Continuous Positive Airway Pressure Impairs Renal Function in Newborn Goats

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Summary

Continuous positive airway pressure (CPAP) is used routinely to improve oxygenation in newborns who have intrapulmonary shunts and hypoxemia that is refractory to usual oxygen therapy. Although the cardiovascular and pulmonary effects of CPAP on newborns are well known, little information is available concerning the effect of CPAP on renal function. Therefore, we determined the effect of CPAP (7.5 cm H₂O) on urine flow, sodium excretion, and glomerular filtration rate in six newborn goats that were lightly anesthetized with methoxyflurane. CPAP decreased urine flow, sodium excretion, and glomerular filtration rate. CPAP also decreased pulse pressure but did not change mean systemic arterial pressure or heart rate. We conclude that CPAP can impair renal function in newborns without significantly altering renal perfusion pressure.

Speculation

Newborns have a decreased glomerular filtration rate and a decreased ability to excrete sodium loads. Continuous positive airway pressure may further impair renal function in newborns who have the respiratory distress syndrome.

Continuous positive airway pressure (CPAP) was introduced by Gregory *et al.* (7) as part of the management of the neonatal respiratory distress syndrome. CPAP is now used routinely to improve oxygenation in newborns who have intrapulmonary shunts and hypoxemia that is refractory to usual oxygen therapy. Although the effects of CPAP on the cardiovascular and pulmonary systems are well known (2, 5, 16, 19, 22), little information is available concerning the effect of CPAP on renal function. Two studies have demonstrated that increasing airway pressure alters renal hemodynamics in newborns (5, 14).

Gabriele *et al.* (5) demonstrated that CPAP (11 mm Hg) decreases cardiac output and renal blood flow in newborn lambs. Furthermore, Moore *et al.* (14) demonstrated that intermittent positive pressure ventilation reverses the normal distribution of renal cortical blood flow in 3- to 5-day-old monkeys. Although these studies demonstrate that increasing airway pressure during all or part of the ventilatory cycle alters renal hemodynamics, they do not provide other essential information about renal function.

The purpose of this study, then, was to further define the effects of CPAP on renal function in newborns. Specifically, we determined urine flow, glomerular filtration rate, and sodium excretion during CPAP in newborn goats.

MATERIALS AND METHODS

Six newborn goats (8 to 17 days old) were lightly anesthetized by inhalation of methoxyflurane. Each goat was placed supine, and its trachea was intubated with a cuffed endotracheal tube. The cuff was inflated to a gas-tight fit, and the tube was connected to an open-circuit anesthesia system (continuous gas flow rate, 6

liters/min; 0.5 to 1.0% methoxyflurane in 30% oxygen). A rigid catheter was placed in line with the endotracheal tube for continuous monitoring of proximal airway pressure. A polyethylene catheter was inserted into a femoral artery and advanced to the ascending aorta for measurement of mean systemic arterial pressure, pulse pressure, and heart rate. A femoral vein was cannulated for administration of fluids. The ureters were cannulated with polyethylene tubing for measurement of urine flow.

Each experiment consisted of six consecutive 30-min periods: two 30-min control periods during which airway pressure was atmospheric; two 30-min experimental periods during which airway pressure was increased to 7.5 cm H₂O (CPAP); and two 30-min recovery periods during which airway pressure was atmospheric. The experimental protocol began when urine flow remained stable ($\pm 10\%$) for two consecutive 30-min periods. CPAP was applied by tightening a screw clamp on the orifice of the anesthesia bag incorporated into the expiratory limb of the anesthesia circuit. Body temperature, measured rectally, was maintained at 37°C by an external heating pad.

Pulmonary, cardiovascular, and renal variables were measured during each of the control, experimental, and recovery periods. The pulmonary variables, arterial PO₂, PCO₂, and pH, were measured at the midpoint of the second 30-min period of each condition, and the cardiovascular variables, heart rate, mean systemic arterial pressure, and pulse pressure, were measured at the midpoint of each 30-min period. The pressures were measured by a Statham P23Db strain gauge manometer and recorded on a Electronics for Medicine DR-8 optical recorder.

