

Hemodynamic Responses to Mechanical Ventilation with PEEP:

The Effect of Hypervolemia

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The hemodynamic effects of prolonged mechanical ventilation with positive end-expiratory pressure (PEEP), with and without blood volume augmentation, were studied in 18 beagles anesthetized with halothane (0.7 per cent end-tidal). Addition of 12 cm H₂O PEEP during mechanical ventilation in normovolemic dogs was associated with reductions of transmural cardiac filling pressures, cardiac index, and stroke index to 50 per cent of control values. Circulatory adaptation did not occur. Filling pressures and flow remained unchanged during the ensuing 8 hours when PEEP was maintained. They returned to control levels when PEEP was discontinued, except for the transmural right ventricular end-diastolic pressure, which remained elevated above control levels. Systemic vascular resistance was unchanged, but pulmonary vascular resistance doubled upon addition of PEEP.

Following autologous whole blood transfusion (25 ml/kg) during mechanical ventilation with PEEP, cardiac index returned to, and remained at, control levels. After PEEP was discontinued, cardiac index increased acutely and remained elevated for the remainder of the study period (as long

as 7 hours). Comparable transfusion during mechanical ventilation without PEEP elevated cardiac index only transiently. Right atrial, pulmonary capillary wedge, and right and left ventricular end-diastolic pressures showed marked increases relative to atmospheric with PEEP and after transfusion. Calculated transmural pressures demonstrated clear reductions with application of PEEP, followed by increases to control levels with transfusion and further increases to above control when PEEP was discontinued. Study of ventricular function curves revealed that changes in cardiac index were related solely to changes in filling pressures and not to changes in ventricular contractility. Transmural pulmonary arterial diastolic pressure rose throughout the 12 hours of study, despite return of pulmonary vascular resistance to control level with removal of PEEP.

Thus, acute decreases in cardiac filling pressure, cardiac index, and stroke index persist consequent to application of PEEP, and circulatory adaptation does not occur. The apparent hemodynamic deterioration may be reversed by blood volume augmentation, but when PEEP is discontinued, hypervolemia with consequent increases in filling pressures and a move along a ventricular function curve will occur. Changes in cardiac index will depend upon the overall state of right and left ventricular contractility. (Key words: Ventilation, mechanical; hemodynamic effects; Heart: function during mechanical ventilation; Blood: volume; mechanical ventilation.)

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ANIMAL AND HUMAN STUDIES have demonstrated that an increase of intrathoracic pressure causes an immediate diminution of central blood volume, lowering of right ventricular filling pressures, and a decrease in cardiac index (CI).^{1,2} The common therapeutic use of ventilation with positive end-expiratory pressure (PEEP) makes it important to understand the hemodynamic effects associated with its onset and discontinuation. The objectives of this study were: 1) to determine whether circulatory depression following

application of PEEP^{1,2} is sustained or whether persistent elevation of airway pressure induces compensatory mechanisms with return of hemodynamic function toward control levels; 2) to study the hemodynamic effects of blood volume augmentation during PEEP; 3) to analyze the hemodynamic response to discontinuation of PEEP once hypervolemia has been produced. Specifically, it was of interest to investigate whether transfusion during PEEP causes a sustained return of CI to control levels, or whether repeated blood volume expansion would be necessary.

Methods

The experiments were performed on 18 purebred male beagles, ranging in weight from 7.8 to 15.3 kg. Endotracheal anesthesia was induced with methohexital (15 mg/kg, iv) and maintained with halothane (end-tidal concentration 0.7 per cent) in oxygen. Muscle relaxation was produced with intermittent

intravenous injection of pancuronium (mean 0.67 mg/hr).[†] Ventilation was controlled using a Harvard animal respirator with a tidal volume (V_T) of 15 ml/kg and respiratory rate of 18 breaths/min. A pressurized Bennett valve attached to the exhalation port of the respirator produced 12 cm H₂O PEEP. End-tidal carbon dioxide and end-tidal halothane were measured by intermittently sampling from the endotracheal tube with a mass spectrometer (Medspect, Scientific Research Instruments, Inc.) and a column chromatograph (Mayo Vapor Analyzer, Ohio Medical Products, Inc.), respectively.

