JCI The Journal of Clinical Investigation

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J Clin Invest. 1981;67(1):264-273. https://doi.org/10.1172/JCI110022.

Research Article

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ABSTRACT We studied the effects of continuous negative external chest pressure (CNECP) produced by a cuirass appliance on lung water and protein transport in sheep with chronic lung lymphatic fistulas. We compared data obtained during periods of mechanical ventilation (base line) to period of CNECP, using identical ventilatory support. Three groups were studied: six sheep were studied before and after application of CNECP for 1 h (control) and again after induction of a pulmonary vascular permeability defect (PVPD) by infusing live *Pseudomonas* bacteria (group I); another six sheep were studied under control conditions before and after prolonged application of CNECP for over 4 h (group II); 10 sheep were studied 24 h after a *Pseudomonas* infusion (PVPD), before and after 4 h of CNECP (group III).

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INTRODUCTION

Noncardiogenic pulmonary edema associated with adult respiratory distress syndrome (ARDS) is characterized by decreased functional residual capacity (FRC), abnormal gas exchange manifested by a high shunt fraction, and an increase in lung water (1, 2). An increased pulmonary capillary permeability to fluid and protein has been postulated as a pathogenetic mechanism leading to the above abnormalities (2–4). Positive end expiratory pressure (PEEP) has been found to improve lung compliance and to decrease shunt fraction, as a consequence of increasing FRC and reopening closed air spaces. However, PEEP may decrease venous return and cardiac output (Q), and may produce barotrauma from high intra-alveolar pressure (5–7). Thus, the use of PEEP is limited in certain cases of ARDS. During ventilation with PEEP the transvascular flux of lung water has been found either to be increased (8) or to be unchanged (9–14).

Continuous negative external chest pressure (CNECP) applied around the chest and upper abdomen can also move the lungs to a higher position on their static pressure volume curve and produce an increase in functional residual capacity. CNECP has been found to be useful in the clinical management of neonates, adolescents, and adults with noncardiogenic pulmonary edema (15–20). Krumpe et al. (21, 22) and Phillips et al. (23) have shown that CNECP offers the advantage of improved cardiac output compared to PEEP at identical increase in FRC. However, the more negative pleural and interstitial pressures during CNECP might result in increased filtration of fluid into

the lung's interstitium, making the pulmonary edema worse.

The purpose of the present study is to document the effects of CNECP on lung compliance, hemodynamics, gas exchange, and lung transvascular water and protein transport in an animal model of increased capillary permeability, and to show how the prolonged application of CNECP affects lung water content.

GLOSSARY OF SYMBOLS

A-aDO_2	Alveolar to arterial oxygen tension gradient
ARDS	Adult respiratory distress syndrome
CNECP	Continuous negative external chest pressure
FRC	Functional residual capacity
P_{alv}	Alveolar pressure
P_{AW}	Airway pressure
PBV	Pulmonary blood volume
PEEP	Positive and expiratory pressure
P_{La}	Left artrial pressure
P_{Pa}	Pulmonary artery pressure
P_{Pl}	Pleural pressure
P_{TV}	Transvascular pressure
PVPD	Pulmonary vascular permeability defect
Q	Cardiac output
Q_L	Lung lymph flow
Q_P	Net pulmonary transvascular albumin transport
R_{PV}	Pulmonary transvascular resistance
V	Volume
V_T	Tidal volume

METHODS

In cross-bred range sheep, we prepared chronic lung lymphatic fistulas by the method of Staub et al. (24). Animals ranged in age from 7 to 16 mo, and weighed between 35 and 50 kg. We cannulated the efferent duct of the caudal mediastinal lymph node at least 5 d before study. This node drains lymph from ~2/3 of the total lung mass (12).

At least 2 d before study, we entered the left thorax and placed cannulas in the pulmonary artery and left atrium. At that time, cannulas were also placed in the carotid artery and internal jugular vein. All thoracotomy incisions were closed in layers and were well healed at the time of experimental study.

