Pediat. Res. *13:* 1112–1120 (1979)

Cardiac output
cardiovascular function
positive end-expiratory pressure
pulmonary compliance
pulmonary function

Cardiopulmonary Consequences of Positive End-Expiratory Pressure

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Summary

Positive end-expiratory pressure (PEEP), while of major benefit in the therapy of pulmonary diseases characterized by low functional residual capacity (FRC), is frequently associated with depression of cardiac output (CO) and specific dynamic compliance (Csp). The cardiopulmonary consequences of sequential increases of PEEP (3, 6, 9, 12, 15 cm H_2O) in normal dogs were studied utilizing an apparatus that permits measurement of FRC by helium dilution while the animal remains on PEEP. It was found that increasing levels of PEEP had no effect on tidal volume (V_T) or inspiratory time, but appeared to lengthen expiratory time by delaying expiratory flow until the preinspiratory period, and led to facilitated expiration. This response occurred immediately upon changes in the level of PEEP and is felt to be reflex in nature. FRC increased and Csp fell as PEEP was increased. This was reflected in a fall in transmission of applied airway pressure to an esophageal balloon. Pulmonary hypertension did not develop in our animals, but net right atrial (RA) pressure was elevated by PEEP. There was no difference in cardiac index (CI) between the control and study groups. Both the magnitude of applied airway pressure and the extent to which it is transmitted across the lungs to the pleural space appear to be determinants of possible effects of PEEP on CO and may explain the diversity of results among reported studies of PEEP. Transmission of pressure is related directly to Csp.

Speculation

Transmission of PEEP to the pleural space is dependent on the level of PEEP and on the preexisting state of the lungs. Transmission of applied airway pressure will be greatest when the Csp of the lungs is highest; it may be reduced significantly if either insufficient or excessive levels are used for a given clinical situation. The pleural pressure *vs.* applied PEEP relationship thus provides a sensitive index of changing status of the lungs, as well as an assessment of therapeutic efficacy.

PEEP can be most effective in the treatment of neonatal respiratory distress and other diseases characterized by low pulmonary dynamic compliance (C), low FRC, and intrapulmonary right-to-left shunts (5, 17, 18, 21, 25, 28, 44, 46, 47). The use of PEEP, however, may be associated with undesirable effects including lowering of CO (14, 15, 17, 24, 26, 28, 44, 46) and overdistention of alveoli leading to a fall in C (5, 6, 12, 27, 44). In the present studies, the time-course of changes in relevant cardiopulmonary parameters induced by PEEP has been evaluated in normal, spontaneously breathing, anesthetized dogs. The objective was to study, comprehensively in each subject, the broad spectrum of changes that may be induced by PEEP and their possible interrelations, and to compare these with control animals that were handled identically except for PEEP. These studies indicate that the extent to which pulmonary C is altered is the important determinant of PEEP transmission to the thorax and of the consequent effects of PEEP on intrathoracic pressures and cardiovascular function. It is also concluded that the antecedent status of the lungs (before PEEP) has predictive value with regard to the effects of PEEP on cardiorespiratory function.

These experiments also revealed that slowing of respiratory frequency and displacement of expiration from inspiration is a regular response to the application of PEEP and that these effects increase as PEEP is increased. Thus, PEEP produces a postinspiratory pause followed by an active expiration that immediately precedes the next inspiration at the highest PEEP. The immediacy with which these changes occur suggests that they are reflex in origin.

Although the term continuous positive airway pressure (CPAP) is used often to describe the application of positive pressure is spontaneously breathing subjects such as ours, we have elected to use the term PEEP. PEEP conveys the fact that the applied pressures are imposed quantitatively at end-expiration, whereas airway pressures vary (perhaps becoming subatmospheric), during inspiration.

MATERIALS AND METHODS

Anesthesia was induced in 12 healthy spontaneously breathing mongrel dogs (13–25 kg) with sodium pentobarbital, 30 mg/kg iv, and maintained with additional iv doses (1–2 mg/kg) when seemingly purposeful motor activity occurred. One to three additional doses were required to maintain a steady level of anesthesia as judged by clinical signs. A cuffed endotracheal tube was inserted and catheters were placed in the RA via the external jugular vein and aorta (Ao) via the femoral artery. A Swan-Ganz catheter was inserted through a femoral vein and advanced to the main pulmonary artery (PA), where the position was confirmed by pressure tracings. Pleural pressure (Ppl) was recorded (52) from an intraesophageal balloon using the technique of Milic-Emili *et al.* (32). Inspiratory and expiratory flow rate ($\dot{Q}_I$ and $\dot{Q}_E$) were recorded from a heated Fleisch pneumotachograph (53); V_T was determined by electronic integration of inspiratory air flow (54). All measurements, including RA, PA, and Ao pressures were displayed on a six-channel pen recorder (55). Gas pressures and pH of arterial and mixed venous blood, and inspired and expired oxygen tensions were measured in a specially modified microanalytic system (56). Hemoglobin-oxygen saturation was determined from nomograms for dogs (39). RA, Ao, and PA pressures, Ppl, $\dot{Q}_I$, $\dot{Q}_E$, and V_T were recorded continuously. Gas pressures, pH, CO, and FRC were determined at the end of each control and test period.

All dogs were observed for 30 min after the placement of catheters and endotracheal tube-pneumotachograph assembly ("control period 1," zero end-expiratory pressure (ZEEP)). The PEEP apparatus for the application of PEEP and maintenance of PEEP during FRC determination (modified after Berman *et al.* (8)), was then connected to the endotracheal tube-pneumotachograph assembly with humidified air flow through the system maintained at 2.0–2.5 liter/min to prevent rebreathing. This flow rate produced a baseline PEEP of 0.6 cm H_2O, which has been termed "minimal PEEP" (MEEP). After 20 min ("control period 2," MEEP), the dogs were divided randomly into two groups: Seven dogs (mean weight, 19.9 kg) were designated the "study group." Experimental protocol for this group included placement

of the expiratory limb of the PEEP-apparatus under water sequentially at 3, 6, 9, 12, and 15 cm H_2O. Each PEEP setting was maintained for 20 min. Five dogs (mean weight, 21.5 kg) were designated the "control group." These dogs were monitored for five successive 20-min periods ("control periods 3–7") with the PEEP apparatus in place and baseline gas flow of 2.0–2.5 liter/min, but without the expiratory tube under water, *i.e.*, with continuous MEEP.