Catheters were placed in the right atrium via the jugular vein, right ventricle via the femoral vein, left ventricle via the carotid artery, pulmonary artery (Swan-Ganz) via the jugular vein, and aorta via the femoral artery. Pressures were measured with transducers (Hewlett Packard Series 267) and recorded on a multichannel recorder (Sanborn System 350). The bladder was catheterized with a #5 French feeding tube for half-hourly measurements of urine flow. A small right thoracotomy was done and a polyethylene catheter with a 10 × 1-cm soft latex balloon was placed in the pleural space to measure pleural pressure. The incision was closed to achieve an airtight seal following re-expansion of the lung with positive pressure. Body temperature was measured with an esophageal thermistor and maintained at a constant level by a heat lamp.

Cardiac output (CO) was measured in duplicate with indocyanine green dye dilution technique and densitometer (Gilford Model 103-IR). All dye curve areas were measured with a planimeter after semilog extrapolation to correct for recirculation. Arterial blood and mixed venous blood were drawn after each CO determination and analyzed immediately for P_{O_2} , P_{CO_2} , and pH using standard electrodes, for oxygen content by the manometric method, and for hematocrit. Blood withdrawn for sampling was replaced with previously drawn autologous blood which had been stored in ACD solution.

The following data were derived:

[†] Pancuronium was kindly donated by Organon, Inc.

ABBREVIATIONS

\overline{BP}	= mean femoral arterial pressure
BSA	= body surface area
Ca_{O_2}	= arterial oxygen content
CI	= cardiac index
CO	= cardiac output
$C\bar{v}_{O_2}$	= mixed venous oxygen content
LVEDP	= left ventricular end-diastolic pressure
LVSWI	= left ventricular stroke work index
PADP	= pulmonary arterial diastolic pressure
PAP	= mean pulmonary arterial pressure
PCWP	= pulmonary capillary wedge pressure
PCWP	= mean pulmonary capillary wedge pressure
PEEP	= positive end-expiratory pressure
PVR	= pulmonary vascular resistance
RAP	= right atrial pressure
\overline{RAP}	= mean right atrial pressure
RVEDP	= right ventricular end-diastolic pressure
RVSWI	= right ventricular stroke work index
SI	= stroke index
SVR	= systemic vascular resistance
SWI	= stroke work index
T_{PADP}	= transmural pulmonary arterial diastolic pressure
V_T	= tidal volume

TABLE 1. Consistency of Temperature, pH, and Carbon Dioxide Tension during 11 Hours of Study

	Pattern of Ventilation			
	Mechanical Ventilation Alone (Control) 1½ Hours	Mechanical Ventilation + PEEP 8 Hours		Mechanical Ventilation after Removal of PEEP 1 Hour
		4 Hours	4 Hours	
Temperature (C)	38.5 ± 0.8	38.5 ± 0.9	38.5 ± 1.4	38.4 ± 1.4
pH	7.38 ± 0.04	7.34 ± 0.03	7.35 ± 0.06	7.34 ± 0.06
P _{CO₂} (torr)	33 ± 4	33 ± 3	31 ± 5	35 ± 6

$$1) CI (l/min/m^2) = \frac{CO}{BSA};$$

where

$$BSA = 0.112 (\text{body weight})^{2/3}$$

$$2) \text{ Systemic vascular resistance (SVR):}$$

$$\frac{\overline{BP} - \overline{RAP}}{CO};$$

Where

\overline{RAP} = mean right atrial pressure

\overline{BP} = mean femoral arterial pressure

$$3) \text{ Pulmonary vascular resistance (PVR):}$$

$$\frac{\overline{PAP} - \overline{PCWP}}{CO}$$

Where

\overline{PAP} = mean pulmonary arterial pressure

\overline{PCWP} = mean pulmonary canillary wedge pressure

$$4) \text{ Left ventricular stroke work index (LVSWI):}$$

$$LVSWI = [(BP - LVEDP) \times 10^{-3}] \times SI$$

Where

LVEDP = left ventricular end-diastolic pressure

SI = stroke index

$$5) \text{ and right ventricular stroke work index (RVSWI):}$$

$$RVSWI = [(\overline{PAP} - RVEDP) \times 10^{-3}] \times SI$$

Where

RVEDP = right ventricular end-diastolic pressure

$$6) \text{ Oxygen consumption:}$$

$$\dot{V}_{O_2} = CO \cdot (Ca_{O_2} - C\bar{v}_{O_2})$$

Where

Ca_{O_2} and $C\bar{v}_{O_2}$ = arterial and mixed venous oxygen contents, respectively

Ventricular function curves were constructed by plotting left and right stroke work indices against transmural atrial pressure. Transmural pressures were derived by referring measured pressures to pleural pressures (*i.e.*, pressure measured relative to atmospheric minus pleural pressure relative to atmospheric). The correlated *t* test was used to test significance of differences between mean values. Results are given as mean values plus or minus the standard deviations of the mean.