To apply negative body surface pressure to the chest and upper abdomen, we fabricated a cuirass with rigid fiberglass and polyurethane material. Sheep were positioned prone in the cuirass, with their sterna resting on a wire support (Fig. 1). Group 1 animals were studied supine (see below). The cuirass was sealed by placing both sheep and cuirass inside a 4-ml plastic bag. After shearing the animal's neck and abdomen, the bag was loosely sealed with 3-in. duct tape. CNECP was produced by connecting a vacuum sourse to a side port on the cuirass. Negative pressures within the cuirass ranged from −60 to −80 cm H_2O. The vacuum source was sufficient to overcome leaks into the cuirass and prevent fluctuations in CNECP, as evidenced by stable end expiratory pleural pressure throughout periods of CNECP. On the day of study, sheep were sedated with intravenous sodium

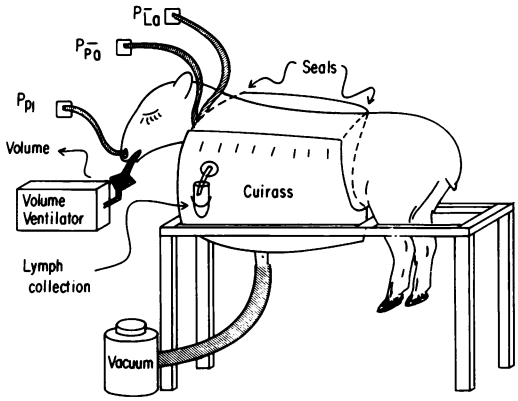

FIGURE 1 Apparatus for study of CNECP in sheep. Seals around cuirass are indicated by dashed lines. Negative pressure of −60 to −80 cm H_2O within the cuirass is produced by vacuum source. Vascular pressure cannulas, esophageal balloon, and lymph cannula are indicated. The lymph cannula exits the cuirass via a 5-Mm hole and is sheathed by a thick walled polyethylene cannula before penetrating the plastic sealing bag.

thiamylal (Serital, Parke-Davis, Div. of Warner-Lambert Co., Morris Plains, N. J.), endotracheally intubated, and mechanically ventilated using 98% oxygen, 2% halothane anesthesia. A 5-cm latex balloon was positioned in the midesophagus to measure pleural pressure (P_{pl}). We measured pulmonary artery pressure (P_{Pa}), left atrial pressure (P_{La}), airway pressure (P_{AW}), and transpulmonary pressure (P_L) using calibrated transducers. Air flow was determined using a heated sieve screen pneumotachygraph (Physiotronics Inc., Houston, Tex.), and electronically integrated to yield volume (V). These data were continuously monitored using a VR-12 optical recorder (Electronics for Medicine, Inc., Pleasantville, N. Y.). Lung volume at FRC was determined by helium dilution; change in FRC produced by applying CNECP was measured by noting the increase in end expiratory lung volume. We recorded static pressure-volume curves using a calibrated 3-liter syringe. Static lung, chest wall, and total thoracic compliances were calculated in the tidal breathing range.

Cardiac output (Q) was determined using indocyanine green dye (25). We injected dye in either the pulmonary artery or left atrium. Blood was aspirated from the carotid artery at 38 ml/min (pump model 950, Harvard Apparatus Co., Millis, Mass.). Dye density was measured with a flow-through densitometer (Guilford Instrument, Oberlin, Ohio).

Pulmonary blood volume (PBV) was determined from Q and the pulmonary transit time of blood (26): PBV = Q × ($CT_{PA-->C}$ − $CT_{LA-->C}$), where $CT_{PA-->C}$ = circulation time of dye from pulmonary artery to carotid, and $CT_{LA-->C}$ = circulation time of dye from left atrium to carotid; the circulation times were measured from the bolus injection to the peak of dye concentration in the carotid artery (26). In seven animals arterial O_2 tension was measured using an IL-113 blood gas analyzer (Instrumentation Laboratory, Inc., Lexington, Mass.) and A-a DO_2 was estimated, assuming $PAO_2 = P_B - P_{halothane} - PH_2O - 1.2\ PaCO_2$.

Lymph was collected in heparinized graduated tubes over 15-min intervals, and flow (Q_L) expressed as milliliters per hour. Lymph collections were pooled over 30-min intervals for subsequent biochemical analysis. Plasma samples were obtained every 60 min. Total protein and albumin concentrations

TABLE I
Summary of Measurements and Calculated Data

Type	Measured data*	Derived or calculated data
Lung mechanics	P_L, P_{pl}, P_{AW}, VC, FRC, V_T	Lung and chest wall compliance, subdivisions of lung volume.
Hemodynamics and gas	P_{Pa}, P_{La}, $\dot{Q}$, PaO_2, PBV	A-aDO_2, transport in grams per hour pulmonary vascular resistance, PBV
Lung lymph kinetics	$\dot{Q}_L$, $(Albumin)_L$, $(Albumin)_p$ $\dot{Q}_p$	Lymph/plasma albumin ratio.
Lung water content	Wet/dry weight Histologic evaluation	Extravascular lung water after CNECP.

in lymph and plasma samples were measured in the clinical laboratories of either the Veterinary Medicine Teaching Hospital, University of California at Davis (SMA-12 Auto-Analyzer) or the Martinez Veterans Administration Medical Center (ACA Auto-Analyzer).

