

# The Effect of Long-term Controlled Mechanical Ventilation with Positive End-expiratory Pressure on Renal Function in Dogs

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The effects of 46 h of mechanical ventilation and PEEP on urinary output, sodium excretion, and renal and cardiovascular function were examined. Dogs sedated with sodium pentobarbital were ventilated using one of three modes: spontaneous ventilation (SV), controlled mechanical ventilation (CMV), or CMV with 10 cmH<sub>2</sub>O positive end-expiratory pressure (CMV with PEEP). Intravenous fluids were given at a constant rate throughout the study and measurements of renal and cardiovascular function were made over four periods. Dogs whose lungs were ventilated with PEEP displayed more than two times the amount of fluid retention seen in the other groups as assessed by mean weight gain. This was due to an initial depression of urine flow, sodium excretion, and free water clearance. Urinary flow rate approximated the rate of fluid infusion by 20 h in SV dogs and by 27 h during CMV, while the maximum during CMV with PEEP occurred at 46 h. There were no significant differences in glomerular filtration rate, renal corticomedullary blood flow distribution, or renal blood flow between groups. During the 46 h, cardiac index increased (SV, +16%; CMV, +19%; CMV with PEEP, +64%), while systemic vascular resistance (SV, -28%; CMV, -30%; CMV with PEEP, -57%), renal vascular resistance (SV, -12%; CMV, -20%; CMV with PEEP, -23%), and mean arterial pressure (SV, -16%; CMV, -15%; CMV with PEEP, -15%) decreased in all groups. This study has demonstrated that when a constant sodium and water load was provided, the SV and CMV groups were rapidly able to adjust the urinary excretion to meet input, while the return of renal function toward normal in the CMV with PEEP group was delayed until almost 46 h from the start of ventilation. (Key words: Kidney: function. Ventilation: controlled mechanical; positive end-expiratory pressure; spontaneous.)

CONTROLLED MECHANICAL VENTILATION with positive end-expiratory pressure (CMV with PEEP) pro-

duces alterations in renal function both in laboratory animals with normal lungs<sup>1,2</sup> and in patients being treated for acute respiratory failure.<sup>3</sup> These consist of a decrease in urine output, urinary sodium excretion, and glomerular filtration rate (GFR). Other investigators have demonstrated a decrease in renal blood flow (RBF)<sup>4</sup> or redistribution of flow within the kidney away from the cortical nephrons.<sup>1</sup> CMV with PEEP also affects cardiovascular hemodynamics. As summarized in a recent review, the renal and cardiovascular changes observed with CMV with PEEP are dependent on many factors including the magnitude of pulmonary and cardiac disease in the experimental animal, the intravascular volume status, the amount of PEEP applied, and the type of anesthetic or sedative agents used.<sup>5</sup> CMV with PEEP decreases transmural atrial distending pressure<sup>1</sup> and cardiac venous return,<sup>6</sup> which in some studies leads to a reduction in cardiac output<sup>1,7,8</sup> and systemic arterial blood pressure.<sup>9</sup> Other work indicates that the left ventricular ejection fraction is unchanged during CMV with PEEP as the increased intrathoracic pressure unloads the left ventricle while decreasing transmural left ventricular pressure.<sup>10,11</sup> These cardiovascular changes acting directly or through reflex neurologic or hormonal

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## Abbreviations

C <sub>H<sub>2</sub>O</sub>	= free water clearance
CI	= cardiac index
C <sub>osm</sub>	= osmolal clearance
CMV	= controlled mechanical ventilation
F <sub>Na</sub>	= fractional excretion of sodium
FF	= filtration fraction
GFR	= glomerular filtration rate
P <sub>A</sub>	= mean systemic arterial pressure
P <sub>IVC</sub>	= mean inferior vena cava pressure
P <sub>pl</sub>	= intrapleural pressure
P <sub>TLA</sub>	= transmural left atrial pressure
P <sub>TRA</sub>	= transmural right atrial pressure
P <sub>Na</sub>	= plasma sodium concentration
P <sub>osm</sub>	= plasma osmolality
PEEP	= positive end-expiratory pressure
RBF	= renal blood flow
RPF	= renal plasma flow
RVR	= renal vascular resistance
SV	= spontaneous ventilation
SVR	= systemic vascular resistance
U <sub>NaV</sub>	= urinary sodium excretion
V	= urinary flow rate

mechanisms have been shown by some investigators to be responsible for the renal effects of CMV with PEEP.<sup>2-5,8,12</sup> Increasing intravascular volume by blood transfusion restores both cardiovascular<sup>7</sup> and renal function<sup>2</sup> in animals that are ventilated with PEEP. This suggests that with prolonged CMV with PEEP, decreased urine output and urinary sodium excretion provide a mechanism for increasing extracellular and intravascular fluid volume, and this in turn may be expected to reverse the initial cardiovascular and renal effects.

In the present study, sedated dogs breathed spontaneously or were subjected to mechanical ventilation with or without 10 cmH<sub>2</sub>O PEEP for 46 h. During this time, an infusion of sodium chloride was maintained at a constant rate and measurements of renal and cardiovascular function were made to determine if those changes that occur immediately after beginning CMV with PEEP persist.

### Materials and Methods

Healthy, female beagle dogs (mean weight 11.1 kg, range 8.7–12.9 kg), free from heartworms, were studied. Three to seven days prior to study, a left thoracotomy was performed under halothane anesthesia and a heparin-filled silastic catheter was sutured into the left atrium. Postoperatively, each dog received antibiotics and free access to food and water until 12 h before the study.