Protocol

The 18 dogs were divided into three study groups consisting of six, ten, and two animals, respectively.

Group 1. Six dogs were studied using a 1.5-hour control period (first control) of mechanical ventilation, 8 hours of mechanical ventilation with PEEP, and one additional hour (second control) following discontinuation of PEEP. The mean time interval from start of anesthesia to the first measurement for this group was 4.5 hours. During this interval the dogs received Ringer's lactate solution at a rate of 30 ml/hour. After the start of the experiment, this infusion rate was reduced to 15 ml/hour because of the added saline solution administered with each CO measurement and the decline in urine flow. A similar fluid replacement regimen was followed in the subsequent study groups. During the first and second

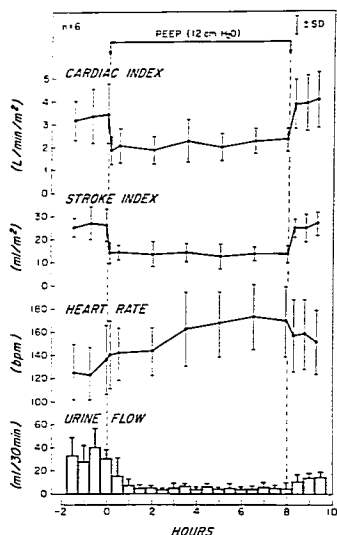


FIG. 1. Application of 12 cm H₂O PEEP was followed by prompt, marked, sustained decreases in cardiac and stroke indices and a gradual but significant increase in heart rate. Urine flow decreased to 15 per cent of the control value during mechanical ventilation without PEEP and remained at this low level for 8 hours. Removal of PEEP after 8 hours was followed by immediate return to control values of all variables except urine flow, which remained below its initial level. Mean values and standard deviations of the mean are shown.

control periods (before and after PEEP), measurements were made at 30-minute intervals. Following application of PEEP, measurements were made at 5 and 30 minutes and thereafter at 1.5-hour intervals.

Group II. (Ten dogs.) After a first set of control measurements during mechanical ventilation, PEEP was applied for 1.5 hours to establish a baseline level during mechanical ventilation with PEEP. Each dog then received a transfusion of 25 ml/kg of autologous blood over a 10–15-minute period and was

studied for 4 subsequent hours. PEEP was then discontinued and the dog followed for an additional 7 hours of mechanical ventilation (second control). Measurements were performed at 0.5-hour intervals until the first hour after transfusion. Subsequently, measurements were made at 1.5–2-hour intervals.

Autologous blood was obtained either five days previously (four dogs) or the morning of the study after infusion of 6 per cent dextran in saline solution in an amount equal to the volume to be shed (six dogs). All blood transfused was filtered through a 40-micron dacron filter (Swank, Pioneer Labs).

Group III. Two dogs received transfusions (21 ml/kg) over a 10-minute period during

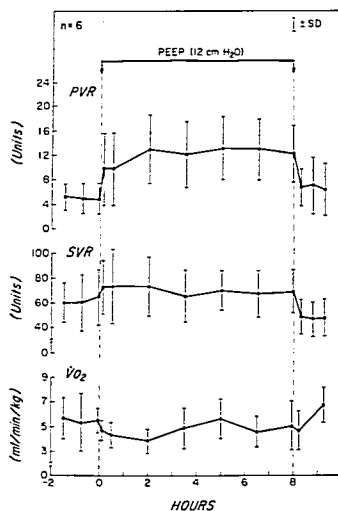


FIG. 2. Systemic vascular resistance (SVR) did not change significantly with application of PEEP, while pulmonary vascular resistance (PVR) more than doubled. The decrease in oxygen consumption (\dot{V}_{O_2}) was not significant. All values returned to control levels promptly after discontinuation of PEEP. Mean values and their standard deviations are shown.

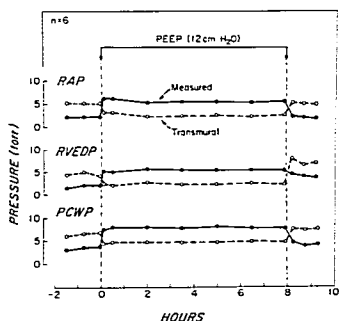


FIG. 3. Patterns of response of right atrial pressure (RAP), right ventricular end-diastolic pressure (RVEDP) (data from three dogs), and pulmonary capillary wedge pressure (PCWP) during 8 hours of PEEP. Note that while pressures measured relative to atmospheric rose, transmural pressures fell when PEEP was applied to normal lungs. The trend was reversed when PEEP was removed.

