

# The Effect of Positive End-Expiratory Pressure Ventilation (PEEP) on Cerebral Blood Flow and Cerebrospinal Fluid Pressure in Goats

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The effect on cerebral blood flow (CBF) and cerebrospinal fluid pressure (CSFP) of mechanical ventilation with positive end-expiratory pressure (PEEP) at 5, 10, and 15 cm H<sub>2</sub>O was studied in 23 paralyzed, ventilated goats which were divided into three treatment groups. Group I received no volume expansion agent to counteract the hemodynamic effects of PEEP. Group II received normal saline to maintain a constant arterial blood pressure (BP), and Group III received a mannitol solution for BP maintenance. In all three groups there were similar increases in central venous pressure (CVP) of approximately 2.5 times the zero PEEP level at 15 cm H<sub>2</sub>O PEEP ( $P < 0.001$ ). In Group I, BP fell an average of 32 per cent, cardiac output fell 47 per cent and cisternal CSFP increased 40 per cent above zero PEEP levels at 15 cm H<sub>2</sub>O PEEP ( $P < 0.01$ ). CBF in this group was decreased 18 per cent when compared with the zero PEEP baseline at 15 cm H<sub>2</sub>O PEEP ( $P < 0.008$ ). In Group II animals there were no significant changes in BP or cardiac output (CO) at any of the PEEP levels. CSFP in this group, at 15 cm H<sub>2</sub>O PEEP, increased 84 per cent above the baseline zero level and CBF decreased 32 per cent at 15 cm H<sub>2</sub>O PEEP when compared to the zero PEEP level ( $P < 0.008$ ). In Group III there were no significant reductions in BP or CO. Unlike Groups I and II, no significant changes in CSFP were observed at any level of PEEP. In addition, CBF in this group did not change significantly from the zero-PEEP baseline level any level of PEEP. Thus, when PEEP therapy is associated with substantial decreases in BP and CO, CBF may decrease as well. Maintenance of BP and CO by volume expansion with a crystalloid solution resulted in a greater reduction in CBF than in the untreated group but maintenance of BP and CO by mannitol infusion resulted in maintenance of CBF at the baseline, pre-PEEP level. The authors conclude that brain interstitial fluid pressure is an important variable in the determination of cerebral blood flow during ventilation with PEEP. (Key words: Blood: volume. Brain: blood flow; intracranial pressure. Cerebrospinal

fluid: pressure. Fluid balance: mannitol. Ventilation: positive end-expiratory pressure.)

MECHANICAL VENTILATION with positive end-expiratory pressure (PEEP) is an effective means of increasing arterial oxygen tension in lung disorders associated with a decrease in functional residual capacity secondary to interstitial edema and alveolar collapse.<sup>1,2</sup> However, the efficacy of PEEP in improving oxygenation of tissues is frequently offset by a concomitant reduction in cardiac output and mean arterial blood pressure. This is generally thought to be, in part, a result of the sustained increase in intrathoracic pressure causing impairment of venous return, 3-6 especially in the hypovolemic state.

The effect of PEEP on the blood flow and oxygen delivery to a given organ may be difficult to predict. Despite the maintenance of cardiac output by blood volume expansion,<sup>4,6</sup> several factors modulating the effect of PEEP may come into play. These include the response of the vascular bed to an increased venous pressure, local effects of relief of hypoxia, and the effects of fluid infusion on interstitial fluid pressures within the organ. Since cerebral blood flow (CBF) manifests substantial autoregulation<sup>7</sup> it might be reasonable to assume that CBF would also be relatively preserved during PEEP. However, because of the unique location of the brain in a compartment of essentially fixed volume, other factors such as cerebrospinal fluid pressure (CSFP) and central venous pressure (CVP) may be of special significance in the regulation of its blood flow. In the present study we have determined the effects of PEEP on CBF and attempted to define the relative roles played by changes in CSFP, CVP, and systemic arterial blood pressure (BP) in the observed changes.