On the initial morning of the study, anesthesia was induced with sodium pentobarbital 30 mg/kg intravenously. A sterile endotracheal tube then was inserted. Each animal was allowed to breathe room air spontaneously, and repeat doses of sodium pentobarbital (3–5 mg/kg) were administered as necessary to provide adequate sedation. A solution of 0.45% NaCl with KCl 20 mEq/l was begun through a peripheral intravenous catheter at 2.0 ml/min and continued throughout the study using a constant infusion pump. A Foley catheter was placed in the urinary bladder and cannulae placed in a carotid artery and internal jugular vein. A 7F flow-directed, thermodilution pulmonary artery catheter was inserted through a femoral vein so that the proximal lumen was positioned in the abdominal inferior vena cava. A continuous infusion of 0.3 ml/min of heparinized saline administered through an Intraflow® (Sorenson) was used to prevent thrombus formation in the intravascular catheters. A soft latex balloon-tipped catheter was placed in the mid-esophagus for intrapleural pressure measurement ( $P_{pi}$ ). All pressures were measured with Statham® transducers (P23db) positioned at the right atrial level and continuously recorded on a Grass® polygraph. Cardiac output was measured in triplicate by the thermodilution technique (Model #9810 Cardiac Output Computer®, Edwards Laboratory). Normother-

mia was maintained with a warming blanket. Weight was measured with a calibrated metabolic balance (Aimex).

During the control period (Period 1), all animals breathed spontaneously until urine output was constant over three 20-min collection periods. Then (time 0) each dog randomly was assigned to one of three ventilatory modes, which was maintained until the conclusion of the study. Six dogs continued spontaneous ventilation (SV), six received controlled mechanical ventilation with zero end-expiratory pressure (CMV), and six received CMV with 10 cmH<sub>2</sub>O PEEP. Controlled ventilation was provided with an Emerson constant volume ventilator and PEEP with a 10 cmH<sub>2</sub>O Boehringer PEEP valve. The animals breathed humidified air supplemented with oxygen as necessary to maintain the arterial oxygen tension greater than 60 mmHg. With controlled ventilation, a tidal volume of 15 ml/kg body weight was selected and respiratory rate adjusted to maintain normocarbica. Expired carbon dioxide tension was monitored continuously using a capnograph (Godart). Dogs ventilated with CMV and CMV with PEEP received pancuronium (0.1 mg/kg) intravenously approximately every 1.5 h. During all measurement periods, dogs were in the prone position, while between these periods, the animals were turned hourly from side to side. The lungs were hyperinflated manually and secretions aspirated as necessary to prevent atelectasis.

There were five study periods over 46 h. Period 1 (the control period) ended at time 0. Period 2 began 1 h 20 min after the conclusion of Period 1 and lasted for 1 h 40 min. Period 3 began at 8:00 A.M. on the second day (approximately 20 h after time 0) and lasted for 2 h. Period 4 began at 3:00 P.M. on the second day (approximately 27 h after time 0) and lasted 2 h. Period 5 began at 8:00 A.M. on the third day (approximately 44 h after time 0) and ended 2 h 20 min later. At least 1 h prior to each study period, a bolus of 3  $\mu$ Ci inulin-<sup>3</sup>H and 0.75 ml 20% paraaminohippurate (PAH) were given intravenously, and an infusion of 100  $\mu$ Ci inulin-<sup>3</sup>H and 6 ml of 20% PAH in 1 l 0.45% NaCl with KCl 20 mEq/l was begun at a rate of 2.0 ml/min, replacing the maintenance intravenous fluid. At the end of the study periods, the solution containing inulin-<sup>3</sup>H and PAH was discontinued and the previous fluid infusion resumed. At the beginning and end of every period, arterial oxygen and carbon dioxide tension and pH were measured. During each study period, the following measurements were made at 20-min intervals: urine volume, urine sodium and potassium concentrations, urine osmolality, mean systemic arterial pressure ( $P_A$ ), pulmonary arterial pressure ( $P_{PA}$ ), right atrial pressure ( $P_{RA}$ ), left atrial pressure ( $P_{LA}$ ), inferior vena cava pressure ( $P_{IVC}$ ), airway pressure ( $P_{Air}$ ), intrapleural pressure,

and body weight (all pressures measured at end-exhalation). Blood samples for hematocrit, sodium and potassium concentration, osmolality, and inulin- $^3\text{H}$  and PAH concentrations were taken at the beginning, middle, and end of each study period. Urinary and plasma inulin- $^3\text{H}$  activities were measured (Intertechnique Beta Counter®) and corrections made for quenching. The standard formula was used to calculate inulin clearance, which was taken as GFR. Reported values for GFR were normalized per square meter with the dog's body surface area calculated as:  $0.112 (\text{body weight})^{2/3}$ . PAH concentration in urine and plasma samples was determined using standard methods.<sup>13</sup> The fraction of PAH cleared by the kidney was determined from peripheral arterial and renal venous samples (see below) taken at the conclusion of Period 5 and was used to calculate the renal clearance of PAH, renal plasma flow (RPF), and filtration fraction (FF). These data combined with the hematocrit allowed for calculation of renal blood flow using standard equations. Renal vascular resistance (RVR) was calculated assuming that carotid pressure equaled renal arterial pressure and abdominal inferior vena cava pressure equaled renal venous pressure. Cardiac output was measured at the beginning and end of each study period. Cardiac index (CI) was calculated from this and the body surface area (see above) and systemic vascular resistance (SVR) was determined using the standard formula. Transmural atrial pressures were calculated as the difference between the intraatrial pressure referenced to atmospheric and the intrapleural pressure. The pressure data, plasma and urinary electrolyte concentrations, and calculated clearances that were determined for each measurement period were averaged and used as the value for the animal for the study period for statistical comparisons. After Periods 2, 3, and 4, a volume of blood from a donor dog equal to that removed by sampling was transfused.

