The Effects of Nasal Continuous Positive Airway Pressure on Cardiac Function in Premature Infants with Minimal Lung Disease: A Crossover Randomized Trial

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Objective To assess the effects of different nasal continuous positive airway pressure (nCPAP) pressures on cardiac performance in preterm infants with minimal lung disease, we conducted a randomized, blinded crossover study.

Study design We studied infants between 28 and 34 weeks' corrected gestational age, treated with nCPAP of 5 cm H_2O, in air. Infants with significant cardiac shunts were excluded. Infants were randomly assigned to nCPAP levels of 4, 6, and 8 cm H_2O for 15 minutes each. Right and left ventricular outputs and left pulmonary artery and superior vena cava flows were measured 15 minutes after each change.

Results Thirty-four infants born at a mean gestational age of 29 weeks with a birth weight of 1.3 kg were studied. There were no significant differences in right and left ventricular outputs and left pulmonary artery and superior vena cava flows at different levels of nCPAP.

Conclusion We investigated the effect of increasing nCPAP levels on cardiac output. We conclude that nCPAP levels between 4 and 8 cm H_2O did not have an effect on cardiac output in stable preterm infants with minimal lung disease. *(J Pediatr 2014;164:726-9)*.

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The use of nasal continuous positive airway pressure (nCPAP) has increased in newborn intensive care units over recent decades.[1,2] nCPAP is proved to facilitate extubation and is used as first-line respiratory support of extremely low birth weight infants.[3] However, controversy exists about the optimal continuous positive airway pressure (CPAP) levels to be used.[4-6] Positive airway pressure maintains alveolar expansion, increases residual capacity of the ventilated lung, and improves oxygenation. Poor aeration of the lungs leads to increased pulmonary vascular resistance and reduced blood flow. Thibeault et al[7] demonstrated that optimization of lung volume in infants affected by evolving chronic lung disease can improve pulmonary blood flow. In contrast, overinflation of the lung causes compression of the vena cava, pulmonary vasculature, and heart.[8] Low systemic blood flow and low superior vena cava (SVC) return are associated with increased morbidity in preterm infants.[9,10] Therefore, the interaction between respiratory support and cardiac output (CO) is critically important. Some neonatologists do not use nCPAP >5 cm H_2O, and others prefer to use nCPAP of ≥7 cm H_2O.[11]

We conducted a randomized, blinded crossover study to investigate the effects of different nCPAP pressures on cardiac performance in preterm infants with minimal lung disease.

Methods

Infants with a postmenstrual age of 28-34 weeks admitted to the Neonatal Intensive and Special Care Nurseries at the Royal Women's Hospital who were treated with nCPAP of 5 cm H_2O in 21% O_2 were eligible. Infants were excluded if they were on inotropic support, had a significant structural anomaly, or had a significant shunt such as a patent ductus arteriosus (PDA), atrial septal defect/persistent foramen ovale, or any ventricular septal defect. We defined a significant atrial septal defect/persistent foramen ovale as having a diameter of >3 mm as measured with color flow Doppler. A significant PDA was >1.5 mm in diameter with a flow

BP	Blood pressure	nCPAP	Nasal continuous positive airway pressure
CO	Cardiac output		
CPAP	Continuous positive airway pressure	PDA	Patent ductus arteriosus
CSA	Cross-sectional area	RVO	Right ventricular output
HR	Heart rate	SVC	Superior vena cava
LPA	Left pulmonary artery	VTI	Velocity-time integral
LVO	Left ventricular output		

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velocity of <3 m/sec and/or a pulsatile flow pattern. Sucrose was used to settle the infants if required. Parents gave written informed consent before enrollment into the study. The study was approved by the Ethics Committee of the Royal Women's Hospital.

Treatment allocation was determined using a random number table. Three nCPAP levels were administered in random order—4 cm, 6 cm, and 8 cm H_2O—according to a card provided in an opaque, sealed randomization envelope. The bedside nurse changed the CPAP levels according to the order on the card, and echocardiographic measurements were taken by a single examiner (F.B.) blinded to the nCPAP level.

F and P Bubble CPAP System (Fisher and Paykel Healthcare, Auckland, New Zealand), the Draeger Babylog VN 500 VN 500 ventilator (Draeger, Luebeck, Germany Germany), or the Draeger Babylog 8000 ventilator Babylog ventilator were used to apply nCPAP. Infants were kept in a supine position during the entire study period to minimize handling and to allow access to the ventral chest for echocardiographic measurements. The prongs remained in the nose during the study period, and attention was paid to optimal positioning of the infant's head and neck. No measures were taken to keep the mouth shut.