Glomerular filtration rate was estimated from the clearance of inulin. Throughout each experiment, a solution of inulin (3 mg/ml in 0.45% sodium chloride) was infused IV at a rate of 0.1 ml/kg/min to maintain plasma inulin at 0.25 mg/ml. For measurements of renal variables, urine was collected at the end of each 30-min period, and a 3 ml blood sample was drawn at the midpoint of each of these periods. The volume of blood withdrawn was replaced by an equal volume of 6% dextran in 0.9% sodium chloride in which the red blood cells from the previous collection period were resuspended. Urine flow and plasma and urine concentrations of sodium and inulin (8) were measured, and the sodium excretion, glomerular filtration rate, and fractional reabsorption of sodium were calculated. In addition, plasma and urine osmolality were measured, and osmolal clearance and free water clearance were calculated.

To analyze the data statistically, we performed a one-way analysis of variance for repeated measurements of the same variable to determine if there was a significant ($P < 0.05$) difference between any of the periods (21). If there was a significant difference, we then performed a Dunnett's multiple range *t* test to determine which means were statistically different ($P < 0.05$) from the mean of the control periods (20).

RESULTS

Urine flow, sodium excretion, and glomerular filtration rate decreased in response to CPAP (7.5 cm H₂O) (Table 1). Osmo

Table 1. *Effect of CPAP on renal variables in newborn goats*¹

Airway pressure (min)	Urine flow (ml/min/kg)	Sodium excretion (μ Eq/min/kg)	Glomerular filtration rate (ml/min/kg)	Osmolal clearance (ml/min/kg)	Free-water clearance (ml/min/kg)
Control (atmospheric)					
0-30	0.023 $\pm$ 0.002 ²	0.380 $\pm$ 0.054	2.00 $\pm$ 0.29	0.039 $\pm$ 0.009	-0.016 $\pm$ 0.001
30-60	0.022 $\pm$ 0.002	0.409 $\pm$ 0.034	1.81 $\pm$ 0.34	0.039 $\pm$ 0.012	-0.017 $\pm$ 0.012
CPAP (7.5 cm H ₂ O)					
60-90	0.012 $\pm$ 0.003 ³	0.208 $\pm$ 0.037 ³	0.90 $\pm$ 0.27 ³	0.024 $\pm$ 0.018	-0.012 $\pm$ 0.012
90-120	0.011 $\pm$ 0.003	0.231 $\pm$ 0.076 ³	1.22 $\pm$ 0.40 ³	0.018 $\pm$ 0.013 ³	-0.001 $\pm$ 0.007
Recovery (atmospheric)					
120-150	0.024 $\pm$ 0.003	0.449 $\pm$ 0.084	2.12 $\pm$ 0.49	0.032 $\pm$ 0.011	-0.008 $\pm$ 0.007
150-180	0.024 $\pm$ 0.002	0.509 $\pm$ 0.143	1.74 $\pm$ 0.17	0.038 $\pm$ 0.007	-0.008 $\pm$ 0.008

¹ n = 6.² Mean $\pm$ 1 S.D.³ Significant difference at the 0.05 level of significance from the mean of the control periods.Table 2. *Effect of CPAP on cardiovascular variables in newborn goats*¹

Airway pressure (min)	Heart rate (beats/min)	Mean arterial pressure (mm Hg)	Pulse pressure (mm Hg)
Control (atmospheric)			
15	166 $\pm$ 8 ²	59 $\pm$ 2	45 $\pm$ 1
45	161 $\pm$ 9	57 $\pm$ 3	45 $\pm$ 1
CPAP (7.5 cm H ₂ O)			
75	163 $\pm$ 6	57 $\pm$ 2	41 $\pm$ 2 ³
105	161 $\pm$ 7	58 $\pm$ 3	41 $\pm$ 2 ³
Recovery (atmospheric)			
135	157 $\pm$ 7	56 $\pm$ 2	45 $\pm$ 2
165	157 $\pm$ 8	56 $\pm$ 3	44 $\pm$ 3

¹ n = 6.² Mean $\pm$ 1 S.D.³ Significant difference at the 0.05 level of significance from the mean of the control periods.

clearance also decreased, but free water clearance did not change significantly (Table 1). Fractional reabsorption of sodium remained constant (98.8%).

Pulse pressure also decreased, but heart rate and mean systemic arterial pressure were unchanged (Table 2).

Arterial blood gases and pH did not change significantly (Table 3).