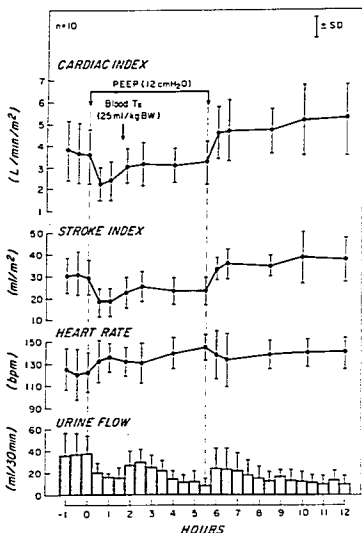


FIG. 4 (above, right). Transfusion of 25 ml/kg autologous blood during mechanical ventilation with PEEP caused an increase in cardiac index from 63 per cent to 85 per cent of values recorded during the first control period (before application of PEEP). The further increase after removal of PEEP to 132 per cent of the first control value was sustained for as long as 7 hours. The changes in urine flow paralleled those in cardiac index during the use of PEEP, but flow did not return to control levels when PEEP was discontinued. Mean values and their standard deviations are shown.

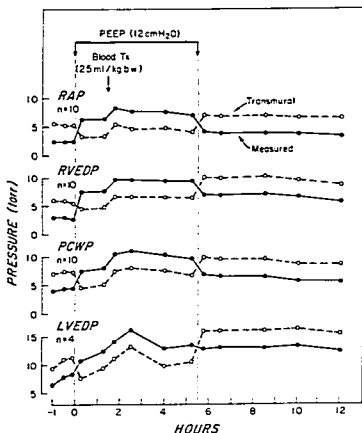


FIG. 5 (below, right). Measured (relative to atmospheric) and transmural (calculated) right and left heart filling pressures showed a response similar to that illustrated in figure 3. Both rose with transfusion. Note that following removal of PEEP, transmural left ventricular end-diastolic pressure (LVEDP) nearly doubled compared with the first control period and was consistent with the increase in cardiac index (fig. 4).

mechanical ventilation, one after 4 hours, the other after 12 hours of anesthesia (0.7 per cent end-tidal halothane).

Measurements in these animals were made twice before transfusion and repeated imme-

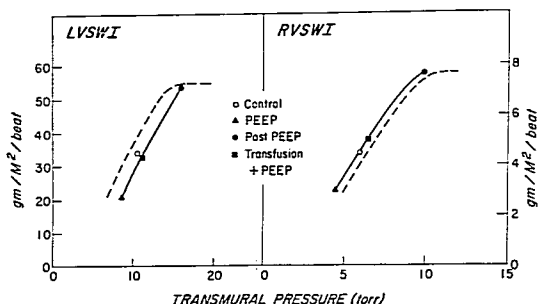


FIG. 6. Ventricular function curves were obtained by plotting transmural right and left ventricular end-diastolic pressures against right and left ventricular stroke work indices (solid lines). Interrupted lines represent values obtained in separate studies following dextran loading in halothane-anesthetized, ventilated dogs.

Mean data from four phases of the experiments are shown: 1) first control state (open circles); 2)

after application of PEEP (solid triangles); 3) after transfusion of 25 ml/kg autologous blood during PEEP (solid squares); 4) second control, after removal of PEEP (closed circles).

These maneuvers caused displacement along function curves, but no change in slope or position to suggest abnormal ventricular function. After PEEP is removed, both ventricles function near the top of their respective ventricular function curves.

diately after transfusion and at 15-minute intervals for one hour thereafter.

Results

Group 1. Figure 1 shows that CI and stroke index (SI) declined precipitously to 45 and 50 per cent of control values when PEEP was applied. These changes persisted unaltered during 8 hours of mechanical ventilation with PEEP and reverted to control values when PEEP was discontinued. The decline in blood

flow during application of PEEP was accompanied by an insignificant ($P > 0.05$) decrease in oxygen consumption and metabolic acidosis (base excess = -3). Heart rate increased 23 per cent ($P < 0.001$) when the early phase of PEEP was compared with the late phase of PEEP. This increase was not sufficient to influence cardiac index significantly.