CO and CI were calculated by a modification of the conventional method using the Fick principle (see Appendix). Surface area was determined from the formula

$$m^2 = 0.112 \times \text{body wt (kg)}^{2/3} \text{ (46)}.$$

FRC was determined by the closed circuit helium dilution method using the apparatus described by Berman *et al.* (8) ("PEEP-apparatus"), which permits measurements while the animals remain on PEEP. Helium concentration was determined with a helium analyzer (57) calibrated with air and known concentrations of helium in air. Helium equilibration was achieved within 60 sec in each study. Dynamic C was calculated as V_T divided by the difference in esophageal pressures at points of zero airflow. Csp was calculated as C divided by FRC. Unpaired data were analyzed by Student's *t* test.

RESULTS

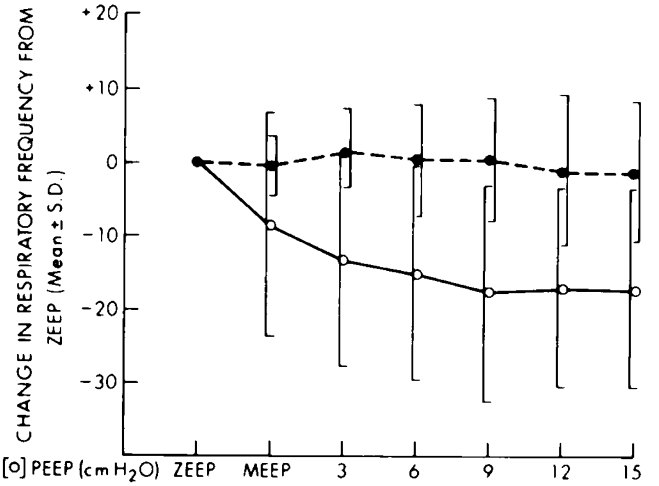
Measurements were begun for both control and study groups after endotracheal intubation (ZEEP) and continued after placement of the PEEP-apparatus with gas flow of 2.0–2.5 liter/min (MEEP). Thereafter, the control group was maintained at MEEP, whereas PEEP was increased sequentially in the study group, as described.

TIDAL VOLUME

At ZEEP, V_T was 148 ± 52 ml in the control group and 113 ± 79 ml in the study group. V_T increased in both groups with MEEP, but the change was not significant ($P < 0.10$). With time (control group) and PEEP (study group), V_T increased, but there was no significant difference between the groups. At 15 cm H_2O PEEP, V_T was 189 ± 103 ml and at the equivalent time period in the control group V_T was 184 ± 45 ml.

FREQUENCY AND BREATHING PATTERNS

MEEP did not produce a significant change in respiratory frequency (Fig. 1) in either group, and there was no change in frequency in the control group for the duration of the procedure. In the study group, however, respiratory frequency fell progressively with increasing PEEP up to 9 cm H_2O, after which there was no further change. This relative bradypnea was associated with no change of inspiratory time, with an increase of expiratory time, and with a displacement of peak expiratory flow from the end-inspiratory period (Fig. 2). Thus, there developed a pause between inspiration and peak expiration, and, at higher levels of PEEP, peak expiration could be characterized as "preinspiratory." Coincidentally, expiration became active as judged from the pleural pressure tracings (Fig. 3). When PEEP was reduced, the inspiratory-expiratory patterns assumed their previous configuration (Fig. 4). These effects were apparent as soon as the PEEP level was changed and they were sustained as long as a particular PEEP was maintained.



PROBABILITIES:						
[●] CONTROL PERIODS vs ZEEP	ns	ns	ns	ns	ns	ns
[o] STUDY PERIODS vs ZEEP	ns	<0.05	<0.025	<0.01	<0.025	<0.025
[o] vs [●]	ns	<0.05	<0.05	<0.025	<0.025	<0.025

Fig. 1. Changes in respiratory frequency from ZEEP. Actual frequencies (mean ± SD) at ZEEP are for the control group [●] 20.0 ± 12.2 bpm and for the study group [O] 28.4 ± 16.6 bpm. Difference is not significant.

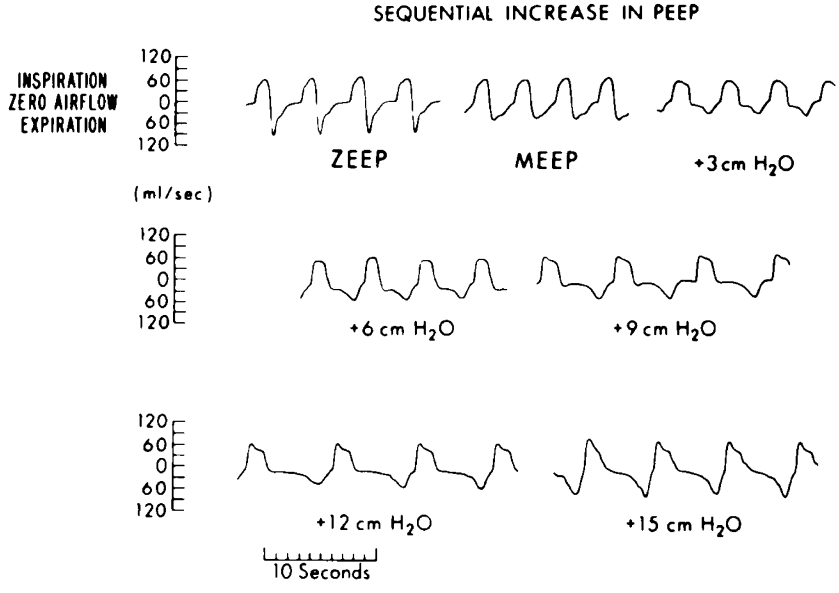


Fig. 2. Changes in respiratory airflow with sequential increases in PEEP. 20 min between changes. Dog S-2.