## Methods

### MEASUREMENT OF CEREBRAL BLOOD FLOW

The experiments were performed on 23 goats ranging in weight from 30-35 kg following a protocol which was approved by the Laboratory Animal Studies

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Committee. Three days before the study, under general anesthesia with pentobarbital, a previously calibrated electromagnetic flow probe (Statham SP 7516) was placed around an internal maxillary artery as described in detail elsewhere.<sup>8</sup> This method for measuring CBF takes advantage of the unique cerebrovascular anatomy of the goat. In this animal the internal maxillary artery (a branch of the external carotid artery) provides virtually all of the blood flow to each half of the brain via the rete mirabile because of a vestigial vertebrobasilar system. The total blood flow to one side of the brain was therefore isolated by surgical ligation of accessible branches of the internal maxillary artery that supply extracerebral structures (inferior dental, temporal, and internal maxillary beyond the ramus anastomoticum). The extracerebral branches that are surgically inaccessible (external ophthalmic, ethmoidal, buccinator) were thrombosed by the injection of 1000–2000 NIH units of thrombin in 0.5 ml saline. The technique of electromagnetic flowmeter monitoring of CBF was utilized because the necessity for larger numbers of measurements precluded the use of radiolabeled microspheres and would have made the use of inert gas washout quite inconvenient. The technique used has been evaluated and used by other investigators<sup>9,10</sup> and has been found to measure only about 5 per cent extracerebral flow with a stable repeatable baseline. Flow probes were calibrated *in vitro* with blood at several hemoglobin concentrations so that corrections could be made for hemodilution.

#### MEASUREMENT OF VASCULAR AND CEREBROSPINAL FLUID PRESSURES

Simultaneous with the surgery for the flow probe, an indwelling arterial catheter was inserted into a branch of the femoral artery. Three days later, on the day of the study, catheters were also placed percutaneously into the superior vena cava via an internal jugular vein, and into the pulmonary artery via a femoral vein (flow directed balloon tipped catheter, Swan Ganz) under local anesthesia with Xylocaine<sup>®</sup>. During the study, the systemic arterial and pulmonary arterial catheters were connected via three-way stopcocks to blood pressure transducers (Statham P23 Db) and the superior vena cava catheter was attached to a water manometer filled with heparinized saline. This system allowed continuous monitoring of systemic arterial blood pressure (BP), pulmonary arterial blood pressure (PAP), and central venous (superior vena cava) pressures (CVP) and intermittent sampling of arterial and mixed venous blood. All pressure measurements were referred to the mid-thoracic level in

the sagittal plane and all transducers were calibrated with mercury manometers.

CSFP was measured with a Cournand needle (BD-18T) inserted percutaneously under local anesthesia with xylocaine<sup>®</sup> into the cisterna magna. During the study, this needle was connected to a water manometer filled with saline. The manometer zero level was adjusted to the estimated tip of the needle and the head was positioned at the level of the heart. With this system, cisternal CSFP was continuously measured and was manually recorded.

#### APPLICATION OF PEEP AND MEASUREMENTS

The goats were paralyzed and ventilated during the study in order to facilitate maintenance of constant  $P_{aCO_2}$  during the application of various PEEP levels. Pancuronium bromide was selected for this purpose because it has been reported to induce minimal changes in arterial blood pressure and does not release histamine.<sup>11</sup> The animals were then intubated with a cuffed endotracheal tube and ventilated with room air using a constant volume respirator with a tidal volume of 15 ml/kg. Since  $P_{aCO_2}$  is known to rise slightly during PEEP due to changes in physiologic dead space,  $P_{aCO_2}$  was rechecked at each PEEP level and the frequency of ventilation was altered by 2–3 breaths/min to ensure the constancy of this variable.

PEEP was applied by placing the expiratory tube at varying levels under water. The order of PEEP application was 0, 5, 10, and 15 cm H<sub>2</sub>O allowing adequate time for equilibration and data collection at each PEEP level. A system was designed so that 2-min collections of expired gas could be made at the end of each steady state using a 30 l Douglas Bag. The gas was sampled for determination of  $P_{CO_2}$  and  $P_{O_2}$  (Radiometer, Copenhagen) and the volume was determined by passing the gas through a calibrated dry gas meter (American Meter Co.). All of the values were expressed under BTPS conditions.