#### RENAL BLOOD FLOW DISTRIBUTION

The intrarenal distribution of blood flow was determined using  $15 \pm 5 \mu\text{m}$  radioactive microspheres<sup>14</sup> labeled with  $^{51}\text{Cr}$ ,  $^{141}\text{Ce}$  or  $^{85}\text{Sr}$  (3M Co. or New England Nuclear) suspended in 10% dextrose with Tween 80. The bottles containing the microspheres were shaken vigorously, and solution containing approximately  $10^5$  microspheres was withdrawn for injection. The total counts per minute of the microspheres to be injected then was determined. Immediately prior to injection, the syringe containing the microspheres was agitated with a Vortex mixer for 5 min. The microspheres were injected into the left atrial catheter over 5 s, and the syringe was flushed repeatedly with a total of 10 ml of

normal saline. Starting 10 s before microspheres were injected, blood was aspirated for 2 min from the femoral artery at a constant rate by a Harvard® pump into a heparinized syringe, while blood from a donor dog was transfused at the same rate as withdrawal. The aspirated blood was placed in gamma-counting tubes and centrifuged for 20 min. The empty 3-ml syringes used for injection were placed in counting tubes to determine the radioactivity not injected. Microspheres labeled with  $^{141}\text{Ce}$  were injected during Period 2, those with  $^{85}\text{Sr}$  during Period 3, and those with  $^{51}\text{Cr}$  during Period 5.

At the conclusion of Period 5, the animals were given a dose of sodium pentobarbital (5 mg/kg), and a midline thoracoabdominal incision was made with an electrocautery. Animals that had been breathing spontaneously had their ventilation manually assisted using a nonrebreathing system during the following procedures that lasted approximately 2 min. A 5-ml blood sample was taken directly from the renal vein, while the PAH infusion was continued. This value was used to determine the fractional renal extraction of PAH for calculation of RPF and RBF. The circulation then was arrested by tightening a noose around the base of the heart and great vessels. The kidneys were removed, and the capsule and perirenal fat separated by blunt dissection. Both kidneys were bisected into upper and lower polar halves. One of the halves of each kidney then was divided into four or five 3-mm slices by cuts made parallel to the original division. The renal slices were dissected carefully by hand into outer cortical, inner cortical, and medullary regions. After determining the weight of the samples, the renal tissue was liquified with 1 M KOH while heated at  $60^\circ \text{C}$ . The samples then were centrifuged and radioactivity counted in appropriate channels.<sup>14</sup>

To insure that the above method of sectioning the renal tissue resulted in cortical and medullary samples that correlated with previously reported techniques, the following calculations were made for each isotope used. Activity per gram of tissue for the outer cortical (Coc), inner cortical (Cic), and medullary (Cm) samples were determined. The total weight of the kidney ( $W_T$ ) and the total activity ( $A_T$ ) were calculated by summing the respective values for the individual samples. Fan *et al.* have demonstrated that in dogs the fractional weights of the outer cortex, inner cortex, and medulla are 0.39, 0.32, and 0.29.<sup>15,16</sup> The calculated activity of the total kidney (calc  $A_T$ ) was determined:

$$\text{Calc } A_T = 0.39(W_T)(C_{oc}) + 0.32(W_T)(C_{ic}) + 0.29(W_T)(C_m).$$

Then calc  $A_T$  was compared with  $A_T$  measured for each isotope. Overall, there was good agreement ( $^{141}\text{Ce}$ , r

= 0.99;  $^{85}\text{Sr}$ ,  $r = 0.97$ ;  $^{51}\text{Cr}$ ,  $r = 0.99$ ), but the results reported are for kidneys in which the calc  $A_T$  deviated from  $A_T$  by less than 10%. When the calculated and measured values agreed for both kidneys in the study animal, the data from the two kidneys were averaged and used as the value for the dog. If data from neither kidney met the above criterion for any isotope, it was assumed that the renal dissection was not accurate and all microsphere data for that animal were discarded. This resulted in microsphere data from 11 dogs (SV,  $n = 3$ ; CMV,  $n = 5$ ; CMV with PEEP,  $n = 3$ ). Percentage of renal blood flow to the outer (% Qoc) and inner cortex (% Qic) were calculated.

$$\% \text{ Qoc} = 0.39(W_T)(\text{Coc})/A_T$$

$$\% \text{ Qic} = 0.32(W_T)(\text{Cic})/A_T$$

Using the activity of the arterial reference flow sample (Aref) and the withdrawal rate (Qref), the blood flow in ml/min to the whole outer (Qoc) and inner cortex (Qic) were calculated.

$$\text{Qoc} = 0.39(W_T)(\text{Coc})/(\text{Aref}/\text{Qref})$$

$$\text{Qic} = 0.32(W_T)(\text{Cic})/(\text{Aref}/\text{Qref})$$

#### EVALUATION OF DATA AND STATISTICAL METHODS

Hemodynamic and renal data and urinary and plasma electrolyte concentrations and osmolality were analyzed statistically using analysis of variance for repeated measurements (groups by times repeated measures design).  $P$  values are reported for group differences ( $G$ ), differences with time ( $T$ ), and group and time interactions ( $TG$ ). Other statistical tests are noted where appropriate. A  $P$  value of less than 0.05 is considered significant. All data are expressed as the mean  $\pm$  SEM.