At the end of four studies, the sheep was removed from the cuirass, the thorax rapidly entered by median sternotomy, and the hilus cross-clamped. One lung was then taken for gravimetric wet/dry weight determination by the method of Pearce et al. (27), as modified by Cross et al., (28); the other lung was used for histologic studies.

The above data were used to calculate derived parameters for comparison of pulmonary mechanics, hemodynamics, lung transvascular water and protein transport, and extravascular lung water content under baseline and CNECP conditions (Table I).

Sheep were divided into three groups on the basis of experimental protocol (Table II). We studied animals under control conditions (groups 1 and 11) and after producing a pulmonary vascular permeability defect (PVPD) by infusing live *Pseudomonas aeruginosa* organisms (groups I and III) (29). In every animal, parameters were measured before (base line) and after application of CNECP. Our initial observations were made in group I. Group II was studied to allow Q_L to reach a steady state after prolonged application of CNECP. Group III was included because a stable pulmonary vascular lesion may not be present until several hours after *Pseudomonas* infusion. The natural history of this lesion suggests that vascular permeability would be increased, and unchanging 24 h after infusion (29). Previous work by Dr. Gorin has demonstrated that Q_L remains constant during halothane anesthesia in the absence of CNECP for 4–6 h (Table III) (30). Details of preparation and study of group III sheep are shown in Fig. 2.

Mean values for these groups are expressed ±SEM. Statistical comparison of parameters measured before and after application of CNECP were made using the Student's *t* test for correlated means. Differences were considered significant if P was <0.05.

TABLE II
Experimental Protocols

Group	Observation times: controls		Period of stabilization after *Pseudomonas* infusion	Observation times: post-*Pseudomonas*	
	Base line	CNECP		Base line	CNECP
	h		*h*	*h*	
I $n = 6$	1	1	2	1	1
II $n = 6$	2	3–5	—	—	—
III $n = 10$	—	—	24	2	3–5

Values are hours during each period of study.

RESULTS

Mechanics and hemodynamics

An increase in FRC, decrease in vascular and pleural pressures, and change in compliance in the tidal breathing range occurred immediately after the onset of CNECP (Fig. 3). No differences in these parameters were noted between the group I and II control sheep or between the I and III *Pseudomonas*-treated sheep. Therefore, combined data is presented in Tables IV–VI for all control studies (groups I and II) and all studies after induction of a vascular permeability defect (groups I and III). FRC volume increased from 43±4 to 60±3% of TLC in *Pseudomonas*-treated sheep ($P < 0.05$). PBV (measured in seven group III animals) decreased from 251±26 to 195±16 ml ($P < 0.05$). Thus, the thorax contained more gas and less blood after CNECP.

Compliance

In Fig. 4 the static pressure volume curves for the lung (Fig. 4A) and total respiratory system (Fig. 4B) are plotted for a typical sheep from group II. Mean changes in compliance after CNECP appear in Table IV. Lung compliance increased by >2 cm H_2O in 8 of 11 control and 9 of 16 *Pseudomonas*-treated sheep and total respiratory compliance increased in 7 of 11 control and in 3 of 16 *Pseudomonas*-treated sheep. However, mean data after CNECP was not significantly different from base line in either group. Chest wall compliance fell in 9 of 11 control and 15 of 16 *Pseudomonas*-treated sheep ($P < 0.05$).

TABLE III
*Lung Lymph Flow during Prolonged Halothane Anesthesia without CNECP**

Number	Hours 1	2	3	4	5	6
n			*ml/h*			
11	3.85±1.78	3.78±1.92	3.55±2.15	3.45±2.15		
10	3.86±1.87				3.30±1.90	
5	2.45±1.09					2.45±0.66

Mean±SEM for each time period.
* Sheep were studied in the prone position during intermittent positive pressure breathing after sedation and anesthesia (as described in the text). Observations were continued in 11 sheep for 4 h, in 10 of these 11 sheep for 5 h, and in 5 of the 11 for 6 h. Lung lymph flows did not change significantly in any sheep during prolonged anesthesia without CNECP.