Simultaneous with the expired gas collection, systemic arterial and pulmonary arterial blood samples were collected anaerobically at appropriate intervals (see below), iced, and analyzed within 10 min using electrodes (Radiometer, Copenhagen) at 37°C for  $P_{O_2}$ ,  $P_{CO_2}$ , and pH. Oxygen saturation and hemoglobin content were determined spectrophotometrically (CO-Oximeter calibrated for goat blood, Instrumentation Laboratory). From these data, oxygen consumption, carbon dioxide production and respiratory quotient were calculated. Cardiac output was calculated using the Fick principle assuming an  $O_2$  capacity of 1.34 ml  $O_2$  for each gram of hemoglobin.

In order to minimize the effects of relief of hypoxia

TABLE 1. Effects of PEEP on Cardiac Output, Pulmonary Artery Pressure, Arterial P<sub>O<sub>2</sub></sub>, Arterial P<sub>CO<sub>2</sub></sub>, pH, and Hemoglobin (Mean ± SEM)

	PEEP (cm H <sub>2</sub> O)			
	0	5	10	15
Group I (Control) (n = 7)				
CO (l/min)	3.80 ± 0.25	3.35 ± 0.30	2.74 ± 0.33*	2.00 ± 0.29*
PAP (torr)	11.5 ± 0.8	17.4 ± 0.8*	21.7 ± 0.8*	23.4 ± 1.0*
Pa <sub>O<sub>2</sub></sub> (torr)	65 ± 2	70 ± 2	77 ± 3*	85 ± 1*
Pa <sub>CO<sub>2</sub></sub> (torr)	29 ± 5	30 ± 1	31 ± 1	30 ± 1
pH	7.43 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.42 ± 0.01
Hb (g/dl)	10.8 ± 1.1	10.7 ± 1.3	10.5 ± 1.3	10.7 ± 1.2
Group II (Saline) (n = 8)				
CO (l/min)	3.92 ± 0.35	3.93 ± 0.24	4.11 ± 0.26	4.07 ± 0.29
PAP (torr)	12.2 ± 1.1	15.8 ± 1.3*	19.0 ± 1.7*	22.4 ± 1.6*
Pa <sub>O<sub>2</sub></sub> (torr)	68 ± 3	74 ± 4	83 ± 4*	90 ± 5*
Pa <sub>CO<sub>2</sub></sub> (torr)	30 ± 1	30 ± 2	29 ± 1	30 ± 2
pH	7.46 ± 0.01	7.46 ± 0.02	7.46 ± 0.2	7.44 ± 0.03
Hb (g/dl)	10.3 ± 0.9	9.9 ± 0.7	9.7 ± 0.8	9.4 ± 0.8*
Group III (Mannitol) (n = 8)				
CO (l/min)	3.53 ± 0.25	3.86 ± 0.24	3.68 ± 0.33	3.90 ± 0.56
PAP (torr)	14.7 ± 1.3	17.0 ± 1.2*	18.9 ± 1.0*	20.7 ± 1.0*
Pa <sub>O<sub>2</sub></sub> (torr)	65 ± 2	76 ± 3*	83 ± 3*	87 ± 4*
Pa <sub>CO<sub>2</sub></sub> (torr)	30 ± 1	29 ± 1	31 ± 1	31 ± 1
pH	7.43 ± 0.01	7.44 ± 0.02	7.42 ± 0.02	7.42 ± 0.02
Hb (g/dl)	10.5 ± 0.9	9.9 ± 0.7	9.6 ± 0.9	9.1 ± 0.6*

\*  $P < 0.01$ , significantly different from zero PEEP.

on CBF, only goats that had a baseline Pa<sub>O<sub>2</sub></sub> of at least 60 torr were included in the study. Seven animals (Group I) were studied at 0, 5, 10, and 15 cm H<sub>2</sub>O PEEP without volume expansion for blood pressure control. At least 30 min elapsed at each PEEP level before any measurements were taken. This time interval was selected because preliminary observations indicated that the steady state for the variables measured was reached within this time period. Eight animals (Group II) were given intravenous normal saline at each PEEP level for the maintenance of BP at baseline levels. Eight animals (Group III) were given mannitol 12.5 per cent at each PEEP level to maintain BP in order to examine the action of an hyperosmotic agent on CSFP and its effect on the CBF response to PEEP.