#### Results

Complete renal and hemodynamic data were obtained from 13 dogs (SV,  $n = 4$ ; CMV,  $n = 5$ ; CMV with PEEP,  $n = 4$ ). Although all three groups of animals had a significant increase (Student's  $t$  test) in body weight by the end of Period 5, the 19.6% gain in the CMV with PEEP group was more than twice that of the other groups (SV,  $10.67 \pm 0.59$  kg to  $11.56 \pm 0.59$  kg; CMV,  $10.85 \pm 0.84$  kg to  $11.78 \pm 1.00$  kg; CMV with PEEP,  $11.97 \pm 1.10$  to  $14.32 \pm 0.74$  kg). In all groups this change in body weight was attributable to sodium and water retention.

During Period 1, a stabilization period in which all animals breathed spontaneously, fluids were administered until urine output remained constant. There were no

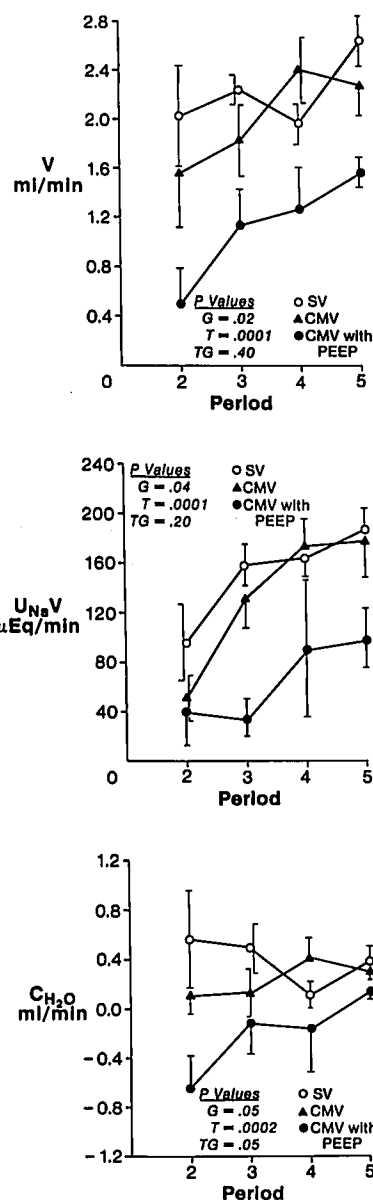


FIG. 1. The mean  $\pm$  SEM urinary flow rate ( $V$ ), urinary sodium excretion ( $U_{Na}V$ ), and free water clearance ( $C_{H_2O}$ ) for the three groups of dogs during each measurement period.  $P$  values for analysis of variance for repeated measurements are given.

significant differences between groups for data measured in Period 1. Mean values of renal function and plasma composition for this period include urinary flow rate ( $V$ ),  $0.92 \pm 0.21$  ml/min; free water clearance ( $C_{H_2O}$ ),  $-0.40 \pm 0.10$  ml/min; urinary sodium excretion ( $U_{Na}V$ ),  $63.0 \pm 12.4$   $\mu\text{Eq}/\text{min}$ ; Hct,  $33.8 \pm 1.6\%$ ; plasma sodium concentration ( $P_{Na}$ ),  $145.0 \pm 0.7$  mEq/l; and plasma osmolality ( $P_{osm}$ ),  $296.2 \pm 2.7$  mOsm/kg. The mean cardiac index was  $3.43 \pm 0.25$   $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ;  $P_A$ ,  $155 \pm 4$  mmHg; and SVR,  $87 \pm 8$  units.

TABLE 1. Renal Data (Mean  $\pm$  SEM)

Group	Period				P Value
	2	3	4	5	
GFR (ml/min)					
SV	92 $\pm$ 14	94 $\pm$ 10	87 $\pm$ 8	89 $\pm$ 6	G = 0.21
CMV	98 $\pm$ 7	104 $\pm$ 8	97 $\pm$ 8	103 $\pm$ 8	T = 0.56
CMV with PEEP	75 $\pm$ 8	79 $\pm$ 7	77 $\pm$ 11	86 $\pm$ 8	TG = 0.61
RBF (ml/min)					
SV	381 $\pm$ 72	356 $\pm$ 49	362 $\pm$ 61	389 $\pm$ 109	G = 0.61
CMV	304 $\pm$ 56	361 $\pm$ 59	332 $\pm$ 47	330 $\pm$ 57	T = 0.38
CMV with PEEP	349 $\pm$ 45	497 $\pm$ 53	392 $\pm$ 79	381 $\pm$ 62	TG = 0.59
RPF (ml/min)					
SV	235 $\pm$ 42	220 $\pm$ 28	219 $\pm$ 35	253 $\pm$ 69	G = 0.46
CMV	202 $\pm$ 42	249 $\pm$ 47	220 $\pm$ 32	225 $\pm$ 40	T = 0.21
CMV with PEEP	228 $\pm$ 31	352 $\pm$ 47	286 $\pm$ 62	279 $\pm$ 43	TG = 0.49
FF					
SV	0.45 $\pm$ 0.12	0.46 $\pm$ 0.09	0.42 $\pm$ 0.07	0.43 $\pm$ 0.11	G = 0.12
CMV	0.54 $\pm$ 0.07	0.46 $\pm$ 0.07	0.47 $\pm$ 0.06	0.50 $\pm$ 0.07	T = 0.23
CMV with PEEP	0.33 $\pm$ 0.02	0.23 $\pm$ 0.02	0.30 $\pm$ 0.05	0.32 $\pm$ 0.03	TG = 0.54
F <sub>Na</sub>					
SV	0.008 $\pm$ 0.003	0.012 $\pm$ 0.002	0.014 $\pm$ 0.003	0.015 $\pm$ 0.002	G = 0.07
CMV	0.004 $\pm$ 0.001	0.009 $\pm$ 0.002	0.012 $\pm$ 0.002	0.012 $\pm$ 0.002	T = 0.0001
CMV with PEEP	0.004 $\pm$ 0.002	0.003 $\pm$ 0.001	0.009 $\pm$ 0.005	0.009 $\pm$ 0.002	TG = 0.67