Systemic vascular resistance was unaffected while pulmonary vascular resistance doubled upon addition of 12 cm H₂O PEEP to mechanical ventilation (fig. 2).

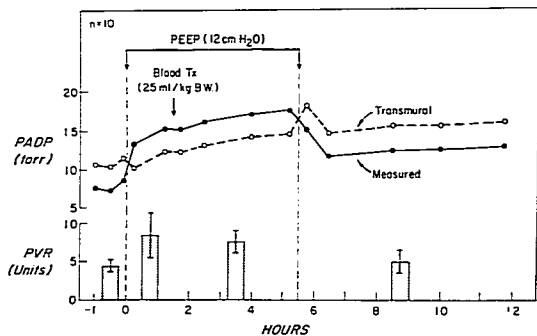
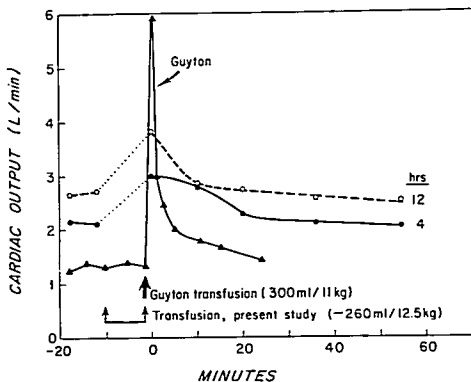


FIG. 7. Mean values of measured (relative to atmospheric) and transmural arterial diastolic pressure (PADD) are shown for the 12-hour experiment. Transmural PADD, an indicator of the right ventricular afterload, is seen to increase from 10.8 torr before initial application of PEEP to 18.4 torr immediately following its removal, and to remain elevated during the remainder of the experiment.

Also shown is mean pulmonary vascular resistance (PVR) (\pm the standard deviation). PVR nearly doubled with application of PEEP, but did not change following transfusion. It returned promptly to control values after removal of PEEP and thus is not responsible for the sustained increase in transmural PADD.

FIG. 8. Cardiac output returned to control levels within 30 minutes when two beagles received transfusions of 21 ml/kg whole blood during mechanical ventilation (without PEEP) at 0.7 per cent end-tidal halothane anesthesia. Transfusions were administered after 4 and 12 hours of anesthesia, respectively. Also shown is a plot of data from Guyton *et al.*,¹² in which cardiac output was measured by the Fick principle, by continuous monitoring of $A-V_{O_2}$ content difference. Differences in technique, including a faster infusion rate, probably explain why in Guyton's experiments the peak cardiac output reached higher levels than those obtained in our experiment. However, the times for return to control levels were identical and brief. Thus, our data suggest that neither mechanical ventilation nor halothane anesthesia is responsible for the sustained increase in cardiac output seen when transfusion is administered in the presence of PEEP (fig. 4).



Urine flow decreased sharply from 35 to 5 ml/30 min when PEEP was applied, and remained at this level. When PEEP was removed, urine flow increased significantly ($P < 0.01$) (fig. 1).

Right atrial pressure, pulmonary capillary wedge pressure, and right-ventricular end-diastolic pressure showed marked changes with institution and removal of PEEP, but remained constant throughout the application of PEEP (table 2, fig. 3). When referred to atmospheric pressure, filling pressures were considerably higher during mechanical ventilation with PEEP. However, when the rise in pleural pressure was taken into account, and vascular pressures calculated as transmural pressures, filling pressures were seen to decline during the period of PEEP application. As discussed later, this fall in filling pressure adequately explains the changes in right and left stroke work indices. Consistency of temperature, pH and carbon dioxide tension throughout the study period is shown in table 1.

Group II. Application of PEEP resulted in changes similar to those observed in Group I. Transfusion of 25 ml/kg blood during mechanical ventilation with PEEP was followed by a sustained increase in CI from 63 to 85 per

cent of the first control value obtained using mechanical ventilation without PEEP (fig. 4). When PEEP was removed (second control), CI increased further to 132 per cent of the level found during the first control period ($P < 0.01$). As shown in figure 4, this increase was sustained for 7 hours following cessation of PEEP.

Changes in flow essentially followed the changes in CI. With removal of PEEP, urine flow increased to a control level. However, after 2 hours flow again decreased and remained significantly lower for the remaining 5 hours ($P < 0.02$).