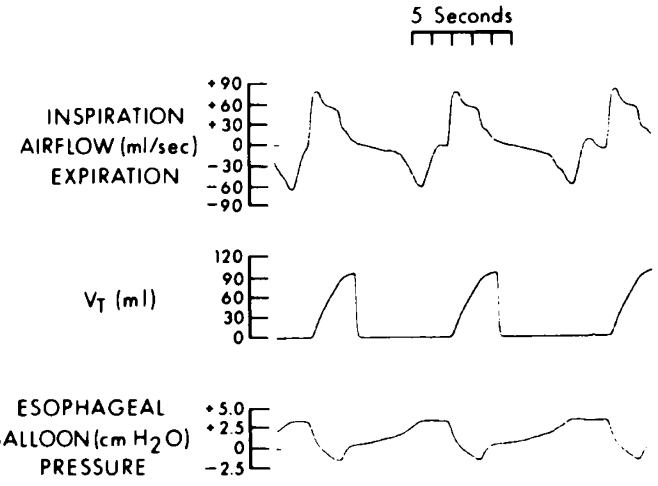


Fig. 3. Respiratory airflow, V_T, and esophageal pressure at PEEP 15 cm H_2O. Dog S-3.

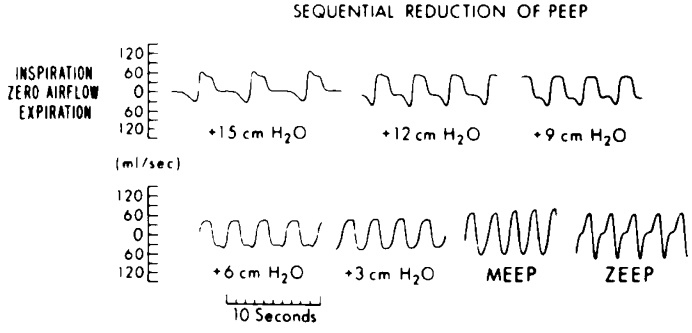


Fig. 4. Changes in respiratory airflow with sequential reduction in PEEP. 6–10 breaths between changes in PEEP. Dog S-5.

In order to test further the effects of PEEP on breathing patterns and to determine whether the maximal effect of 15 cm H_2O PEEP was related to the stepwise increase of pressure or to the abrupt pressure change per se (*i.e.*, whether or not the volume history of the lung was the determining factor), we conducted an additional maneuver with 10 animals (five study and five control). After the basic experimental protocol had been completed, PEEP was abruptly increased from MEEP to 15 cm H_2O (Fig. 5). This was followed by an apneic interval before breathing was resumed. The new breathing pattern, however, was characterized by slow frequency, initial reduction of peak expiratory flow rate, and displacement of expiration to the immediate preinspiratory period.

FRC AND Csp

There was no significant change of FRC in either group with MEEP (Fig. 6). At higher levels of PEEP, however, there was a significant progressive increase of FRC in the study group, whereas FRC of the control group did not change significantly (Fig. 6).

Csp (Fig. 7) did not change with MEEP in either group. With PEEP of 6 cm H_2O and more, there was a significant fall of Csp in the study group as compared both with the control group and the period of MEEP. With increasing FRC and decreasing Csp, there was a reduction in transmission of PEEP to the esophageal balloon (Fig. 8). Thus, at 3 cm H_2O PEEP, an average 91% of the pressure was transmitted to the balloon; at 9 cm H_2O PEEP, about 30% was transmitted and only slightly less was transmitted at 12 and 15 cm H_2O PEEP.

MINUTE VENTILATION

MEEP did not affect minute ventilation significantly. However, minute ventilation of the study group was lower than that of control group at comparable periods during PEEP breathing (Fig. 9).

