions in which we have found it to be most useful, specifically for MAS and other causes of PAH.

The negative pressure chamber functions to maintain a continuous distending airway pressure. Increasing transpulmonary pressure (negative or positive) benefits oxygenation while ventilation is controlled by IMV. Interestingly, we found that the amount of ventilation needed to provide adequate oxygenation was considerably less when equivalent amounts of CNP were substituted for PEEP. An increase in Pa_{O_2} occurred in all groups of patients with the initiation of CNP. Improvement in oxygenation varied according to the diagnostic category, the most significant effect being seen within minutes, in infants with non-MAS PAH.

Ventilator treatment strategies for MAS traditionally have minimized the use of PEEP to preclude the risk of air-trapping. When applying CNP to the MAS group, neither changes in Pa_{CO_2} nor air leaks occurred, while Pa_{O_2} significantly increased. PIP remained essentially the same for the first 72 hours in CNP. Oxygenation was maintained at a higher level than in the other disease categories, because of extreme lability of Pa_{O_2}. The early improvement in oxygenation may reflect better matching of ventilation and perfusion. Areas of lung that were

TABLE 5—Changes in Arterial Blood Gases and Venilatory Parameters Over Time in CNP[a]

	PRE	1 hour	12 hours	24 hours	36 hours	48 hours	60 hours	72 hours
pH	7.33	7.35	7.36	7.35	7.34	7.33	7.33	7.31*
P_{CO_2}	53	51	54	55	57	59*	56	59*
P_{O_2}	38	75*	68*	58*	57*	59*	57*	60*
Pa/A_{O_2}	0.057	0.126*	0.136*	0.121*	0.134*	0.158*	0.193*	0.226*
PIP	33	31	26*	26*	24*	24*	22*	21*
PEEP	3	0*	0*	1*	1*	2*	2*	2*
IMV	73	64	44*	37*	32*	30*	26*	21*
$\overline{Paw}$	12.8	8.3*	5.3*	5.3*	5.3*	5.8*	5.1*	5.0*
FI_{O_2}	1.0	0.98	0.85*	0.83*	0.79*	0.73*	0.65	0.57*
CNP (cm H_2O)	—	5	5	3.5*	3*	2*	1.5*	1*

[a]For abbreviations see text.
*$P < 0.05$, ANOVA compared to PRE CNP.

underventilated, due to plugging of airways with meconium and inflammatory debris, may have received improved ventilation.

It is well established that continuous distending pressure in the treatment of RDS serves to increase functional residual capacity (FRC) and improve oxygenation.[15–17] The reasons for CNP alone being apparently more effective than equal or greater amounts of PEEP, increased inspiratory to expiratory ratio, higher PIP, or greater respiratory frequencies, are not clear. Infants with RDS will have unequal ventilation due to non-uniform breathing, an overly compliant chest wall with non-compliant lungs, and areas of focal atelectasis. Some alveoli expand earlier and to a greater extent than others during IMV and PEEP, leading to uneven distribution of ventilation. Perhaps CNP permits more uniform alveolar recruitment. Since CNP is applied evenly around the thorax during the entire respiratory cycle, it may help to stabilize the chest wall and lead to a more uniform application of distending pressure and to a larger FRC than that attained by the addition of PEEP. The least effective response to CNP was noted in infants with PIE. While their Pa_{O_2} increased to acceptable levels, there was little improvement in Pa/A_{O_2} ratio over 72 hours. $\overline{Paw}$ was lessened as lower pH and higher Pa_{CO_2} levels were tolerated to allow for resorption of interstitial air. In the infants surviving PIE, it was resolved by the time CNP was discontinued. Ventilation for these patients on CNP was maintained with less $\overline{Paw}$ (and acceptable oxygenation) than was needed prior to CNP. Prior to CNP, the use of increasing amounts of PEEP led to radiographic worsening of PIE. Initiating low levels of CNP appeared to stabilize the lungs radiographically, allowing the level of positive pressure ventilation to be gradually decreased. In spite of these observations, infants in the PIE group suffered the greatest morbidity and mortality.