Hypotension induced by PEEP generally occurred soon after its application (less than one minute). In Groups II and III, if blood pressure remained low after 2 min, fluid was infused until baseline blood pressure was restored. Our experience with these animals indicated that arterial blood pressure was a good index of cardiac output if extensive peripheral vasoconstriction was avoided by volume expansion soon after the application of PEEP. Therefore, fluid infusion was always begun within 2 min of the onset of hypotension. All data are reported as means ± SE, and  $P$  values were determined by analysis of covariance or Student's  $t$  test.  $P$  values less than 0.01 were considered significant.

## Results

The effects of 0, 5, 10, and 15 cm H<sub>2</sub>O PEEP and volume expansion on cardiac output, pulmonary artery pressure, arterial blood gas tensions, arterial pH and Hb in the three groups of animals studied are summarized in table 1. In Group I, CO fell progressively from 3.80 ± 0.25 l/min at zero PEEP to 2.00 ± 0.29 l/min at 15 cm H<sub>2</sub>O PEEP. In Groups II and III CO did not change significantly from control levels. PAP increased from 11.5 ± 0.8 to 23.4 ± 1.0 torr at 15 cm H<sub>2</sub>O PEEP in Group I animals, an increase of 103 per cent above baseline. In Group II the PAP increase was 83 per cent above baseline and in Group III the increase was 40 per cent above baseline. All changes were significant when compared to baseline values. Pa<sub>CO<sub>2</sub></sub> was deliberately held close to 30 torr corresponding to an arterial pH value of 7.40 to 7.45 in the goat. Pa<sub>O<sub>2</sub></sub>, as expected, rose progressively and to a comparable magnitude with PEEP in all groups. Although not summarized in the table, oxygen consumption and CO<sub>2</sub> production did not change significantly with PEEP in Groups I or III. Oxygen consumption and CO<sub>2</sub> production decreased 10 per cent and 15 per cent from zero PEEP values only in Group II animals at 10 and 15 cm H<sub>2</sub>O PEEP, respectively ( $P < 0.01$ ).

The effects of PEEP on mean arterial blood pressure (BP), CVP, CSFP, and CBF are summarized in table 2. BP decreased significantly in Group I animals

at 5, 10, and 15 cm H<sub>2</sub>O PEEP when compared to the zero-PEEP baseline of 103 ± 3 torr. In Groups II and III, BP was maintained as close to baseline values as possible and no values were significantly different from the baseline in either group. The increases in CVP at each PEEP level in each group were statistically significant when compared to the respective controls for all three groups (*P* < 0.001).

The changes in BP and CO observed in Group I were prevented by the infusion of saline in Group II, requiring 272 ± 80 ml, 354 ± 76 ml, and 273 ± 72 ml at 5, 10, and 15 cm H<sub>2</sub>O PEEP, respectively. Similarly, BP and CO changes in Group III were prevented by the infusion of mannitol requiring 107 ± 29 ml, 93 ± 23 ml, 168 ± 48 ml at 5, 10, and 15 cm H<sub>2</sub>O PEEP, respectively.

In Group I, control CSFP averaged 9.5 ± 0.5 cm H<sub>2</sub>O and increased significantly at 10 and 15 cm H<sub>2</sub>O PEEP progressing to 13.3 ± 0.6 cm H<sub>2</sub>O at 15 cm H<sub>2</sub>O of PEEP (*P* < 0.001). In Group II animals, an even greater rise in cisternal CSFP occurred, increasing significantly at 10 and 15 cm H<sub>2</sub>O PEEP from 10.0 ± 0.6 cm H<sub>2</sub>O to 18.4 ± 1.5 cm H<sub>2</sub>O at 15 cm H<sub>2</sub>O (*P* < 0.001). Group III animals demonstrated no significant increase in cisternal CSFP at any PEEP level in contrast to Groups I and II. The per cent changes from zero PEEP level in CSFP are shown graphically in figure 1.

Cerebral blood flow changes with PEEP are illustrated in figure 2 and are summarized in table 2. In the control state in Group I, CBF averaged 73 ± 3 ml/min. CBF fell progressively with increasing PEEP to 57 ± 4 ml/min at 15 cm H<sub>2</sub>O PEEP (*P* < 0.008).