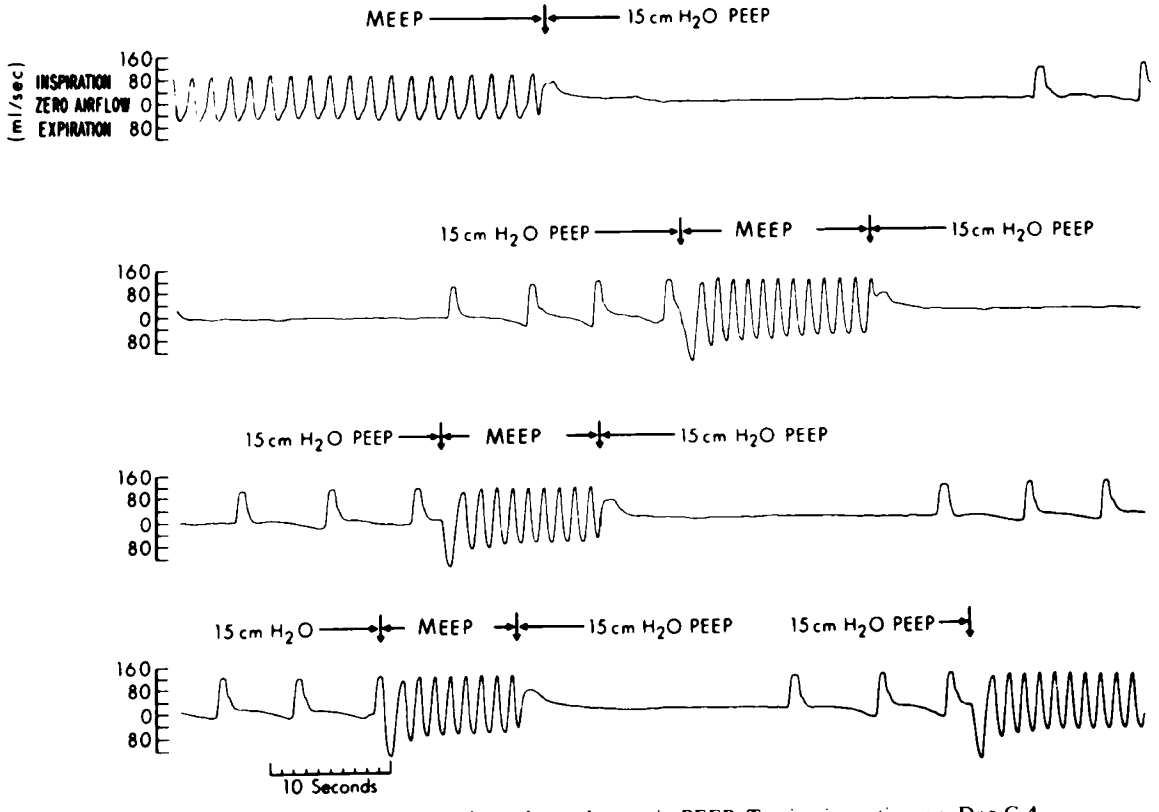
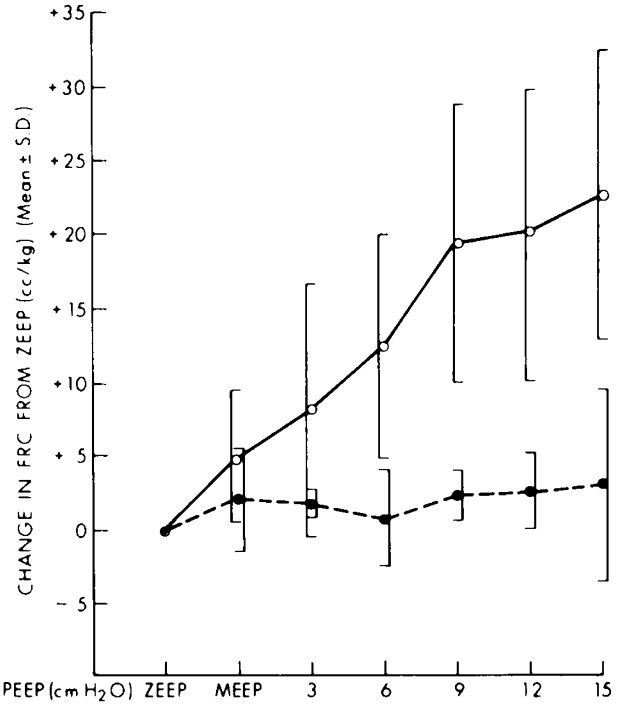
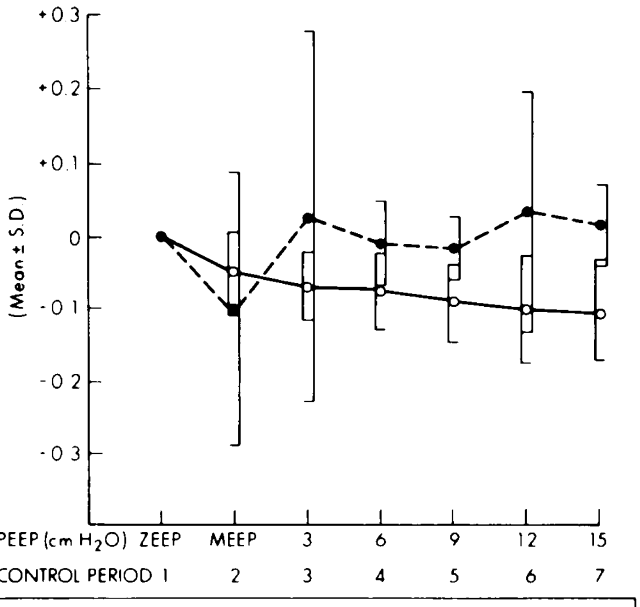


Fig. 5. Respiratory airflow during abrupt large changes in PEEP. Tracing is continuous. Dog C-4.



PROBABILITIES:						
[●] CONTROL PERIODS vs ZEEP	ns	ns	ns	ns	ns	ns
[o] STUDY PERIODS vs ZEEP	ns	<0.025	<0.01	<0.01	<0.01	<0.01
[o] vs [●]	ns	ns	<0.01	<0.01	<0.01	<0.01

Fig. 6. Changes in FRC from ZEEP. Actual FRC (mean ± SD) at ZEEP are for the control group [●] 22.0 ± 8.3 ml/kg and for the study group [○] 25.6 ± 5.9 ml/kg. Difference is not significant.



PROBABILITIES:						
[●] CONTROL PERIODS vs ZEEP	ns	ns	ns	ns	ns	ns
[o] STUDY PERIODS vs ZEEP	ns	ns	<0.05	<0.01	<0.01	<0.01
[o] vs [●]	ns	ns	<0.05	<0.025	<0.05	<0.01

Fig. 7. Changes in Csp from ZEEP. Actual Csp (mean ± SD) at ZEEP are for the control group [●] 0.22 ± 0.24 ml/cm H_2O/ml and for the study group [○] 0.14 ± 0.08 ml/cm H_2O/ml. Difference is not significant.

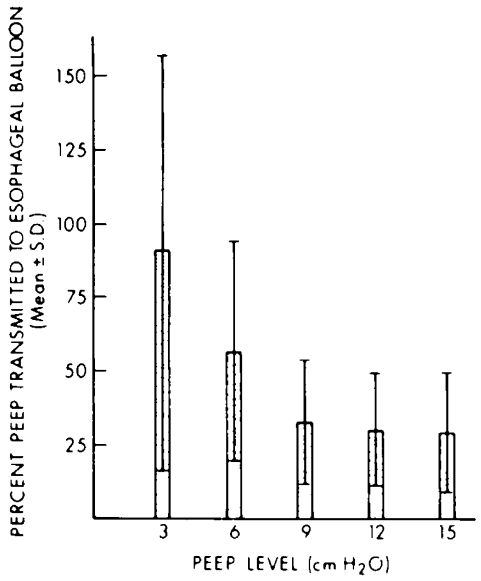
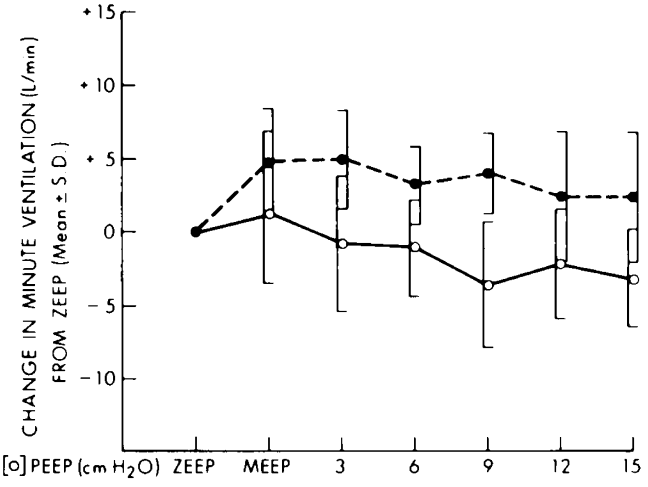


Fig. 8. Mean ± SD percent of applied airway pressure (PEEP) apparently transmitted to esophageal balloon at each level of PEEP.