Radiographically the non-MAS PAH group had only mild parenchymal pulmonary disease. The major problem was hemodynamic. Multiple infusions of crystalloid or colloid and vasopressor agents were required to maintain a mean systemic blood pressure of 40 mm Hg prior to the initiation of CNP. After the onset of CNP, blood pressure increased and cardiovascular function stabilized by 36 hours, and none of the infants required further blood pressure support.

The gradual drop in $\overline{Paw}$ does not explain the immediate improvement in oxygenation, given the fact that generally the amount of CNP substituted for the PEEP was equal or greater than that used immediately prior to entry into CNP. Increased venous return and improved cardiac output is a potential advantage of CNP compared to PEEP. This has been reported in animal models utilizing a chest cuirass so that right atrial pressure became more negative than venous pressure in the rest of the body.[18,19] The negative pressure chamber used in our patients, however, would only facilitate venous return from the head and hence the theoretical benefit to right ventricular output would be small. We speculate that the rapid improvement in oxygenation reflects increased pulmonary blood flow. The increase in transpulmonary pressure should be the same on equivalent amounts of PEEP and negative end-expiratory pressure. However, we applied negative pressure continually, and there may have been an increase in transpulmonary pressure, as the baseline was lowered from 0 to −5 cm H_2O, and therefore the distance to peak inspiratory pressure became greater. This may have helped to dilate the pulmonary vascular bed and increase pulmonary blood flow. Patients were also ventilated with higher levels of PEEP (up to 9 cm H_2O), however, as one of the coventional strategies of increasing oxygenation. Table 4 shows the highest level of PEEP used and the corresponding Pa_{O_2} prior to placement into CNP in all patients other than those with PIE. While these higher levels of PEEP (mean = 5.6 cm H_2O) did not result in improved Pa_{O_2} (mean = 37 torr), the lower level of CNP did (Table 5). Since we did not measure transpulmonary pressure, we do not know the effect of various amounts of PEEP or CNP on this variable.

Other factors may play a more direct role in right to

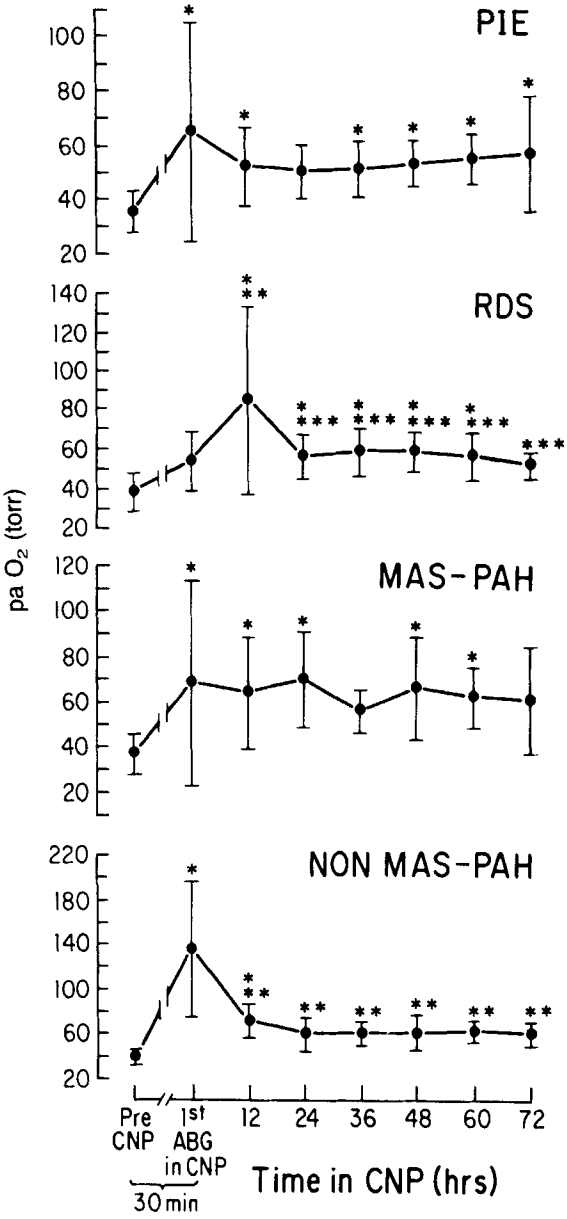

Fig. 1. Changes in Pa_{O_2} over time in CNP. Significant ($P < 0.05$) changes (by ANOVA) of repeated measures at various time points: *Compared to pre-CNP; **compared to 1st test in CNP; ***compared to 12 hr. Note difference in Pa_{O_2} scales for each group.