This represented a 23 per cent decrease in CBF at a PEEP value of 15 cm H<sub>2</sub>O when compared with control. In Group II, the saline-infused group, baseline CBF averaged 71 ± 3 ml/min and showed a steady decrease with increasing PEEP levels. CBF was 48 ± 4 ml/min at a PEEP level 15 cm H<sub>2</sub>O corresponding to a 33 per cent reduction (*P* < 0.008). Group III animals (mannitol infusion) demonstrated an average baseline CBF of 69 ± 6 ml/min. This was not statistically different from the averages of Groups I and II in the control state. With increasing PEEP, CBF in Group III averaged 73 ± 5, 69 ± 6, and 66 ± 5 ml/min at 5, 10, and 15 cm H<sub>2</sub>O PEEP, respectively. Thus, there was no significant change in Group III at any level of PEEP when compared to baseline (zero PEEP) values.

### Discussion

This study confirms previous findings concerning the general hemodynamic consequences of PEEP<sup>3-6</sup> in animals with normal lung compliance. In the absence of volume expansion, cardiac output and systemic arterial blood pressure decreased in inverse proportion to the level of PEEP applied. There were significant reductions in BP at all PEEP levels in Group I animals and parallel decreases in CO. In Groups II and III maintenance of BP with volume expansion resulted in preservation of cardiac output at all PEEP levels. However, in all three groups central venous and pulmonary artery pressures increased progressively with increased PEEP.

In addition to these generally accepted phenomena,

TABLE 2. Effect of PEEP on Mean Arterial Pressure, Central Venous Pressure, Cisternal Cerebrospinal Fluid Pressure, and Cerebral Blood Flow (Mean ± SEM)

	PEEP (cm H <sub>2</sub> O)			
	0	5	10	15
Group I (Control) (n = 7)				
BP (torr)	103 ± 3	95 ± 3 <sup>‡</sup>	78 ± 1 <sup>‡</sup>	70 ± 1 <sup>‡</sup>
CVP (cm H <sub>2</sub> O)	5.4 ± 0.4	8.5 ± 0.7*	10.7 ± 0.5*	13.3 ± 0.5*
CSFP (cm H <sub>2</sub> O)	9.5 ± 0.5	10.9 ± 1.1	11.8 ± 0.8*	13.3 ± 0.6*
CBF (ml/min)	73 ± 3	67 ± 4 <sup>‡</sup>	60 ± 5 <sup>‡</sup>	57 ± 4 <sup>‡</sup>
Group II (Saline) (n = 8)				
BP (torr)	112 ± 4	112 ± 5	115 ± 6	115 ± 6
CVP (cm H <sub>2</sub> O)	5.1 ± 0.5	7.2 ± 0.4*	10.1 ± 0.5*	13.2 ± 0.9*
CSFP (cm H <sub>2</sub> O)	10.0 ± 0.6	12.2 ± 0.8	15.5 ± 1.7*	18.4 ± 1.5*
CBF (ml/min)	71 ± 3	61 ± 4 <sup>‡</sup>	54 ± 4 <sup>‡</sup>	48 ± 4 <sup>‡</sup>
Group III (Mannitol) (n = 8)				
BP (torr)	102 ± 7	104 ± 7	105 ± 6	110 ± 7
CVP (cm H <sub>2</sub> O)	5.4 ± 0.5	8.9 ± 0.6*	11.1 ± 0.5*	12.8 ± 0.7*
CSFP (cm H <sub>2</sub> O)	11.0 ± 1.2	12.2 ± 1.4	12.5 ± 1.4	12.5 ± 1.3
CBF (ml/min)	69 ± 6	73 ± 5	69 ± 6	66 ± 5

\* *P* < 0.001 significantly different from zero PEEP.  
† *P* < 0.008 significantly different from zero PEEP.

‡ *P* < 0.01 significantly different from zero PEEP.