SV (n = 4): spontaneous ventilation; CMV (n = 5): controlled mechanical ventilation; CMV with PEEP (n = 4): controlled mechanical ventilation with positive end-expiratory pressure; GFR: glomerular filtration rate; RBF: renal blood flow; RPF: renal plasma flow; FF:

filtration fraction; F<sub>Na</sub>: fractional excretion of sodium.

P value is for analysis of variance for repeated measurements. P values are reported for group differences (G), differences with time (T), and group and time interactions (TG).

#### RENAL DATA

**SV and CMV:** Urinary flow rates approximated the rate of fluid infusion (2.3 ml/min) by Period 3 in dogs breathing spontaneously and by Period 4 in dogs whose lungs were ventilated mechanically (fig. 1).  $U_{Na}V$  increased in both groups after Period 2, so that by Period 5, it approached the rate of sodium chloride administration (200  $\mu$ Eq/min) (fig. 1). This was accompanied by an increase in fractional excretion of sodium (F<sub>Na</sub>) in both groups from Periods 2 to 5 (table 1). After initiation of the selected ventilatory mode,  $C_{H_2O}$  was positive for the SV and CMV groups (fig. 1). GFR, RBF, RPF, or FF did not differ between the groups and did not change throughout the study (table 1). The retention of sodium and water decreased the hematocrit in the CMV dogs after Period 2 (fig. 2). There was a decrease in plasma osmolality in both groups after Period 3 (fig. 2). In contrast, plasma sodium concentration was not significantly different over this time.

**CMV with PEEP:** The urinary flow rate was least in Period 2 in the dogs ventilated with PEEP, and in spite of an increase in subsequent periods, it remained less than that of the other ventilatory modes (fig. 1). Although the SV and CMV groups had increased their urinary sodium excretion from Periods 2 to 3,  $U_{Na}V$  was lowest during this time in dogs ventilated with PEEP (fig. 1). Although F<sub>Na</sub> had significantly increased

in the PEEP group by Period 5, it remained lower than that of the SV dogs (table 1) in the last measurement period. Free water clearance was negative during Period 2 only for the CMV with PEEP group but became positive by Period 5 (fig. 1). This is contrasted to the SV and CMV groups in which  $C_{H_2O}$  was positive throughout. GFR, RBF, RPF, and FF of the CMV with PEEP group did not change during the study and did not differ from values of the other experimental groups (table 1).

Water retention produced a decrease in hematocrit by Period 3 (fig. 2). The hematocrit of dogs ventilated with PEEP was less than the other animals' after Period 2, but the difference was not statistically significant (p, G = 0.11, TG = 0.17). Posm decreased more in the CMV with PEEP group than in dogs ventilated with the other modes.  $P_{Na}$  was lower than that of the other groups during Periods 2, 3, and 4 (fig. 2).

#### DISTRIBUTION OF RENAL BLOOD FLOW

The intrarenal distribution of blood flow was measured both as percentage of total renal blood flow and as absolute flow to the inner and outer renal cortices (fig. 3). Analysis of the distribution of RBF demonstrated that the changes of the groups over time did not differ significantly from each other (the P value for the TG interaction did not reach statistical significance but ap-

proached it for blood flow to the outer cortex). Although total RBF did not change, there was an increase in absolute outer cortical flow for the mean value of all groups over the measurement periods.

### HEMODYNAMIC DATA

There were significant changes in cardiac index, mean arterial pressure, and systemic vascular resistance over the 46 h (fig. 4). CI increased for all groups, but the change was largest in the animals ventilated with PEEP.  $P_A$  decreased in all groups after Period 2. SVR decreased from Period 2 with all ventilatory modes, but the CMV with PEEP group, which had the highest SVR in Period 2, had the lowest values in Periods 3, 4, and 5. This decrease in SVR was associated with the increase in CI.

Transmural left atrial pressure ( $P_{TLA}$ ) and right atrial pressure ( $P_{TRA}$ ) did not change with time, but there was a large intragroup variability (table 2).

During all periods, the CMV with PEEP group had the greatest abdominal vena cava mean pressure, although the difference between groups was not statistically significant (table 2). There were no consistent changes in  $P_{IVC}$  with time for any group. With all ventilatory modes, RVR decreased after Period 2 (table 2).