Measurements were taken 15 minutes after each change of nCPAP settings and included SVC Doppler, Doppler in the aorta and pulmonary artery, left pulmonary artery (LPA) Doppler, and PDA Doppler, and SVC diameter. Aortic, pulmonary, LPA, and PDA diameters were measured before the start of the study. Echocardiographic measurements were performed with a GE Vivid-I portable cardiac ultrasound machine (General Electric, Fairfield, Connecticut) using a 10-MHz sector array transducer incorporating color flow and pulsed-wave Doppler. All vessel diameters were measured in 2 dimensions—the pulmonary diameter at the hinges of the pulmonary valve, the aortic diameter at the sinotubular junction, the LPA diameter after the pulmonary bifurcation, and the SVC diameter in systole and diastole at the funnel of the SVC.[10,12-15] The pulsed-wave Doppler traces were obtained by placing the gate just distal to the point where the diameter was measured. CO was measured in mL/kg/min and calculated as follows: CO (mL/kg/min) = (velocity-time integral [VTI; cm^2] × heart rate [HR; min^{-1}] × cross-sectional area [CSA; cm] at the point of velocity measurement)/weight (kg). VTI is measured with pulsed Doppler and is calculated from the area under the curve of the spectral trace, and the CSA is calculated from the diameter of the vessel: CSA = (diameter^2 × π)/4. Each diameter was measured 3 times and then averaged. Three VTIs were averaged for the calculation of left ventricular output (LVO), right ventricular output (RVO), and LPA flow, and 10 VTIs were averaged for the calculation of SVC flow. Blood pressure (BP), HR, oxygen saturations, and oxygen requirement were recorded 10 minutes after the nCPAP change. BP was recorded by use of a Intellivue 70 (Philips Electronics Australia, Sydney, Australia) with an appropriate-sized cuff.

For a paired comparison, a sample size of 34 infants in each group was calculated to be sufficient to detect a 0.5-SD difference in RVO with 80% power and an α of .05. The primary outcome for analysis was the difference in RVO in infants treated with nCPAP levels of 4 cm and 8 cm H_2O. Analysis was done independently using ANOVA and Student paired *t* test. Other outcomes included the change in BP and HR. Analyses were performed using Stata 12 (StataCorp, College Station, Texas).

Results

Between December 2011 and August 2012, 67 parents were approached for consent and 34 infants were studied and included in this analysis (**Figure**). The study population consisted of 25 boys and 9 girls with a median (IQR) gestational age at birth of 28.8 (28.2-30.4) weeks and a median (IQR) weight of 1.3 (1-1.6) kg (**Table I**).

None of the infants required supplemental oxygen during the study period. There was no significant effect of nCPAP levels on any cardiovascular variable, including RVO, LVO, SVC flow, LPA flow, BP, and HR (**Table II**).

Discussion

This study demonstrated unchanged CO at nCPAP levels of 4, 6, and 8 cm H_2O in stable preterm infants with minimal lung disease. This finding was not anticipated as increases in airway pressure previously were demonstrated to reduce RVO. De Waal et al demonstrated a decrease in RVO after an increase in peak end-expiratory pressure from 5 to 8 cm H_2O in conventionally ventilated infants, and an increase of mean airway pressure of 8 to 14 cm H_2O in oscillated term and preterm infants in the first 3 days of life. Infants were ventilated because of multiple causes of respiratory compromise and no information was given about the severity of lung disease. In those infants, RVO decreased significantly in response to an increase in positive end-expiratory pressures, but there were no significant changes in SVC flow and left heart function.[16,17]

Two studies compared cardiac function in premature infants ready to be taken off nCPAP. Abdel-Hardy et al[18] found that nCPAP reduces SVC flow and RVO in 4- to 18-day-old

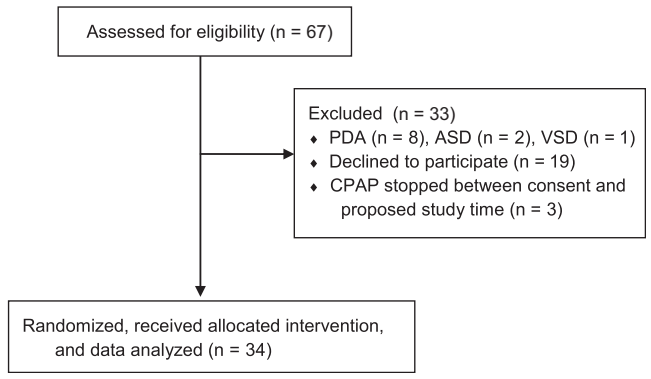

Figure. Patient recruitment for the study. *ASD*, atrial septal defect; *VSD*, ventricular septal defect.