Vascular, pleural, and transvascular pressures

Significant decreases ($P < 0.05$, paired t test) occurred in both control and *Pseudomonas*-treated groups for mean pulmonary artery, left atrial, and pleural pressures (Table V). During prolonged exposure to CNECP for 3–4 h a further decrease in P_{Pa} occurred, as shown in Fig. 5 for 10 sheep in group III. An immediate increase in P_{Pa} occurred when CNECP was stopped. Only one of 22 sheep studied had an increase in P_{La} (+2 cm H_2O). Transvascular pressure (P_{TV}) across the pulmonary artery ($P_{Pa} - P_{pl}$) decreased in 6 of 11 control and 7 of 15 *Pseudomonas*-treated sheep. Group mean changes in P_{TV} were not significantly different from base line although a trend toward a small decline in P_{TV} occurred in both control and *Pseudomonas*-treated sheep.

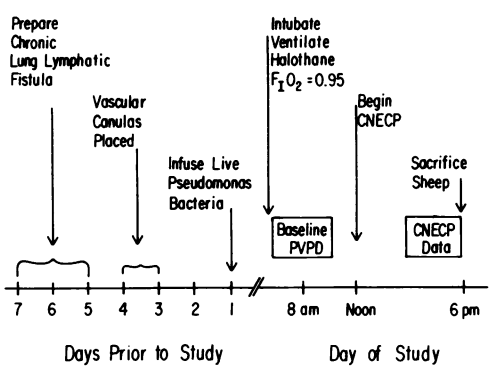

FIGURE 2 Study design for group III animals: the sequence of preparation of animals induction of a pulmonary vascular permeability defect by infusion of live *Pseudomonas* bacteria, and physiologic studies before and after CNECP (during a period of steady-state lymph flow [Table V]) are indicated.

Cardiac output

After CNECP cardiac output decreased 17.5±8.49% (mean±SEM) of base-line values, whereas the pulmonary vascular resistance (R_{PV}) increased 29.6±12.7% (mean±SEM) of base-line values (Table IV).

Cardiac output fell by 0.1 liters/min or more in 6 of 8 control and 7 of 13 *Pseudomonas*-treated sheep. Although P_{Pa} and P_{La} each fell, $P_{Pa} - P_{La}$ remained unchanged after CNECP. A significant correlation was present between change in Q and change in R_{PV} (regression coefficient = 0.77, $P < 0.001$) (Fig. 6).

A-a D_{O_2} on 98% oxygen decreased from 203±29 to 122±24 mm Hg in seven sheep in which arterial blood gas data was available ($P < 0.05$).

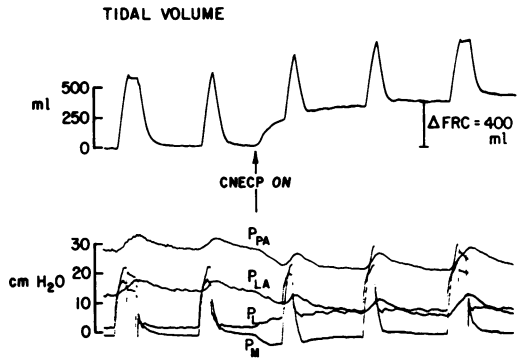

FIGURE 3 Time-based recording (20 s) of tidal volume and pressure measurements before and after CNECP. After CNECP and immediate increase in FRC of 400 cc occurs; mean pulmonary artery, left atrial and mouth pressures (P_m) all fall. At the higher FRC during CNECP lung recoil pressure is increased, while mouth pressure remains atmospheric. Lung and total respiratory system compliance during tidal breathing both decrease after CNECP (first vs. fifth breath), and peak inflation pressure is higher.

TABLE IV
Static Lung, Total Respiratory System, and Chest Wall Compliance Changes during CNECP

	Lung compliance	Total respiratory system compliance	Chest wall compliance
		cm³/cm H₂O	
Controls*			
Base line	45.8±4.5	26.9±2.4	79.9±12.7
CNECP	59.7±5.4	28.9±4.1	58.6±11.2
P value	NS	NS	<0.05
Pseudomonas‡			
Base line	38.3±2.8	25.1±1.4	83.0±8.2
CNECP	41.8±5.5	24.5±3.3	59.8±7.7
P value	NS	NS	<0.05

Values are mean±SEM.
* Groups I and II, n = 11; compliance was not measured in one animal.
‡ Groups I and III, n = 16.