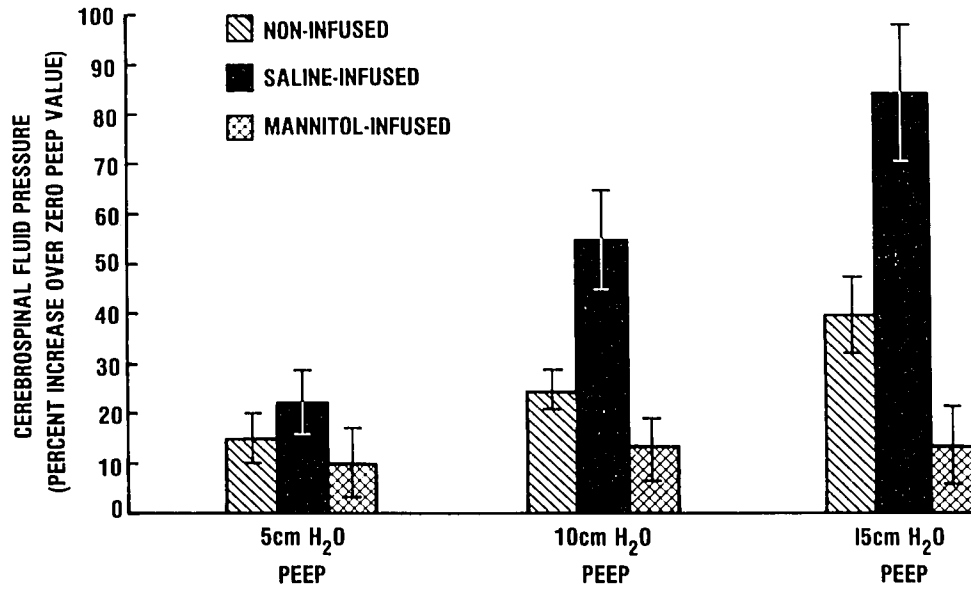


FIG. 1. Cisternal (CSFP) averaged for each group of animals expressed as the per cent increase over the zero PEEP value for each level of PEEP. Bars represent one SEM. CSFP at 10 and 15 cm H<sub>2</sub>O PEEP was different from zero PEEP levels of CSFP in Group I and Group II animals ( $P < 0.001$ ).

two further observations resulted from our study. First, the application of PEEP increased directly measured cisternal CSFP. This increase was intensified when volume expansion was achieved by saline infusion but obviated when volume expansion was achieved by infusion of an osmotically active agent, mannitol. Second, significant reductions in CBF occurred with progressive increases in PEEP in the non-infused animals. These changes were intensified during saline infusion but were eliminated when mannitol was used for volume expansion.

The differences between the non-infused and the saline-infused groups may have been the result of increased brain interstitial fluid pressure resulting from the extravasation of a fraction of the fluid given for volume expansion<sup>12</sup> acting in concert with other pulmonary and hemodynamic changes known to result from PEEP therapy. This hypothesis is supported by the data from the mannitol-infused group where no change in CSFP was observed, suggesting a critical role for CSFP in the reductions in CBF seen with PEEP in the non-infused and saline-infused groups.

