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# *Renal Function during Application of Positive End-expiratory Pressure in Swine: Effects of Hydration*

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**The possibility that the deleterious renal effects of positive end-expiratory pressure (PEEP) might be avoided by prevention of its attendant cardiovascular effects with increasing intravascular volume was investigated in two groups of anesthetized swine. Group 1 (12 swine) were maintained at a normovolemic state and Group 2 (11 swine) were volume expanded with an infusion of lactated Ringer's solution. In normovolemic swine (Group 1), the addition of PEEP to controlled mechanical ventilation (CMV) caused significant decreases in cardiac output and mean aortic pressure. In addition, decreases in urinary output and osmolar, free water, and creatinine clearance occurred. Change from CMV to CMV + PEEP in Group 1 also produced increases in plasma ADH from 4.6 ± 2.4 to 10.2 ± 7 pg/ml ($P < 0.01$) and renin from 1.8 ± 1.0 to 4.7 ± 1.6 ng·ml$^{-1}$·h$^{-1}$ ($P < 0.01$), epinephrine from 133 ± 23 to 1,060 ± 636 pg/ml ($P < 0.03$) and norepinephrine from 46 ± 15 to 1,427 ± 839 pg/ml ($P < 0.03$). In hydrated swine (Group 2) addition of PEEP to CMV was not accompanied by any significant change in hemodynamic, renal, or hormonal variables. It is concluded that the short-term renal effects of PEEP are mainly due to hormonal responses that are activated by decrease in perfusion pressure. These responses can be obviated by intravascular volume expansion. (Key words: Heart: cardiac output; hydration. Hormones: antidiuretics; renin; adrenergic. Kidney: blood flow; function; urine output. Ventilation: positive end-expiratory pressure.)**

CONTROLLED MECHANICAL VENTILATION (CMV) with positive end-expiratory pressure (PEEP) is commonly employed for the management of patients with acute respiratory failure. Increased airway pressure during CMV + PEEP causes reduction in cardiac output and blood pressure by decreasing venous return or compromising left ventricular function or its distensibility.[1] Fluid retention and impairment of renal function are also frequent consequences of CMV + PEEP.[2,3] The observed decrease in venous return during CMV + PEEP may alter renal function either directly by decreasing renal perfusion or through reflex changes in hormonal secretions.[4] This study was designed to ascertain if the acute hormonal and renal changes that are observed during application of CMV + PEEP can be prevented by maintenance of a normal perfusion pressure by hydration.

## Methods

Twenty-three swine of either sex weighing 14.5 ± 2.2 kg were sedated with halothane/$O_2$ via cone mask until an ear vein was cannulated. Anesthesia was induced with alpha-D-glucochloralose (40 mg/kg, iv) and maintained with subsequent doses (20 mg/kg, iv) administered at the end of each study period, which was approximately every 90 min. Swine were placed supine, and the trachea was intubated with a cuffed endotracheal tube; thereafter, CMV was instituted (model 900C, Siemens Servo Ventilator®, Elk Grove Village, Illinois) with $F_{I_{O_2}}$ 0.4 at a minute volume sufficient to maintain normocapnia. Animals were paralyzed with continuous iv infusion of succinylcholine (0.1%). Catheters were inserted into the aorta and inferior vena cava below the diaphragm by cutdown of the femoral artery and vein, respectively. A thermistor-tipped pulmonary artery catheter was placed via the right external jugular vein. A catheter was advanced to the right atrium via the left external jugular vein. Catheters were hydrostatically connected to quartz transducers (model 1290A, Hewlett-Packard®, Waltham, Massachusetts) for continuous measurement of inferior vena cava pressure (IVCP), right atrial pressure (RAP), pulmonary artery pressure (PAP), and mean arterial pressure (MAP). Transducer-tipped catheters (Millar Industries, Houston, Texas) were placed between the visceral and parietal pleura in the left hemithorax via the fourth intercostal space at the midaxillary line and in the left ventricle via a femoral artery for measurement of pleural pressure ($P_{Pl}$) and left ventricular end-diastolic pressure (LVEDP), respectively. A urinary bladder catheter was surgically placed for urine collection. Heart rate (HR) was calculated from an ECG that was traced with pressures on a multichannel recorder (model 7758A,