### Discussion

While CMV with PEEP may be used for many days to treat patients with respiratory failure, previous studies have assessed the renal changes during this form of respiratory support for only brief periods. This study examined renal and cardiovascular changes during the three modes of ventilation for 46 h. The immediate responses to CMV with PEEP have been studied extensively<sup>1-4,6-9</sup> and reviewed recently,<sup>5</sup> and, therefore, they have not been repeated in our study. The usual clinical care for critically ill patients was applied to our animals in an attempt to simulate prolonged respiratory support. Mean systemic arterial pressure was higher than expected in all groups during the study periods. Although pentobarbital has only transient effects on cardiovascular dynamics,<sup>17</sup> stress or stimulation produces an elevation in  $P_A$  in pentobarbital-anesthetized dogs.<sup>18</sup> Since dogs of all three ventilatory modes received pentobarbital, any renal or hemodynamic effect from the sedation would be similar in all groups. The animals in our study were normal and did not have lungs with a low compliance or altered pulmonary vasculature, as is usually the case with acute respiratory failure. Animals with no pulmonary disease have been used routinely in

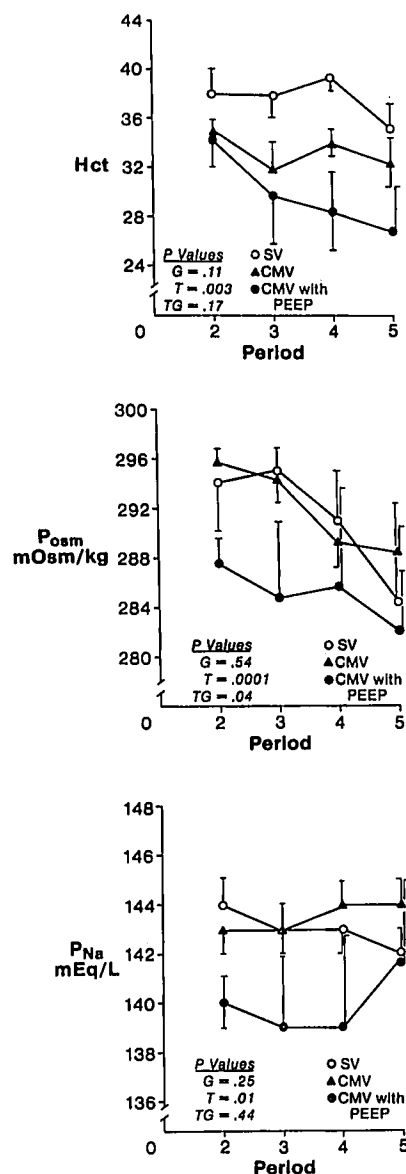


FIG. 2. The mean  $\pm$  SEM hematocrit (Hct), plasma osmolality ( $P_{osm}$ ), and plasma sodium concentration ( $P_{Na}$ ) for the three groups of dogs during each measurement period.  $P$  values for analysis of variance for repeated measurements are given.

the study of PEEP, and it is understood that this may differ from the usual clinical situation.

Although all groups had significant fluid retention manifested by weight gain over the study, the change in dogs ventilated with PEEP was twice that of the other two groups. The positive fluid balance in the PEEP group resulted from both a negative  $C_{H_2O}$  and sodium retained with water. Numerous investigators have demonstrated that addition of PEEP to CMV reduced urinary flow rate,<sup>1-4,8</sup> but with continued ventilation, urinary

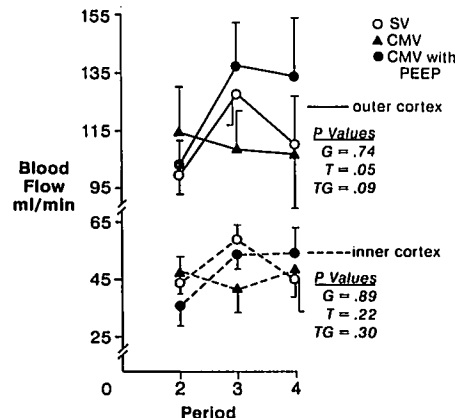
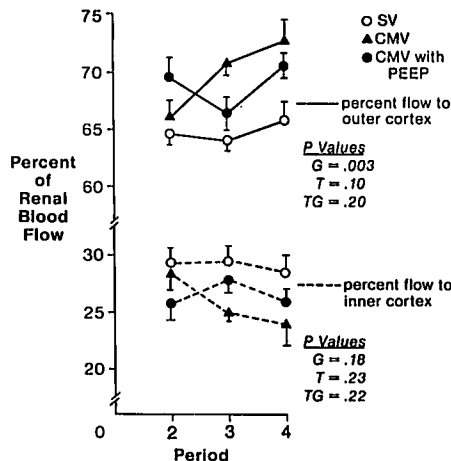
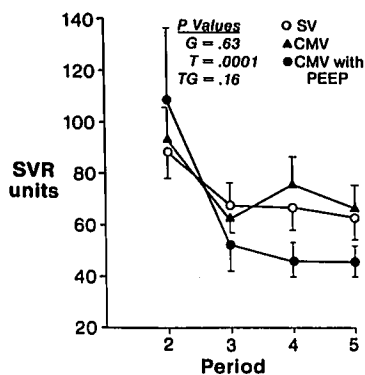
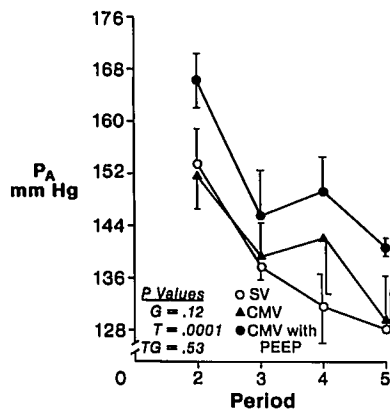
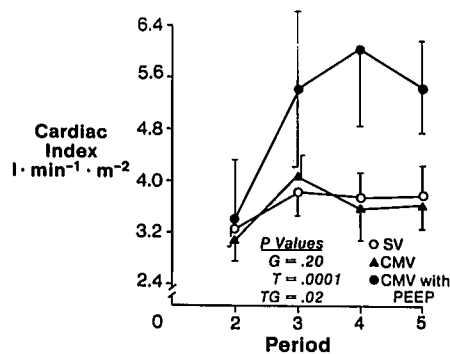