DISCUSSION

This study demonstrates that CPAP can impair renal function in newborn goats. Specifically, CPAP (7.5 cm H₂O) decreased urine flow, sodium excretion, and glomerular filtration rate.

This study was performed on newborn goats that did not have significant pulmonary disease, and one might anticipate that their hemodynamic response to CPAP would be greater than that of newborns who have the respiratory distress syndrome and decreased lung compliance. However, a similar cardiovascular response, decreased pulse pressure and unchanged heart rate and mean systemic arterial pressure, has been reported in newborns with the respiratory distress syndrome during treatment with CPAP (9.0 to 27.1 cm H₂O) (2, 7). Thus, CPAP may also impair renal function in newborns with the respiratory distress syndrome.

Although this study was not designed to determine the mechanism of the renal response to CPAP, our findings allow us to rule out certain possibilities and speculate upon the mechanism. Three possible mechanisms are changes in renal perfusion pressure, changes in circulating hormones, and changes in renal sympathetic nervous activity. Changes in renal perfusion pressure can be ruled

Table 3. *Lack of effect of CPAP on pulmonary variables in newborn goats*¹

Atmospheric pressure (min)	pH	PaO ₂ (mm Hg)	PaCO ₂ (mm Hg)
Control (atmospheric)			
45	7.29 $\pm$ 0.06 ²	78.9 $\pm$ 24.6	42.3 $\pm$ 11.4
CPAP (7.5 cm H ₂ O)			
105	7.31 $\pm$ 0.06	85.7 $\pm$ 22.9	39.9 $\pm$ 6.2
Recovery (atmospheric)			
165	7.37 $\pm$ 0.11	88.8 $\pm$ 23.7	37.7 $\pm$ 7.2

¹ n = 6.² Mean $\pm$ 1 S.D.

out because this variable did not change significantly in our study, as indicated by unchanged mean systemic arterial pressure (Table 2). Although much emphasis has been placed on changes in circulating concentrations of antidiuretic hormone during increased airway pressure in both infants (14) and adults (6, 18), antidiuretic hormone also seems unlikely to be the mechanism of the renal response to CPAP because free water clearance did not decrease in our study (Table 1).

Others have suggested that changes in renal function during increased airway pressure are predominantly caused by changes in renal hemodynamics rather than by changes primarily related to antidiuretic hormone (12). Renal hemodynamic changes during CPAP may be caused by alterations in renal sympathetic nervous activity. In support of this is the finding that renal denervation eliminates the renal response to continuous positive-pressure ventilation (CPPV) in dogs (4). In this study, the renal responses of the intact right kidney and the denervated left kidney were compared during CPPV. CPPV decreased urine flow, sodium excretion, effective renal plasma flow, and the glomerular filtration rate in the intact right kidney but did not change these variables in the denervated left kidney. Inasmuch as both kidneys were exposed to the same hormones, antidiuretic hormone seems unlikely to have played a role in the renal response. Rather, these findings suggest that impaired renal function during CPPV is secondary to increased renal sympathetic nervous activity.

Renal sympathetic nervous activity can be affected by changes in the arterial carbon dioxide tension (15), by activation of cardiopulmonary receptors (9), and by changes in the activity of carotid sinus and aortic arch baroreceptors (10, 11). Changes in carbon dioxide tension seem unlikely to be responsible for increased renal sympathetic nervous activity during CPAP because carbon dioxide tension did not change significantly in our study (Table 3). Activation of cardiopulmonary baroreceptors which have vagal affer-

ents also seems unlikely to be responsible. Previous experiments have shown that bilateral cervical vagotomy does not alter the cardiovascular (13, 17) or the renal (1, 3) response to increased airway pressure. However, because denervation of the aortic arch and carotid sinus baroreceptors eliminates the renal response to CPPV (3), changes in the activity of the carotid sinus and aortic arch baroreceptors during CPAP may well increase renal sympathetic nervous activity.

Thus, we suggest that increased airway pressure decreases cardiac output, which, in turn decreases carotid sinus and aortic arch baroreceptor activity. Integration of these nerve signals from the arterial baroreceptors by the central nervous system results in increased renal sympathetic nervous activity, and this increases renal vascular resistance and decreases glomerular filtration rate. The decrease in urine flow and sodium excretion appears to result from the decreased glomerular filtration rate.

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