Right- and left-sided filling pressures (pre-load) in Group II responded to application of PEEP in a manner similar to that observed in Group I (fig. 5). Pressures measured relative to atmospheric increased and decreased with application and removal of PEEP, whereas transmural pressures changed in the opposite direction. Transfusion during PEEP increased both pressures, and with removal of PEEP there was a sustained increase in transmural filling pressures above levels measured during the first control period. This was most pronounced for RVEDP and LVEDP, which rose approximately 50 per cent above values measured during the first control period.

Ventricular Function. (Table 2, figs. 6 and 7.) When transmural RVEDP and LVEDP were plotted against the stroke work indices, the relationship was essentially linear. In figure 6, these curves are plotted together with ventricular function curves obtained in separate studies in our laboratory following dextran loading of normal, halothane-anesthetized beagles. The slopes and positions of the curves were identical.

Application of PEEP did not increase transmural pulmonary arterial diastolic pressure (T_{PADP}) in either group (fig. 7). In Group II transfusion during PEEP caused a gradual significant increase in T_{PADP} ($P < 0.05$), which rose further to 18.4 ± 3.5 torr following removal of PEEP, a level almost 50 per cent higher than noted before (10.8 ± 2.2 torr) and after initial application of PEEP ($P < 0.01$). It then levelled off at 15.8 ± 2.7 torr for the ensuing 7 hours (fig. 7). Figure 7 also shows that pulmonary vascular resistance increased significantly during PEEP, returned to control levels with its removal, and was not influenced by transfusion.

Group III (Transfusion without PEEP.) Transfusion of 21 ml/kg blood during mechanical ventilation caused an acute increase in

CO, which returned to control level within 30 minutes (fig. 8).

Discussion

The four principal findings in this study were: 1) a reduction in ventricular filling pressure is the cause of the decreases in cardiac index and stroke index observed when ventilation is altered by addition of PEEP to mechanical ventilation; 2) once such a decrease has occurred, it persists for prolonged periods (8 hours) without evidence of compensation; 3) augmentation of blood volume by transfusion reverses these changes; 4) the hemodynamic consequences of relative hypervolemia will become evident once PEEP is discontinued.

Increased intrathoracic pressure has been demonstrated to decrease both cardiac output and stroke volume.¹ If ventricular filling pressures are referred to atmospheric pressure, then they may be seen to rise when intrathoracic pressure is increased and the hemodynamic consequences may be misinterpreted. By referring pressures to pleural pressure, a fall in filling pressure was seen to occur (see figs. 3 and 5 and tables 2 and 3), and it

TABLE 2. Changes in Vascular and Pleural Pressures and in Systemic and Pulmonary Vascular Resistance with Application and Removal of PEEP in Group I*

	Pattern of Ventilation			
	Mechanical Ventilation (Control) 1½ Hours	Mechanical Ventilation + PEEP 8 Hours		Mechanical Ventilation after Removal of PEEP 1 Hour
		4 Hours	4 Hours	
Pleural pressure (torr)	-3.1 ± 1.0	3.0 ± 0.81	3.1 ± 1.01	-3.0 ± 0.95
RAP (torr)	2.2 ± 1.0	5.8 ± 0.91	5.5 ± 0.61	2.0 ± 0.85
Transmural RAP (torr)	5.3 ± 1.0	2.8 ± 1.01	2.4 ± 0.61	5.0 ± 0.85
PCWP (torr)	3.4 ± 1.3	7.9 ± 1.41	7.9 ± 1.51	4.5 ± 1.15
Transmural PCWP (torr)	6.5 ± 1.3	4.9 ± 1.41	4.8 ± 1.51	7.5 ± 1.15
RVEDP (torr)	1.9 ± 1.0	5.3 ± 1.2	5.2 ± 1.3	4.1 ± 3.2
Transmural RVEDP (torr)	5.0 ± 1.0	2.3 ± 1.2	2.1 ± 1.3	7.1 ± 3.2
SVR (units)	62.0 ± 19.7	71.0 ± 23.7	67.2 ± 17.7	46.8 ± 14.1
PVR (units)	5.0 ± 2.3	$11.1 \pm 5.4†$	$12.7 \pm 4.7†$	$6.6 \pm 3.8§$

* By referring hemodynamic pressures to pleural pressure rather than atmospheric, and thus obtaining transmural pressure, it is demonstrated that PEEP decreases the preload.

Note: Values during the late phase of PEEP were not significantly different from those during the early phase of PEEP. The data are from six dogs, except for RVEDP, which represents data from three dogs only.

† $P < 0.05$ compared with first control value.