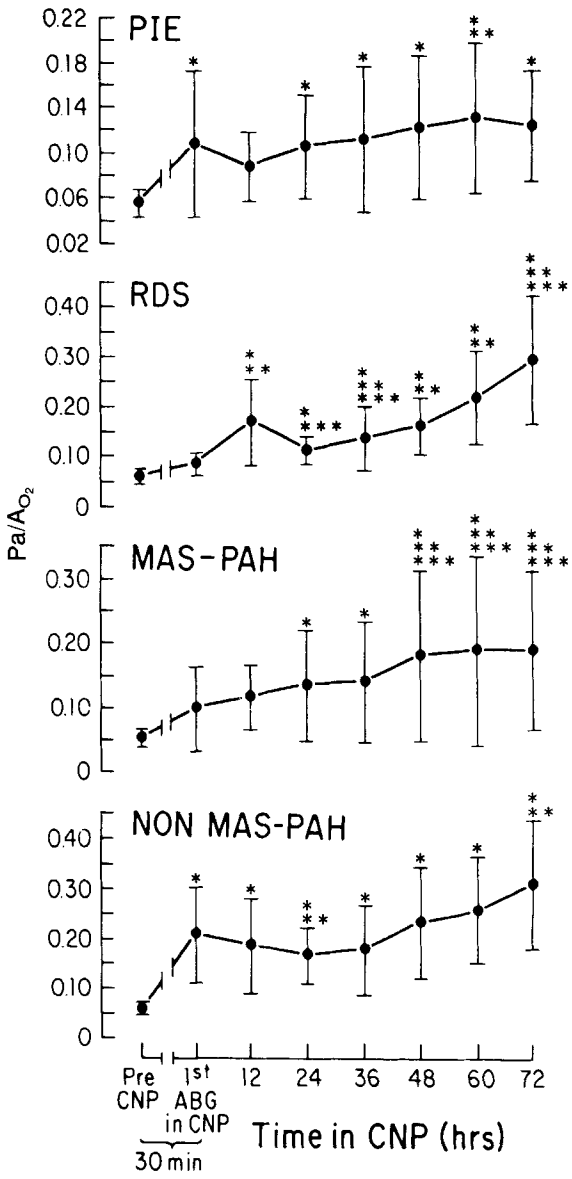

Fig. 2. Changes in Pa/A_{O_2} meter over time in CNP. Significant ($P < 0.05$) changes (by ANOVA) of repeated measures at various time points: *Compared to pre-CNP; **compared to 1st test in CNP; ***compared to 12 hr. Note difference in Pa/A_{O_2} scales for each group.

left extrapulmonary shunting through the patent ductus arteriosus and foramen ovale. There were no changes in arterial blood gases in CNP (pH or Pa_{CO_2}) other than the improved oxygenation. A higher Pa_{O_2} would further decrease pulmonary vascular resistance and essentially break the cycle of rapid pressure ventilation and its negative effects on cardiac output. A direct correlation between increasing $\overline{Paw}$ and decreasing cardiac output in a normal lung model prior to any decline in arterial blood pressure has been previously shown.[20] The gradual decrease in positive pressure ventilation may have augmented venous return, diminished right ventricular overload, and ventricular interdependence. With an increase of pulmonary blood flow, left ventricular end-diastolic volume and a greater stroke volume, systolic pressure may have improved. It may also be possible that tapering the dosage of vasopressors decreased pulmonary vascular resistance. Nevertheless, infants in this group had 100% survival, the most marked response to CNP with no attendant pulmonary or neurologic complications, and required CNP and positive pressure for the least amount of time.