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Hewlett-Packard). When a plateau in the LVEDP recording was absent, it was measured at a point corresponding to the peak of the QRS complex. All intrathoracic pressures were converted to transmural (TM) values by subtracting $P_{PI}$ from the measured pressure. Cardiac output (CO) was determined as the mean of three thermodilution runs (model 9520A, American Edwards, Santa Ana, California). A 3-ml indicator solution (0–2° C 5% dextrose in water) was injected via the right atrial catheter at end expiration. A femoral vein was used for fluid administration. Pulmonary artery blood temperature was maintained at 38.0 ± .5° C by an external thermal blanket and warming lamps.

After instrumentation, the swine were randomized into two groups.

Group 1 (normovolemic): Twelve animals received sufficient lactated Ringer's solution (LR) to maintain $LVEDP_{TM}$ at 5 ± 1 mmHg throughout the study. Group 2 (hyrated): Eleven animals were volume expanded to and maintained at a $LVEDP_{TM}$ of 10 ± 1 mmHg with LR during the entire study period. Steady state was considered reached after two consecutive 15-min periods of equal (±10%) urine flow. Hormonal, renal, and hemodynamic data were collected 60 min post-steady-state. Then 15 $cmH_2O$ PEEP was added in 5 $cmH_2O$/2–3 min increments to the CMV. Study data were obtained after 60 min of CMV + PEEP.

Specimens were collected for measurement of arterial blood gases/*p*H, plasma renin and ADH hormone, plasma and urine osmolality ($P_{OSM}$ and $U_{OSM}$), plasma and urine sodium ($P_{Na}$ and $U_{Na}$), urine flow/min ($\dot{V}U$), and plasma and urine creatinine ($P_{cr}$ and $U_{cr}$). In 12 animals plasma for epinephrine (Epi) and norepinephrine (Norepi) was also collected. Urine analysis was performed on a sample collected during the last 15 min of each study period. Arterial blood samples for hormone and catecholamine assays were placed in chilled collection tubes containing EDTA–$Na_2$ and heparin, respectively, and immediately placed in an ice-water bath until the plasma was retrieved following 0–4° C centrifugation (within 20 min or less). Plasma for hormone determinations was stored at −70° C until subsequent radioimmunoassay was performed (Bioscience Laboratory, Miami, Florida). Catecholamine levels were measured via radioenzymatic assay (Critical Care Medicine Research Laboratory, USNH, Bethesda, Maryland) in glutathione preserved plasma at −70° C.

Osmolar ($C_{OSM}$), free water ($C_{H_2O}$), and creatinine ($C_{cr}$) clearances and sodium excretion ($U_{Na}\dot{V}$) were calculated with the following formulas:

$$C_{OSM} = \frac{U_{OSM} \times \dot{V}U}{P_{OSM}}$$

$$C_{H_2O} = \dot{V}U - C_{OSM}$$

$$C_{cr} = \frac{U_{cr} \times \dot{V}U}{P_{cr}}$$

$$U_{Na}\dot{V} = U_{Na} \times \dot{V}U$$

Data are expressed as mean ± one standard deviation (SD). Student's *t* test for unpaired and paired observations were employed for statistical comparisons between and within groups, respectively. Differences in means were considered significant when *P* values were less than 0.05.