PROBABILITIES:						
[●] CONTROL PERIODS vs ZEEP	ns	ns	ns	ns	ns	ns
[o] STUDY PERIODS vs ZEEP	ns	ns	ns	ns	ns	ns
[o] vs [●]	ns	<0.025	<0.025	<0.01	<0.05	<0.025

Fig. 9. Changes in minute ventilation from ZEEP. Actual ventilation (mean ± SD) at ZEEP are for the control group [●] 3.0 ± 1.6 liter/min and for the study group [○] 3.2 ± 1.4 liter/min. Difference is not significant.

BLOOD GAS TENSIONS AND pH

When the two groups were compared, there were no significant differences of pHa, $PaCO_2$, and PaO_2. However, two animals of the study group responded differently than the rest, *i.e.*, increasing PEEP did not result in any difference in $PaCO_2$, PaO_2, and pHa as compared with the control group (Study group 2, Table 1). Conversely, pHa and PaO_2 fell and $PaCO_2$ increased in the other five animals of the study group (Study group 5, Table 1).

CARDIOVASCULAR FUNCTION

Heart rate and systemic arterial pressure did not change significantly with either MEEP or PEEP, whereas CI fell during the period of study in both groups, there being no difference between study and control groups (Table 2). Mean PA pressure (*i.e.*, PA

Table 1. *Change in arterial pH and blood gas tensions with time (control group) and with PEEP (study group) (absolute values given in ZEEP column)*

Control period			3	4	5	6	7
PEEP level (cm H_2O)	ZEEP	MEEP	+3	+6	+9	+12	+15
Arterial pH							
Control group	7.364 ± 0.036	−0.012 ± 0.025	−0.005 ± 0.025	−0.006 ± 0.037	−0.0004 ± 0.037	−0.016 ± 0.031	−0.016 ± 0.030
Study group 5	7.386 ± 0.035	−0.051 ± 0.049	−0.081 ± 0.022	−0.085 ± 0.034	−0.089 ± 0.22	−0.112 ± 0.035	−0.120 ± 0.033
P value	NS	NS	<0.01	<0.025	<0.01	<0.01	<0.01
Study group 2	7.361 ± 0.004	+0.027 ± 0.006	+0.020 ± 0.010	−0.006 ± 0.008	+0.024 ± 0.023	−0.023 ± 0.009	+0.033 ± 0.011
P value	NS	NS	NS	NS	NS	NS	NS
PaO_2							
Control group	76.24 ± 5.94	+11.68 ± 14.69	+13.12 ± 15.00	+6.38 ± 5.99	+17.00 ± 16.02	+16.10 ± 12.23	+8.10 ± 5.84
Study group 5	80.16 ± 11.09	+1.50 ± 9.76	−3.14 ± 9.82	−4.62 ± 12.66	−4.74 ± 10.32	−11.46 ± 18.08	−8.30 ± 17.80
P value	NS	NS	<0.05	NS	<0.025	<0.025	<0.05
Study group 2	76.55 ± 0.92	+11.80 ± 2.40	+8.35 ± 11.53	+9.70 ± 10.89	+10.45 ± 12.52	+4.80 ± 11.46	+13.45 ± 1.63
P value	NS	NS	NS	NS	NS	NS	NS
$PaCO_2$							
Control group	32.92 ± 2.24	−0.54 ± 4.55	+0.60 ± 4.26	+0.66 ± 4.30	−0.12 ± 4.72	−3.18 ± 1.52	−0.100 ± 2.27
Study group 5	27.12 ± 3.51	+5.20 ± 4.80	+6.70 ± 2.83	+8.94 ± 4.83	+10.76 ± 6.23	+13.48 ± 7.25	+12.68 ± 5.21
P value	NS	<0.05	<0.025	<0.025	<0.01	<0.01	<0.01
Study group 2	34.7 ± 3.68	−4.9 ± 5.59	−4.65 ± 3.04	−4.75 ± 4.17	−6.45 ± 1.34	+0.90 ± 6.93	−7.50 ± 2.26
P value	NS	NS	NS	NS	NS	NS	<0.01

Table 2. *Heart rate (bpm), systemic mean arterial pressure (mmHg) and cardiac index (liter/min/m^2) (mean ± SD)*[1]

	Control period	1	2	3	4	5	6	7
	PEEP (cm H_2O)	ZEEP	MEEP	+3	+6	+9	+12	+15
Heart rate	Control group	187.2 ± 16.6	182.4 ± 17.3	184.8 ± 17.2	182.4 ± 17.3	178.8 ± 23.8	172:8 ± 25.6	170.4 ± 25.7
	Study group	187.7 ± 37.7	192.0 ± 36.7	183.4 ± 38.9	185.7 ± 32.8	185.1 ± 32.4	184.3 ± 39.6	180.9 ± 35.9
Mean arterial	Control group	148.7 ± 19.2	146.8 ± 19.3	145.8 ± 22.0	141.9 ± 25.2	142.9 ± 22.8	146.2 ± 20.0	148.3 ± 23.0
	Study group	155.9 ± 14.2	157.3 ± 17.6	152.6 ± 16.8	155.6 ± 18.4	150.2 ± 21.3	154.5 ± 23.0	148.8 ± 23.9
Cardiac index	Control group	4.0 ± 3.1	2.4 ± 1.4	2.3 ± 1.5	2.2 ± 1.2	2.1 ± 1.0	1.7 ± 0.9	1.6 ± 0.2
	Study group	3.0 ± 1.5	2.2 ± 0.9	2.3 ± 1.0	2.2 ± 1.5	1.8 ± 0.5	2.0 ± 0.3	1.1 ± 0.7

[1] There is no significant difference between the two groups for any parameter at any level.

pressure referred to atmospheric pressure) increased progressively with increasing PEEP (Figure 10a), but mean *net* or *transmural* PA pressure (*i.e.*, mean PA pressure minus esophageal pressure) did not change significantly with PEEP up to 15 cm H_20 and there was no difference between the two groups (Figure 10b). Similarly, mean RA pressure (*i.e.*, referred to atmospheric pressure) increased progressively with increasing PEEP (Figure 11a); however, unlike net PA pressure, net RA pressure of the study group was significantly elevated during PEEP breathing and significantly higher than net RA pressure of the control group (Figure 11b).