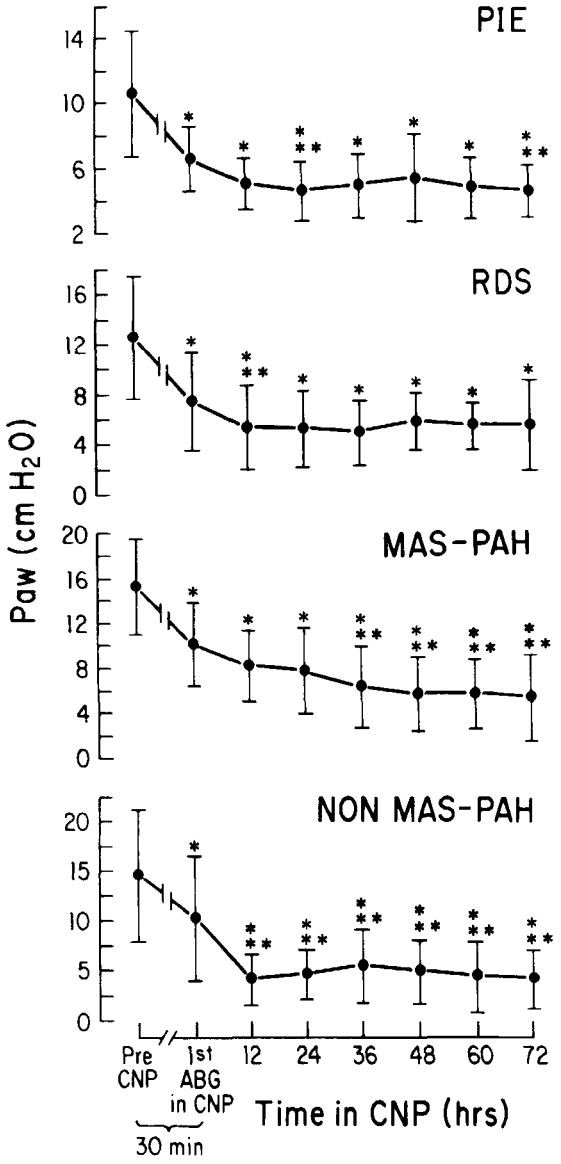

Fig. 3. Changes in Paw over time in CNP. Significant ($P < 0.05$) changes (by ANOVA) of repeated measures at various time points: *Compared to pre-CNP; **compared to 1st test in CNP; ***compared to 12 hr. Note difference in $\overline{Paw}$ scales for each group.

Observed complications of CNP were minimal, considering the gravity of illness in each infant undergoing CNP treatment. Only one infant developed a pneumothorax while in CNP. The incidence of IVH in the smallest infants with PIE and RDS was not different from other patients treated in our unit requiring maximal IMV. No difference in IVH was shown previously when intermittent negative and positive airway ventilation was used in infants with RDS.[2,21] However, concerns still exist for the possible relation of IVH to the mechanical impedance of venous return from the cerebral circulation, due to the iris diaphragm around the neck. In our patients, the sickest, low birthweight patients with PIE were the ones who had extension of IVH. In these patients, who are at greatest risk for IVH, treatment with CNP utilizing the isolette device may be contraindicated.

While we have had success in rescuing certain infants with CNP, our numbers are relatively small and there is no control group, therefore these results should not be generalized. The only certain observation to be stated is that there was an acute improvement in oxygenation in conjunction with the start of CNP. Similarly, since we did not routinely employ other physiologic measurements such as cardiac output, central venous pressure, pulmonary mechanics, or functional residual capacity in these patients we can only speculate as to the difference in physiologic effects of negative and positive pressure ventilation. Unfortunately, the majority of information in the literature about neonatal negative pressure ventilation reflects clinical studies and observations. To date, little has been reported regarding the underlying physiology of CNP in neonates. Furthermore, all previous work dealt with negative pressure ventilation alone or in combination with IPPB. We could find no report in the literature of studies on the combined use of CNP and IMV.

While we are not advocating routine use of CNP, it does appear to have a role in the management of infants who have failed maximal conventional therapy. Considering the 11 infants who had to be removed from CNP prior to being given an adequate therapeutic trial, we feel that CNP should not be used in the following circumstances: 1) incompletely evacuated pneumothorax, 2) hemodynamic unstability (shock), and 3) predominant left-to-right shunt (PDA). The possibility of developing or extending an IVH, especially in infants weighing less than 1,500 g when using the isolette must be weighed against the potential advantages. Animal studies to more clearly define the physiological events and changes during treatment with CNP and IMV, and prospective clinical trials of CNP are in progress.

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