‡ $P < 0.001$ compared with first control value.

§ $P < 0.05$, second control compared with mechanical ventilation + PEEP.

¶ $P < 0.001$, second control compared with mechanical ventilation + PEEP.

TABLE 3. The Hemodynamic Events of Hypervolemia during and after PEEP in Group II*

	Pattern of Ventilation			
	Mechanical Ventilation (Control) 1 Hour	Mechanical Ventilation - PEEP 1½ Hours	Mechanical Ventilation - PEEP - Transfusion 4 Hours	Mechanical Ventilation after Removal of PEEP 7 Hours
RAP (torr)	2.3 ± 0.8	5.1 ± 0.71	7.7 ± 0.61 [†]	3.6 ± 0.21 [#]
Transmural RAP (torr)	5.2 ± 0.9	2.0 ± 0.81	4.8 ± 2.21 [†]	6.8 ± 1.31 [#]
PCWP (torr)	4.2 ± 1.5	7.8 ± 1.51	10.5 ± 1.21 [†]	6.2 ± 1.21 [#]
Transmural PCWP (torr)	7.2 ± 1.2	4.8 ± 1.51	7.5 ± 1.2 [†]	9.3 ± 1.21 [#]
RVEDP (torr)	3.0 ± 1.3	7.5 ± 1.91	9.5 ± 2.41 [§]	6.9 ± 3.71
Transmural RVEDP (torr)	6.0 ± 1.3	4.5 ± 1.91	6.6 ± 2.5 [§]	9.9 ± 3.51
LVEDP (torr)	7.5 ± 3.1	11.5 ± 3.71	14.0 ± 3.21	13.0 ± 2.51
Transmural LVEDP (torr)	10.5 ± 2.9	8.4 ± 3.51	11.0 ± 3.0 [§]	16.0 ± 2.41 [‡]
Pleural pressure (torr)	-3.0 ± 1.2	3.1 ± 1.1 [†]	2.9 ± 1.0 [†]	-3.1 ± 1.5 [#]
SVR (units)	53.6 ± 19.4	65.8 ± 13.0	57.0 ± 9.0	41.7 ± 10.2
PVR (units)	4.4 ± 0.8	8.3 ± 3.01	7.4 ± 1.51	4.7 ± 1.5 [#]

* It is evident that transmural filling pressures (except RAP) return to control levels with transfusion and that filling pressures increase with removal of PEEP. For further discussion see text.

† P < 0.05 compared with control.

‡ P < 0.001 compared with control.

§ P < 0.05 compared with mechanical ventilation + PEEP.

¶ P < 0.001 compared with mechanical ventilation + PEEP.

‡ P < 0.01 compared with mechanical ventilation + PEEP + transfusion.

P < 0.001 compared with mechanical ventilation + PEEP + transfusion.

became evident that the decrease in flow was not secondary to impaired ventricular function, but merely represented a move along a ventricular function curve (fig. 6). Similarly, the responses to blood volume augmentation and to discontinuation of PEEP are represented by moves along this same curve, for both right and left ventricles. It is noteworthy that among the factors influencing right ventricular "afterload," T_{PADP} was unchanged with the application of PEEP in the face of a doubling of pulmonary vascular resistance. Of even greater interest is the significant rise in T_{PADP} when PEEP was removed after transfusion had taken place (fig. 7). Patients with severe, acute pulmonary disease or mitral valve disease frequently have high pulmonary vascular resistance. Hypervolemia is also common, particularly when an attempt is made (by intravenous fluid administration) to maintain adequate blood flow in the face of mechanical ventilation with high mean airway pressures. Withdrawal of PEEP in these patients may lead to a marked increase in right ventricular "afterload" (i.e., PVR, T_{PADP} , and $\bar{P}AP$), and probably explains why removal of PEEP or even cessation of mechanical ventila-

tion may be associated with a paradoxical fall in CI,⁶ i.e., the enhanced "venous return" in the hypervolemic patient is tantamount to a rapid autotransfusion which cannot be handled appropriately by the failing right ventricle. Application of PEEP under these circumstances may prove beneficial in terms of improved gas exchange, and increased flow. The data of Trichet *et al.*⁷ and Beach *et al.*⁸ suggest that both can occur.