DISCUSSION

It is of interest that MEEP produced no changes other than a small increase of V_T and a decrease of peak $\dot{Q}_E$. Although not significant statistically, these changes may be a reflection of improved ventilation associated with addition of small end-expiratory pressures after breathing at ZEEP (8).

CARDIAC INDEX

Variability of CI in both control and study groups was wide, which may be a result of possible inaccuracies in the method used to determine CO (Appendix). However, it is also noted that the range of CI in pentobarbital-anesthetized dogs as reported by others (3, 27) is wide, albeit the values given are generally higher than those obtained by the authors during PEEP and at equivalent times in control dogs. Because PEEP-exposed subjects were compared with nonexposed subjects, in contrast with the studies of others (27), we may suggest that changes in CI recorded during PEEP may not be attributable categorically to PEEP and it may not necessarily be concluded that in normal lungs PEEP is "well transmitted to the pleural space" (27). Control subjects need to be evaluated in experiments in order to make these determinations. Our studies of transmission at progressively increasing PEEP (Fig. 8) and of the course of CI (Table 2) bear this out. However, under conditions in which transmission of PEEP may actually increase as pressure is increased (see following sections), alterations of CI may be expected.

ANTICIPATED CARDIOPULMONARY EFFECTS OF PEEP

Several effects were expected and in accord with the findings of others:

1) FRC increased directly with PEEP (5, 6, 9, 16, 18, 22, 24, 26, 28, 44). This is a desired effect when PEEP is used for treatment of low FRC, low Csp states, because increased FRC indicates recruitment of collapsed alveoli, stabilization of patent alveoli, shift of the closing capacity, and improved Csp (1, 7, 18, 21, 22, 28, 34, 40, 43, 44, 46), which result in improved oxygenation and decreased work of breathing. In two dogs of the study group (Study group 2, Table 1) $PaCO_2$ was lower and PaO_2 higher

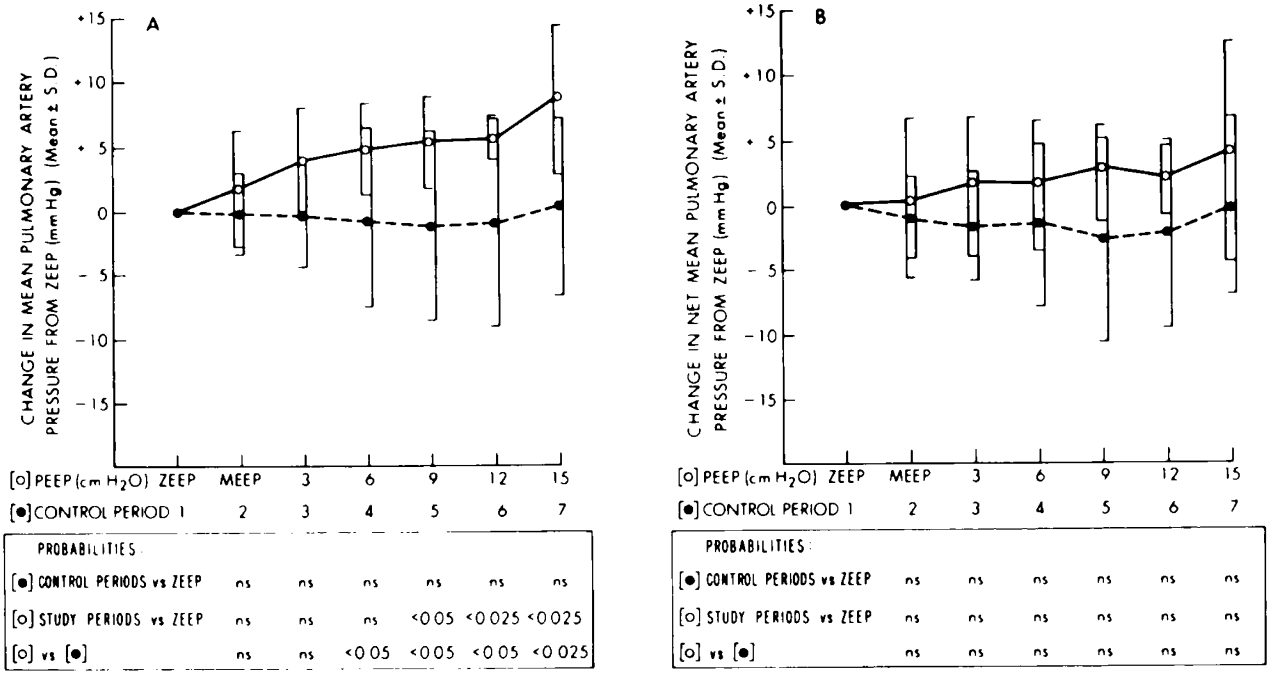


Fig. 10. (*A*) Changes in mean PA pressure from ZEEP. Actual pressures (mean ± SD) at ZEEP are for the control group [●] 19.3 ± 13.1 mm Hg and for the study group [○] 16.7 ± 4.7 mm Hg. Difference is not significant. (*B*) Changes in mean net PA pressure from ZEEP. Actual net pressures (mean ± SD) at ZEEP are for the control group [●] 18.9 ± 12.4 mm Hg and for the study group [○] 16.5 ± 5.0 mm Hg. Difference is not significant.