FIG. 3. The mean  $\pm$  SEM blood flow and per cent of renal blood flow to the outer cortical and inner cortical nephrons as measured with radioactive microspheres during Periods 2, 3, and 5 in the three groups of dogs. *P* values for analysis of variance for repeated measurements are given.



flow increased in our study. Animals that were ventilated mechanically without PEEP excreted fluid at a rate equal to that of the intravenous infusion at a time later than those breathing spontaneously.  $C_{H_2O}$  was positive for the SV and CMV groups during all measurement periods and became positive with PEEP only during Period 5. The positive water balance in the latter group produced decreases in hematocrit, plasma osmolality, and plasma sodium concentration. These changes are similar to those noted by Sladen *et al.* in patients ventilated for respiratory failure.<sup>19</sup> Short-term studies have demonstrated no change in the negative  $C_{H_2O}$  when PEEP was added to CMV.<sup>4,20</sup> By the end of 46 h, the CMV with PEEP group was able to excrete free water, and this resulted in an increase in  $P_{Na}$  from Periods 4 to 5. Other studies consistently have found a decrease in  $U_{Na}V$  after initiating PEEP.<sup>1-3</sup> In our PEEP group,  $U_{Na}V$  was lower than that of the other groups in Period 3. By Period 5,  $U_{Na}V$  had increased in dogs ventilated with PEEP but had not reached the rate of sodium infusion as occurred in the other groups. Similarly,  $F_{ENa}$  was lower in the PEEP group than the others during Period 5, although it had increased from Period 2. Therefore,  $C_{H_2O}$  was altered more rapidly than  $U_{Na}V$  and  $F_{ENa}$ , and at the termination of the study, the dogs whose lungs were ventilated with PEEP still were retaining sodium and water, although at a rate less than initially.

In the present study, RBF and RPF were derived from PAH clearances. Calculation of PAH clearance requires the determination of renal fractional extraction,

FIG. 4. The mean  $\pm$  SEM cardiac index, mean systemic arterial pressure ( $P_A$ ), and systemic vascular resistance (SVR) for the three groups of dogs during each measurement period. *P* values for analysis of variance for repeated measurements are given.

TABLE 2. Hemodynamic Data (Mean  $\pm$  SEM)

Group	Period				P Value
	2	3	4	5	
$P_{TLA}$ (mmHg)					
SV	13.5 $\pm$ 1.7	10.6 $\pm$ 1.6	11.4 $\pm$ 1.9	12.7 $\pm$ 1.4	G = 0.83
CMV	10.7 $\pm$ 0.7	9.6 $\pm$ 1.8	9.4 $\pm$ 0.9	9.7 $\pm$ 1.6	T = 0.42
CMV with PEEP	11.7 $\pm$ 2.5	11.8 $\pm$ 2.1	8.9 $\pm$ 1.4	10.2 $\pm$ 1.6	TG = 0.07
$P_{TRA}$ (mmHg)					
SV	5.6 $\pm$ 0.6	5.7 $\pm$ 1.1	5.0 $\pm$ 1.1	7.3 $\pm$ 0.9	G = 0.46
CMV	4.8 $\pm$ 1.4	4.4 $\pm$ 1.3	5.2 $\pm$ 1.3	5.7 $\pm$ 1.1	T = 0.72
CMV with PEEP	5.0 $\pm$ 1.0	5.6 $\pm$ 0.7	5.0 $\pm$ 0.5	5.1 $\pm$ 0.3	TG = 0.003
$P_{IVC}$ (mmHg)					
SV	5.0 $\pm$ 1.0	6.3 $\pm$ 0.3	7.7 $\pm$ 1.1	8.4 $\pm$ 1.3	G = 0.30
CMV	7.0 $\pm$ 2.8	7.2 $\pm$ 1.1	6.4 $\pm$ 1.3	6.4 $\pm$ 1.0	T = 0.53
CMV with PEEP	8.1 $\pm$ 0.9	9.5 $\pm$ 0.9	8.2 $\pm$ 0.5	9.7 $\pm$ 0.4	TG = 0.27
RVR (units)					
SV	434 $\pm$ 84	414 $\pm$ 75	369 $\pm$ 59	382 $\pm$ 99	G = 0.74
CMV	529 $\pm$ 77	406 $\pm$ 70	428 $\pm$ 46	422 $\pm$ 79	T = 0.05
CMV with PEEP	480 $\pm$ 73	282 $\pm$ 32	442 $\pm$ 138	368 $\pm$ 53	TG = 0.61

SV (n = 4): spontaneous ventilation; CMV (n = 5): controlled mechanical ventilation; CMV with PEEP (n = 4): controlled mechanical ventilation with positive end-expiratory pressure;  $P_{TLA}$ : transmural left atrial pressure;  $P_{TRA}$ : transmural right atrial pressure;  $P_{IVC}$ : mean

inferior vena cava pressure; RVR: renal vascular resistance.