## Results

There was no significant difference in initial weight between normovolemic (14.1 ± 1.6 kg) and hydrated (14.3 ± 2.8 kg) swine; thus measured and calculated variables were not indexed for comparisons. Normovolemic swine received a total Ringer's lactate infusion of 346 ± 39 ml while those in the hydrated group received 881 ± 108 ml. The sodium load was 45.1 ± 5.4 and 114.6 ± 14.1 mEq in the normovolemic and hydrated animals, respectively. Normovolemic swine had a $P_{Na}$ of 137 ± 8 and 132 ± 11 mEq/l and a $P_{OSM}$ of 289 ± 21 and 277 ± 18 mOsm/kg $H_2O$ during CMV and CMV + PEEP, respectively. $U_{Na}\dot{V}$ decreased significantly from 13.2 ± 7.8 mEq/min on CMV to 4.2 ± 2.2 during CMV + PEEP. During CMV and CMV + PEEP the hydrated animals exhibited a $UNa\dot{V}$ of 126 ± 42.3 and 114.3 ± 48.7 mEq/min, respectively.

Hemodynamics, renal function data and hormone levels are summarized in figures 1–3. Arterial blood gases/*p*H were statistically similar and within normal limits throughout the study periods in both groups. The addition of 15 $cmH_2O$ PEEP to the ventilatory pattern of normovolemic (Group 1) animals precipitated a 35% reduction in CO ($P < 0.05$), a 22% increase in HR ($P < 0.05$), a 20% decrease in MAP ($P < 0.05$) along with significant deterioration in renal function (fig. 2), and increased plasma ADH level and renin activity (fig. 3). Plasma Epi increased from 46 ± 15 to 1,427 ± 839 pg/ml ($P < 0.03$), and Norepi concentration increased from 133 ± 23 to 1060 ± 636 pg/ml ($P < 0.03$). Hydration to a $LVEDP_{TM}$ of 10 ± 1 mmHg (Group 2) during CMV + PEEP prevented significant alteration in CO, HR, MAP, renal function, ADH level, or renin activity. Plasma Epi and Norepi levels were similar at 10 ± 4 and 6 ± 3 pg/ml during CMV and CMV + PEEP, respectively. IVCP was significantly increased from 6.3 ± 1.3 to 12.6 ± 3.7 mmHg and from 11.5 ± 1.9 to 15.5 ± 3.2 mmHg during CMV + PEEP in normovolemic and hydrated swine, respectively.

## Discussion

Previous studies have shown that the addition of PEEP to mechanical ventilation causes a decrease in urine output, glomerular filtration rate, and sodium excretion.[5] The observed alterations in renal function during the application of PEEP have been attributed to several mechanisms. In studies demonstrating alteration in renal function, a concomitant decrease in cardiac output also has been observed.[6,7] Since diminished cardiac output may decrease renal perfusion, glomerular filtration rate, and thereby urine flow, a decrease in cardiac output has been suggested as a cause for alteration in renal function during PEEP therapy. However, Qvist *et al.*[8] noted a persistent decrease in urinary flow, despite an increase in cardiac output values to almost pre-PEEP levels. Hall *et al.*[9] suggested that the redistribution of flow from the cortical to the juxtamedullary nephrons might be an important contributory factor in initiating depression of renal function during PEEP therapy. However, a recent study from the same laboratory, using radioactive microsphere technique, failed to demonstrate any redistribution of renal blood flow during ventilation with PEEP.[10] The increase in inferior vena caval pressure that parallels the application of PEEP, increases renal and hepatic vein pressure. Marquez *et al.*[11] suggested that the increase in vena caval pressure during CMV + PEEP may affect renal function. However, Priebe *et al.*[10] reported that selected release of hepatic congestion during PEEP by means of a vena cava to jugular venous shunt did not restore renal function. In our study, a significant increase in IVCP was noted in both groups. But deterioration in renal function was only observed in the normovolemic (Group 1) swine. Our results support the conclusion by Priebe *et al.*[10] that hepatic and renal congestion *per se* does not appear to be the cause for changes in renal function during PEEP. Mullins *et al.*,[12] using a model with autologous blood mechanically pumped at a constant flow into the renal artery during control and then PEEP therapy, observed that PEEP did not cause any significant change in renal function and concluded that maintenance of arterial pressure and renal perfusion will prevent deterioration in renal function.