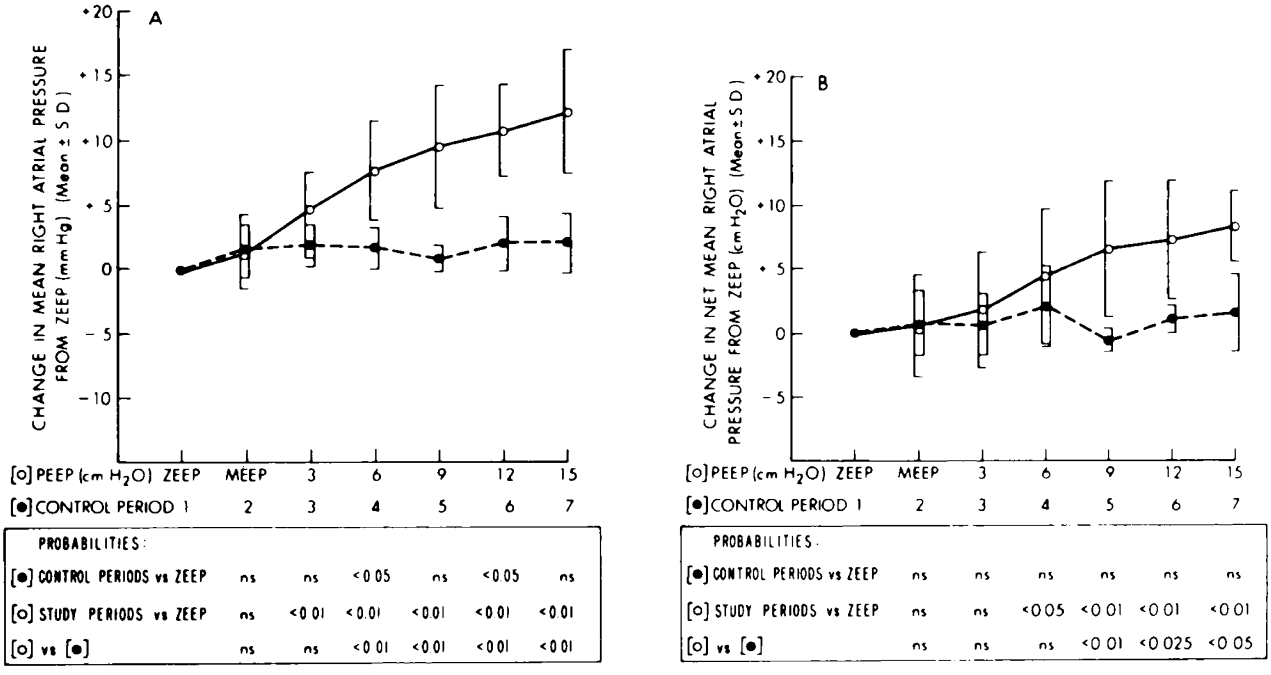


Fig. 11. (*A*) Changes in mean RA pressures from ZEEP. Actual pressures (mean ± SD) at ZEEP are for the control group [●] −4 ± 0.7 mm Hg and for the study group [○] −2.6 ± 3.1 mm Hg. Difference is not significant. (*B*) Changes in mean net RA pressure from ZEEP. Actual net pressures (mean ± SD) at ZEEP are for the control group [●] −4.4 ± 1.0 mm Hg and for the study group [○] −2.8 ± 3.9 mm Hg. Difference is not significant.

during MEEP and PEEP than during ZEEP. This could have resulted from correction of low FRC, low Csp (31) with the application of airway pressure. Because, however, gas tensions and pH were not significantly different from the control group, it may be suggested that MEEP (to which control dogs were also exposed) was as effective as higher pressures in producing these changes.

2) Csp decreased with increasing PEEP as the normal lungs of our subjects were expanded above their resting position (5, 6, 27, 44). As a consequence, the work of breathing would be expected to increase and this could be a factor (along with the "reflex" changes of respiratory frequency and rhythm) underlying the elevation of $PaCO_2$ and depression of PaO_2 in five dogs of the study group (Table 1). A similar effect would be expected when very high levels of PEEP are applied to lungs in the low FRC, low Csp state (see following sections). Other factors that should also be taken into account include the possibility that overinflation itself may adversely affect the alveolar surfactant system (20) and thus, further compromise Csp, and the observation that surfactants may be conserved (51) when PEEP effectively reverses the low FRC, low Csp state. Both these opposite effects could be produced in any given lung: They would be related to the proportional population of previously sound and abnormal alveolar units.

3) PEEP produced no change in heart rate or systemic arterial pressure in agreement with the reports of other investigators (4, 21, 22, 29). In contrast, continuous positive pressure breathing

(CPPB) and mechanical ventilation may alter heart rate (37, 40) and systemic pressure (26) significantly.

PLEURAL TRANSMISSION OF PEEP

Attenuated transmission of PEEP to the pleural space and to intrathoracic viscera has been noted (6, 21, 27, 36). Our studies provide further insights into this phenomenon and permit correlations with consequential effects on cardiopulmonary function.

1) Transmission of PEEP to the pleural space was attenuated at all pressure levels, the attenuation being greater as PEEP, and thus, FRC increased and Csp decreased. This finding is in accord with expansion of normal lungs above resting volume and the changing slope of Csp as maximal lung volumes are approached. PEEP transmission was minimal when FRC was close to total lung capacity (38) (Figs. 6 and 8), and from these data, it may be suggested that transmission of about 25–30% indicates that the limits of lung distensibility are being approached.

When PEEP is applied therapeutically to low FRC, low Csp lungs pleural transmission may increase at first as alveolar stability is improved. This would be followed by a fall in transmission as volume and distensibility limits of the lung are approached, as perhaps was the case in reported clinical studies (6, 21) in which 4–10 cm H_2O PEEP was used. An additional consideration pertains to abnormal lungs: Because of their lower-than-normal Csp, the minimal acceptable percent transmission may also be lower than normal. Additional studies are needed to establish this potentially useful clinical determination.

2) The variable transmission of PEEP also serves to reinforce the need to record "net" pressure in low compliance intrathoracic vessels (*e.g.*, atria and PA) rather than either "absolute" pressures or net pressures wherein 100% transmission is assumed. The potential errors are illustrated in Figures 10 and 11. It is obvious that pulmonary hypertension (net pressure) did not develop in our subjects, whereas RA net pressure did increase significantly. It may be suggested from these findings (but not from the absolute pressures) that RA and also right ventricular end-diastolic pressures are elevated by PEEP. This is not due to an afterloading stress on the heart (*e.g.*, pulmonary hypertension), but perhaps due to preloading or early myocardial decompensation. More definitive speculations cannot be made because CI of the study and control groups did not differ significantly.