P value is for analysis of variance for repeated measurements. P values are reported for group differences (G), differences with time (T), and group and time interactions (TG).

which was measured at the conclusion of Period 5 when renal venous blood was sampled. Since the value determined for each animal was used for all calculations of PAH clearance in that animal, some inaccuracies may have been introduced if extraction changed throughout the study. There were no significant differences in GFR, RBF, RPF, or FF between groups and no changes within groups over the four measurement periods. Other investigators have reported varied effects of PEEP on GFR and RBF.<sup>1-4,21</sup> Nonuniformity of the intravascular volume of animals used in these studies may account for these differences. In our study, the initial measurements of GFR and RBF during PEEP were made after significant fluid retention had occurred, and hence, changes in GFR and RBF already may have abated. Any acute changes in RBF during CMV with PEEP appear to be quickly reversed, while changes in sodium and water retention persist. Thus, it is likely that the decreased sodium excretion seen with PEEP is not entirely due to a decrease in RBF. Redistribution of renal blood flow is one suggested cause of decreased sodium excretion.<sup>22,23</sup> Using the <sup>85</sup>Kr washout technique, Hall *et al.* observed a redistribution in RBF from outer to inner cortex when PEEP was used.<sup>1</sup> Microsphere studies have failed to duplicate these results.<sup>2</sup> Differences in technique that are summarized elsewhere<sup>24-26</sup> may account for the apparent inconsistency. In our study, the percentage of RBF to the inner and outer cortex in dogs ventilated with PEEP was the same in Periods 2 and 5, while  $C_{H_2O}$  became positive and V and  $U_{Na}V$  increased. While these changed with time for all ventilatory modes,

intrarenal blood flow distribution did not change significantly. Thus, our data are consistent with other studies of RBF distribution with PEEP where microsphere techniques were used.<sup>2</sup> This suggests that mechanisms other than changes in RBF or its distribution must be responsible for the sodium retention observed when PEEP is applied.

Schrier and Early, using volume expanded dogs, have demonstrated that a reduction in hematocrit produced an increase in renal sodium excretion, free water reabsorption, RBF, and RPF and a decrease in RVR.<sup>27</sup> They suggested that the change in Hct altered sodium reabsorption through an effect on hydrostatic and oncotic pressures in the peritubular capillaries. In contrast to the above findings, as Hct decreased there were no changes in RBF or RPF, while free water clearance increased in our study. It therefore is unlikely that the decline in Hct was the cause of the renal changes that we observed.

Acute cardiovascular changes occurring after institution of PEEP include a decrease in venous return and left ventricular end-diastolic volume,<sup>6,7,10</sup> which lead to a decrease in cardiac output in some experimental settings.<sup>7</sup> Transmural atrial and ventricular pressures are not adequate measures of left ventricular end-diastolic volume during CMV with PEEP.<sup>10</sup> This may be due to difficulties associated with measurement of intrapleural pressure in the area of the heart, differences in intrapleural and intrapericardial pressure, or changes in ventricular compliance with PEEP. In our study, CI increased in the CMV with PEEP group after Period 2



without significant changes in  $P_{TLA}$  or  $P_{TRA}$ . Detailed analyses by Prewitt *et al.* indicate that when intrathoracic pressure is increased by CMV with PEEP, left ventricular function is improved.<sup>6</sup> The 64% increase in CI that we observed from Periods 2 to 5 in the CMV with PEEP group was likely the result of improved ventricular performance combined with a greater preload as intravascular volume increased with fluid retention. The CMV with PEEP animals also experienced the greatest decrease in SVR ( $-57\%$ ). In dogs, Ziegler *et al.*<sup>28</sup> and in humans Annat *et al.*<sup>8</sup> have measured an increase in peripheral renin concentration during ventilation with PEEP. In addition to the direct effect of PEEP on augmenting left ventricular function, it appears that with chronic CMV with PEEP there also is a reduction in SVR. Hormone-mediated vasoconstriction, which may have been necessary initially to maintain systemic arterial pressure, was reduced as intravascular filling occurred.

During prolonged CMV with PEEP, the increase in urine flow rate and  $U_{Na}V$  took place after the improvement in CI. In contrast, Priebe *et al.* demonstrated that renal function during CMV with PEEP could be restored by transfusion, even though cardiac output was not increased significantly.<sup>2</sup> They suggested that a decrease in intravascular volume initiated neural and hormonal changes, which affected renal function. Transfusion, by increasing intravascular volume, improved the renal, but not hemodynamic, function in their experimental preparation. Cardiovascular and fluid homeostasis is maintained through several integrated neural and hormonal systems. These effectors also act directly on the kidney. Fewell and Bond have shown that in dogs, aortic arch and carotid sinus baroreceptors<sup>12</sup> and renal innervation<sup>4</sup> are necessary for antidiuresis and antinatriuresis during ventilation with PEEP. Both high- and low-pressure stretch receptors have been shown to affect vasopressin<sup>29,30</sup> and renin<sup>31-33</sup> secretion. In patients whose lungs were ventilated mechanically, addition of 10 cmH<sub>2</sub>O PEEP produced an increase in plasma renin activity and urinary antidiuretic hormone.<sup>8</sup> Our data suggest that after initiation of PEEP, hemodynamic stability is maintained by mechanisms that simultaneously affect renal function.

The present study demonstrates that sedated dogs breathing spontaneously or whose lungs are ventilated mechanically are quickly able to adjust urinary sodium and water excretion to match the rate of input. During CMV with PEEP, hemodynamic changes activated compensatory neural and hormonal responses, which both preserved perfusion pressure and produced an increase in extracellular volume by urinary sodium and water retention. The expansion of extracellular fluid volume provided a stimulus whereby the more rapidly acting

effectors were no longer necessary for maintaining circulatory homeostasis. It would be expected that when intravascular volume had increased sufficiently in the CMV with PEEP group, urinary sodium excretion then would equal intake, although the duration of our study was not sufficient to assess this.

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