Besides hemodynamic impairment, PEEP is known to change the activity of different hormonal systems that are acting on the kidney. In a model with constant perfusion pressure, Fewell and Bond[13] suggested that an increase in sympathetic tone during PEEP therapy

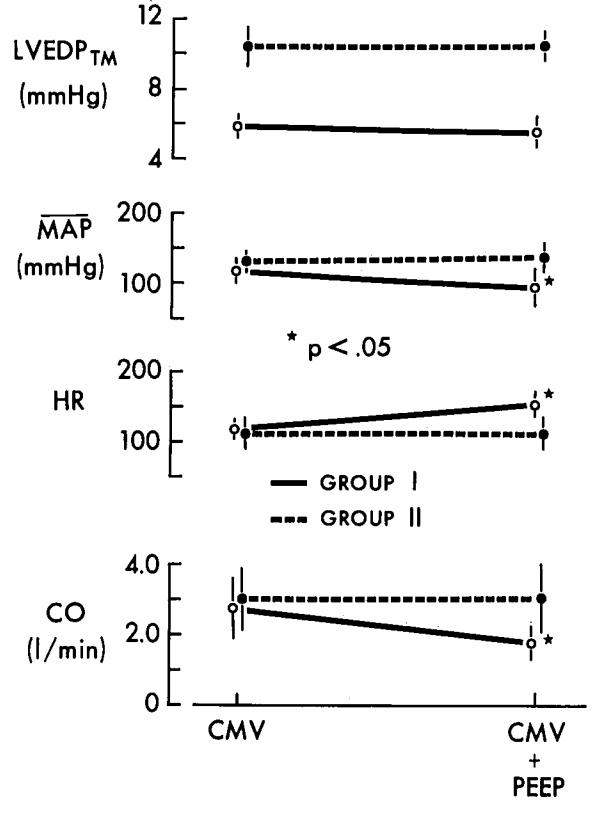


FIG. 1. Hemodynamics during CMV and CMV + PEEP in Group 1 (normovolemic) and Group 2 (hydrated) swine (mean ± SD).

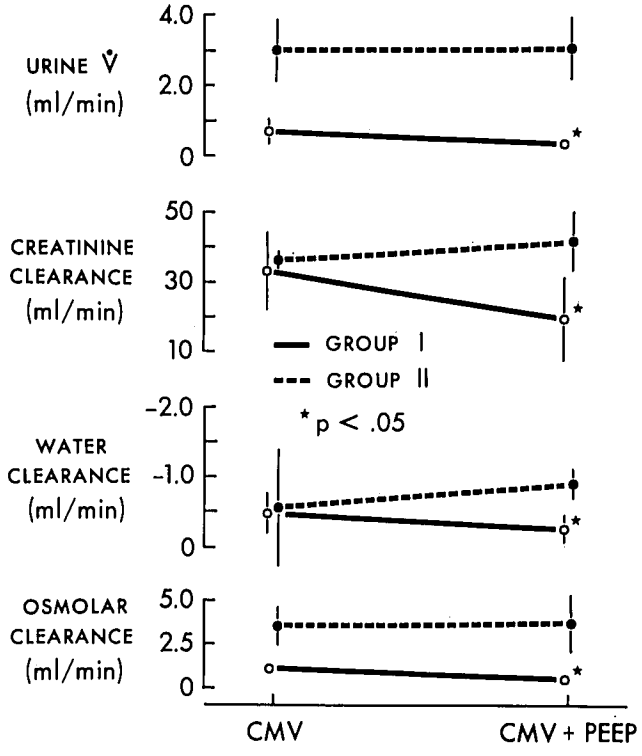


FIG. 2. Renal function data during CMV and CMV + PEEP in normovolemic (Group 1) and hydrated (Group 2) swine (mean ± SD).