3) It has been suggested that venous return to the thorax is impeded by transmission of PEEP to intrathoracic viscera (25, 27, 33, 35, 43, 44). For normal lungs and within the limits of our experimental protocol this does not seem to be the case: At the highest lung volumes and at the highest PEEP, Csp is lowest and pleural transmission is least. Thus, the fall of Csp has a protective effect on the cardiovascular system. Conversely, when PEEP is used for treatment of the low FRC, low Csp lung, pleural transmission should increase as PEEP increases and Csp improves. Thus, the effects of PEEP on venous return would be maximal when its therapeutic efficacy is maximal. These variations between PEEP, pleural transmission, and venous return may explain the wide diversity of results in the literature (14–18, 21, 24–27, 30, 33, 35, 37, 43, 44, 46, 47) and emphasize again the need to note pleural transmission of PEEP when evaluating its effects both in the clinical and laboratory settings.

EFFECTS OF PEEP ON RESPIRATORY RHYTHM

Application of PEEP produces bradypnea sometimes preceded by apnea; a pause between inspiration and expiration; and active preinspiratory expiratory efforts (Figs. 2–5).

Periods of apnea after PEEP have been reported by others (41, 42). The response is immediate and, thus, seems to be reflex in nature. Our studies indicate that this inhibitory effect, which is probably mediated through vagal afferents in response to stretch (41), produces bradypnea when PEEP is applied or changed slowly and apnea followed by bradypnea when the change is abrupt.

With increasing levels of PEEP, there develops a progressively longer delay between inspiration and expiration. This delay, which may be due to a postinspiratory contraction of the diaphragm as described by Gautier *et al.* (19), increases the period of the respiratory cycle and augments bradypnea. Because V_T increases during PEEP, but is not significantly different from control, it is apparent that bradypnea accounts for the reduction of minute ventilation.

Expiration, which becomes immediately preinspiratory especially at higher levels of PEEP, is active. The immediacy with which this occurs after PEEP suggests that it also is reflex in nature, perhaps related to stretching of the lungs as FRC is increased. In addition to increasing the work of breathing, active preinspiratory expiration could complicate and compromise mechanical ventilation of the lungs.

The inspiratory drive itself does not seem to be affected by PEEP. Thus, peak inspiratory flow rate, V_T, and inspiratory time do not change with increasing PEEP.

CONCLUSION

PEEP and its variations (CPAP, CPPB, CDP, CNP) have become widespread clinical therapy for improving oxygenation in patients with lung disease in which there is decreased FRC, decreased pulmonary C, and right-to-left shunting through nonventilated pulmonary segments. We have shown in spontaneously breathing healthy dogs that application of PEEP does not change heart rate, systemic arterial pressure or CI. Whereas PEEP increases FRC, in the healthy lung it causes alveolar overdistention leading to a fall in Csp, which may be associated with elevation of $PaCO_2$ and fall in pHa. PEEP does not cause net pulmonary hypertension, but may result in elevation of net RA pressure, possibly as an expression of either increased preload or myocardial decompensation. The degree to which PEEP affects CI will, in part, be dependent on the transmission of the applied airway pressure to the intrathoracic structures, which in turn is dependent on the Csp of the lungs. Highly compliant lungs will transmit most of the airway pressure to intrathoracic vessels, impeding venous return. Poorly compliant lungs do so less well, with little or no effect on CI. Csp, then, would seem to be a major parameter to be considered in the evaluation of the cardiopulmonary consequences of PEEP. PEEP also produces bradypnea, or apnea followed by bradypnea, and a dissociation of expiration from inspiration in which expiration becomes active and occurs immediately before the next inspiration. These effects seem to occur reflexly.

APPENDIX

Conventional measurement of CO using the Fick principle entails substitution in the formula

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

where $\dot{V}_{O_2}$ = O_2 consumption (ml/min), $C(a - \bar{v})\ O_2$ = arterial minus mixed venous O_2 content (ml/liter), and CO is expressed as liter/min.

For the purposes of our studies CaO_2 and $C\bar{v}O_2$ (aortic and pulmonary arterial blood, respectively) were determined directly before the start of each He rebreathing procedure for FRC measurement.

$\dot{V}_{O_2}$ during the period of rebreathing was estimated from the following equation:

$$\dot{V}_{O_2} = ViO_2 - V_fO_2$$

ViO_2 = total volume of O_2 initially available to the dog at the beginning of rebreathing, *i.e.*, the volume of O_2 in the rebreathing system plus the volume of O_2 in the dog's lungs. V_fO_2 = volume of O_2 remaining in the rebreathing system and in the lungs at the end of the rebreathing period. The total volume of gas in the lungs

at the beginning and end of rebreathing was taken as the calculated FRC. The rebreathing system included the rebreathing bag and apparatus dead space.

Estimation of ViO_2: The volume of gas in the rebreathing apparatus and the fractional content of O_2 (FO_2) in this gas were measured directly. The volume of gas in the lungs was the FRC and the F_AO_2 was calculated from the alveolar air equation. For the latter, it was assumed that P_ACO_2 equals $PaCO_2$ and that R equals 0.8. Because all lungs were normal by macroscopic examination postmortem, no significant arterial-alveolar CO_2 gradient was expected (49) and because all animals had been fasted 12 hr before study and had established regular breathing patterns for at least 15 min before each study, the authors believe that the assumed R is reasonable and comparable animal to animal.

Estimation of V_fO_2: This calculation was straightforward assuming that O_2 equilibration in the rebreathing system and lungs had been achieved in essentially the same time required for He equilibration during the rebreathing period. This assumption is probably correct, because reported differences in gas-mixing efficiency of a given lung for He and O_2 (45) should not have resulted in significant differences in equilibration times during the 60-sec periods of rebreathing. Thus, V_fO_2 was determined by direct measurement of FO_2 in the rebreathing apparatus and V_fO_2 equalled the product of (FO_2) and (total gas volume of rebreathing apparatus plus FRC).

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57. Model D helium analyzer, Quintron Instrument Co., Milwaukee, Wisconsin.
58. This research was supported by grants from the National Heart, Lung and Blood Institute, National Institutes of Health HL 16137 and HL 07060.
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60. Received for publication May 16, 1978.
61. Accepted for publication November 7, 1978

0031-3998/79/1310-1112 $02.00/0

Printed in U. S. A.