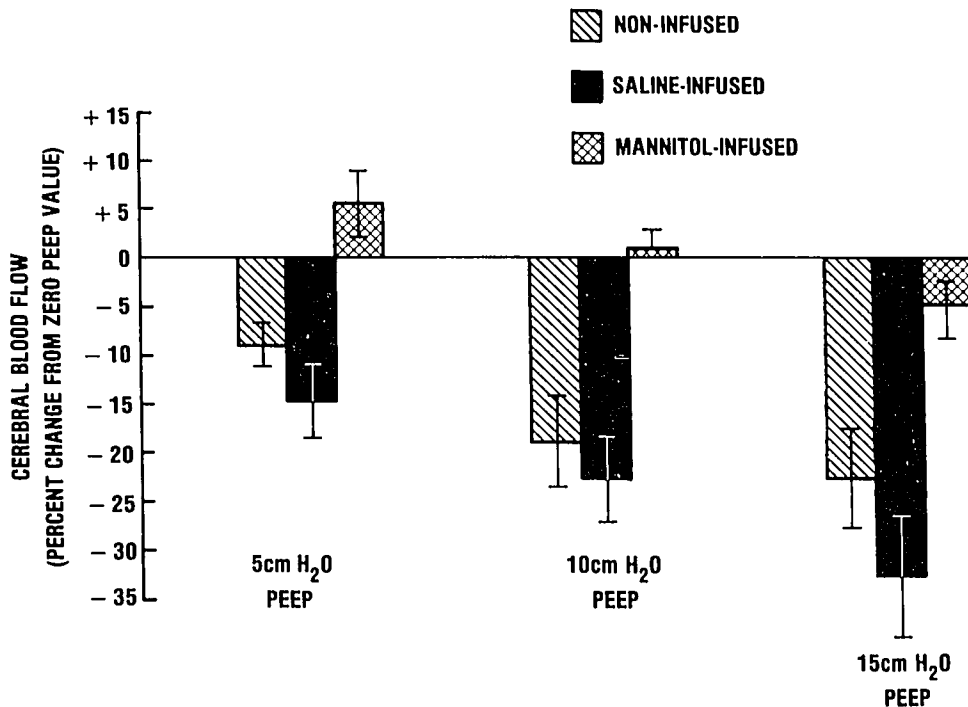


FIG. 2. Cerebral blood flow (CBF) averaged for each group of animals expressed as the per cent change from the zero PEEP value at each level of PEEP. Bars represent one SEM. CBF values at 5, 10, and 15 cm H<sub>2</sub>O PEEP were different from zero PEEP values in Group I and Group II animals ( $P < 0.008$ ).

Although previous investigators have induced CBF reductions by elevating CSFP alone, the CSFP levels at which CBF was reduced generally exceeded the highest CSFP levels obtained in our study.<sup>13-17</sup> Part of this discrepancy in the CSFP threshold for CBF reduction previously reported and that seen during PEEP in our animals may be reconciled if variations in brain interstitial fluid pressure induced by methodologic differences in raising CSFP, elevation of CVP, and brain shifts are accounted for in the analysis.

The effects of infusion of fluid into the subarachnoid space as well as both supratentorial and infratentorial space-occupying lesions on CBF have been examined by Johnston *et al.*<sup>18,19</sup> revealing a critical dependence of the changes in CBF on the method used for increasing CSFP. Elevations in CVP and in jugular venous pressure have been reported to cause either no change in CBF<sup>20,21</sup> or decreases in CBF.<sup>13</sup> Jugular venous compression alone would not be expected to alter CBF because cerebral venous drainage also occurs via the vertebral venous plexus.<sup>22</sup> During PEEP, however, the high level of sustained intrathoracic pressure induces elevations of pressure in all systemic veins including the vertebral venous plexus, thus diminishing the effectiveness of this network as a cerebral venous outflow tract. Finally, if shifts of brain tissue occur during PEEP, as proposed by two groups,<sup>23,24</sup> venous outflow channels may be compressed intracranially causing an increase in brain interstitial fluid pressure and a decrease in cerebral perfusion pressure which is not reflected in the CVP.

#### MANNITOL INFUSION

The use of mannitol to increase CBF in pathologic states with or without increased CSFP is well recognized.<sup>7,25,26</sup> It is possible that the mannitol-infused group exhibited no significant changes in CBF with PEEP because the tendency of PEEP to reduce CBF as seen in the non-infused and saline groups, was counterbalanced by the ability of mannitol to increase CBF. This would support the hypothesis that brain interstitial fluid pressure is a key parameter in the determination of CBF under these circumstances. Consistent with our data are the findings of Bruce *et al.*<sup>27</sup> where mannitol significantly increased CBF in patients with elevated CSFP and cerebral edema without an appreciable increase in CSFP. Their observation was best explained by the direct relief of cerebral edema and the reexpansion of the collapsed microcirculation consequent to a reduction in brain interstitial fluid pressure.

Our findings are of potential clinical significance

since they demonstrate that despite maintenance of BP and CO with saline, CBF may be compromised in the subject with normal lung compliance ventilated with PEEP. In the presence of normal lung compliance, our data represent the greatest theoretical detrimental effect on CBF since the transmission of airway pressure to the vascular compartment, and thus the influence on CBF, are maximized under these conditions. With decreases in lung compliance, the magnitude of the effect of PEEP on CBF would be expected to be diminished proportionately since the effect of PEEP on CSFP has been shown to be dependent on lung compliance.<sup>28</sup>

Failure to treat the hemodynamic consequences of PEEP (Group I) has also been shown to result in CBF reductions. Mannitol, but not saline, when given by slow infusion to maintain hemodynamics resulted in preservation of CSFP and CBF at pretreatment, zero PEEP levels.

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