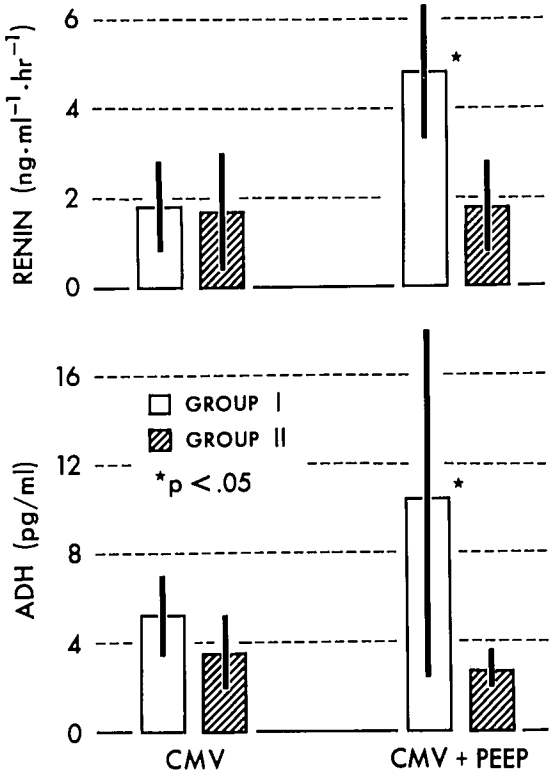


FIG. 3. Antidiuretic hormone (ADH) level and renin activity during CMV and CMV + PEEP in normovolemic (Group 1) and hydrated (Group 2) swine (mean ± SD).

contributes to the renal function deterioration. Increases in prostaglandins, renin–angiotensin–aldostrone, and ADH secretion also have been shown to accompany the deterioration in renal function during PEEP therapy.[4,6,7] However, evidence suggests that these hormonal changes can be compensated for when hemodynamics are maintained. In a recent review of the changes in kidney function during CMV and PEEP therapy, Berry[5] suggested that the renal effects of CMV + PEEP can be prevented by increasing intravascular volume. Priebe *et al.*[10] have shown that transfusion of 25 ml/kg of autologous blood during PEEP can restore the renal function of dogs to control values. The present study demonstrates that restoring intravascular volume by crystalloids in swine will also restore renal as well as hemodynamic function to pre-PEEP values. This conclusion supports our clinical observation that aggressive fluid therapy will prevent adverse cardiovascular and renal affects of PEEP. Venus *et al.*[14] reported in 15 patients, suffering from adult respiratory distress syndrome who required up to 25 $cmH_2O$ PEEP, that maintenance of an average positive fluid balance of 3.5 l prevented any hemodynamic instability and maintained urine flow and renal function.

In our first group of animals, the decrease in functional intravascular volume during PEEP application may have been sensed by atrial baroreceptors. Stimulation of these receptors may have precipitated an increase in ADH and renin release and marked increase in renal sympathetic activity. In the second group of animals, hydration prevented a receptor response, maintained CO and MAP, and prevented changes in ADH, renin, Epi, and Norepi levels. Infusion of Ringer's lactate in the hydrated group also could have altered the renin angiotensin and catecholamine values via the juxtaglomerular apparatus. Although we did not measure intravascular volume, our results suggest that PEEP affects renal function by decreasing the functional intravascular volume. Since increasing lung volume with PEEP may cause anterior shifting and twisting of the heart,[15] intracardiac pressures obtained via hydrostatically linked transducer–catheter systems may be inaccurate. Therefore, we measured LVEDP with a transducer-tipped catheter to obviate problems with determining the zero pressure point position for the transducer. Directly measured LVEDP then was converted to a transmural value to delete the effect of airway pressure. Maintenance of $LVEDP_{TM}$ at 10 mmHg preserved renal and hemodynamic variables. The fact that in hydrated swine CO improved slightly during PEEP application suggests that ventricular function or distensibility was not adversely affected by lung inflation or an increase in intravascular volume.

From the present study we conclude that maintenance of normal functional intravascular volume and perfusion pressure by aggressive hydration will prevent adverse effects of PEEP on renal function.

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