The results obtained in Group I indicate that the reduction in blood flow consequent to the application of PEEP is persistent and that hemodynamic adaptation is not apparent during a period of 8 hours. This is also reflected in the decline in urine flow, which we believe is best explained by a reduction or redistribution in renal blood flow.^{8,9} Pertinent to the problem of urine flow is the fact that transfusion during mechanical ventilation with PEEP was also associated with an increase in urine flow, suggesting that cardiac output is a dominant factor over other mechanisms such as increased ADH secretion or reflexes mediated via intrathoracic structures.⁹

The only change of a compensatory nature we observed was an increase in heart rate,

which was insufficient to alter CI significantly. Feisal *et al.*¹⁰ demonstrated in short-term experiments circulatory adaptation to increase airway pressure, consisting of tachycardia (through a beta-adrenergic reflex mechanism) and a significant increase in systemic vascular resistance. We were unable to demonstrate a significant change in systemic vascular resistance in response to mechanical ventilation with PEEP. It is possible that adaptation in our dogs was blocked by general anesthesia. However, there is no evidence that halothane prevents a compensatory increase in cardiac index. In fact, Bahlman and co-workers¹¹ found that cardiac index increases with time in halothane-anesthetized, mechanically ventilated man: after one hour of halothane anesthesia (1 per cent end-tidal), cardiac index had decreased to 78 per cent of control value, but it rose again and after five hours of anesthesia had reached 107 per cent of control. Thus, halothane is not a likely explanation for the constancy of the cardiac index in this study. Although inadequate fluid replacement could account for the absence of the anticipated increase of cardiac index, we believe the contrary because of the consistency of transmural filling pressures during mechanical ventilation with PEEP and the return of these variables to control values when PEEP was removed (fig. 3). In Group I animals, a positive water balance led to a mean increase in body weight of 650 g over 16 hours, and subcutaneous edema of head and front legs was noted towards the end of the experiment. Such extravascular sequestration of fluid following addition of PEEP is predictable from the Starling equation due to the increased hydrostatic pressure in systemic capillaries.

Lack of circulatory adaptation during PEEP implies that the reduction in blood flow consequent to the clinical application of PEEP requires treatment. Once PEEP has been implemented, the hemodynamic consequences of excessive crystalloid and colloid administration may become manifest only after discontinuation of PEEP. With an abrupt fall in airway pressure, acute redistribution of intravascular volume from the capacitance bed to the central circulation (the reverse of what occurs when PEEP is applied) may acutely increase cardiac filling pressures, an event

well illustrated in these studies. The attendant response of the right ventricle will depend on the state of its contractility and the changes in pulmonary vascular impedance. In addition, intravascular volume may continue to increase over a period of hours or days as sequestered fluid is reabsorbed. This phenomenon of net intravascular inflow is equally predictable from the Starling equation. It emphasizes the importance of close observation of hemodynamic performance and blood-gas exchange following removal of PEEP, especially in patients whose ventricles may be functioning on the flat portion of their Frank-Starling curves.

In the absence of chronically applied PEEP, the acute hemodynamic response to blood volume expansion may vary. For example, using barbiturate-anesthetized dogs, Guyton¹² found the rapid rise of CO following transfusion of 27 ml/kg whole blood reverted to control levels within 30 minutes. Presumably the capacitance bed was capable of dilating to accept the additional volume. Since our animals were subjected to *prolonged* anesthesia with a different agent (halothane), it was important to determine whether time or anesthesia could account for the altered response to transfusion. As shown in figure 8, this was not the case. The response to acute volume expansion in the absence of PEEP was similar to the data presented by Guyton.¹² Therefore, we must conclude that our findings are not due solely to the anesthetic drug used.

In conclusion, application and discontinuation of PEEP may cause hemodynamic changes, depending on the magnitude of the airway pressure transmitted to the heart, to the central circulation, and to the pleural space. Depending on the state of ventricular function, a decrease in airway pressure in the presence of hypervolemia may be accompanied by a paradoxical decrease in blood flow if contractility is impaired and/or right ventricular afterload increases significantly. Under these conditions, evaluation of performance based on right atrial or pulmonary capillary wedge pressure may be misleading. It is important to appreciate that vascular pressures measured during mechanical ventilation with PEEP may seem normal or elevated, but may in fact be inadequate to main-

tain ventricular filling pressures, depending on the attendant pressure transmitted to the pleural space. During mechanical ventilation, especially with added PEEP or in the presence of increased intra-abdominal pressure (and consequently elevated pleural pressure), only transmural filling pressures will reflect accurately the hemodynamic status and responses to therapy. In these circumstances, right and left heart filling pressures measured relative to atmospheric pressure are unreliable.

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