Water and protein transport

Lymph flow. In acute studies performed after infusion of live *P. aeruginosa*, we noted progressive fall in Q_L during the first 30–60 min after application of CNECP. This finding prompted inclusion of groups II and III in the investigation. When we included a longer observation period during CNECP, a trend toward stabilization of Q_L became more apparent. In most animals, steady-state lymph flow (defined as a variation in Q_L of <1 ml/h) was reached within 1 h after the onset of CNECP. Table VI compares lymph flow during the entire CNECP period, to these periods of steady-state lymph flow. In groups II and III, an excess lymph flow was seen in the first 1 h after CNECP compared to the steady-state period. No effects of CNECP on Q_L was seen in group I animals (Table VII), perhaps because of this failure to reach steady-state lymph flow. CNECP significantly reduced Q_L in all studies (groups II and III) where CNECP was applied for 3–4 h.

Pulmonary transvascular albumin transport. Net pulmonary transvascular albumin transport (Q_p) also fell significantly after prolonged application of CNECP in both controls and sheep with PVPD (Table VII). This effect was not seen in group I animals. The difference between group I post-*Pseudomonas* and group III data is presumably due to the failure of group I to reach a steady-state during the shorter period of CNECP. Lung/plasma albumin ratios did not change appreciably after CNECP in any group (Table VII).

Lung water content

Histology. Postmortem tissue was obtained for histologic study in four group III animals. In two animals, lung tissue was fixed in vivo by transthoracic needle puncture and instillation of 10 ml of 2.5% glutaraldehyde in indocyanine green under low pressure. This was done in one sheep during CNECP, and in another immediately after cessation of CNECP. In two more animals, tissue was fixed by perfusing the lung via the pulmonary artery with 2.5% glutaraldehyde at 25 cm H_2O pressure. The pulmonary hilus in these animals were cross-clamped within 10 min of cessation of CNECP.

Routine histology revealed minimal inflammatory changes and no evidence of pulmonary edema (Fig. 7).

Gravimetric wet weight/dry weight ratio. In four group III animals the mean extravascular lung water/dry weight of the lung was found to be 4.60. This was not significantly different from the value of 4.80 reported by Brigham et al. for nine sheep who had received pseudomonas infusion but had not been exposed to CNECP (30). The wet/dry ratios in our group III sheep were higher than laboratory control sheep

TABLE V
Hemodynamic Changes during CNECP

	P_{Pa}	P_{La}	P_{pl}	P_{TV}	Q	R_{PV}
			cm H₂O		*liters/min*	*liters/min/cm H²O*
Controls*						
Base line	25.5±2.15	5.34±1.87	−1.25±0.33	26.7±2.26	2.22±0.33	11.1±2.05
CNECP	18.7±2.50	−0.82±1.09	−5.58±0.43	23.9±2.05	1.64±0.28	14.9±3.72
P value	<0.05	<0.05	<0.05	NS	<0.05	NS
Pseudomonas‡						
Base line	27.3±1.65	7.77±1.11	−1.59±0.31	28.6±1.84	2.19±0.28	15.0±5.29
CNECP	20.7±1.53	1.14±1.12	−5.87±0.65	25.7±1.66	1.94±0.26	12.8±2.30
P value	<0.05	<0.05	<0.05	NS	<0.05	NS

Values are mean±SEM.
* Groups I and II.
‡ Groups I and III.

TABLE VI
Time-course of Change in Lymph Flow during Application of CNECP

	Lymph flow for total period*	Lymph flow during steady state‡	*P* value
	ml/h		
Controls (group II)	4.95±1.01	4.13±0.79	<0.05
Pseudomonas (group III)	9.59±1.66	8.11±1.48	<0.005

Values are mean±SEM.
* Total period, including data from first 1 h after the onset of CNECP.
‡ Lymph flow during steady state period excluding data from the first 1 h after CNECP. *P* values compare lymph flow for the total period to lymph flow during steady state.

that had been exposed to neither pseudomonas nor CNECP (4.13). However this increase reflects only a 2% increase in fractional water content of the lung (Fig. 8).

DISCUSSION

After the application of CNECP we noted a significant decrease in transvascular water and protein transport (Fig. 9). These changes were large enough to constitute a reversal of the PVPD produced by infusion of live *Pseudomonas* bacteria. The changes after CNECP reported for groups II and III were not observed during prolonged anesthesia in preliminary studies (Table III) and therefore were attributed to the effects of CNECP.

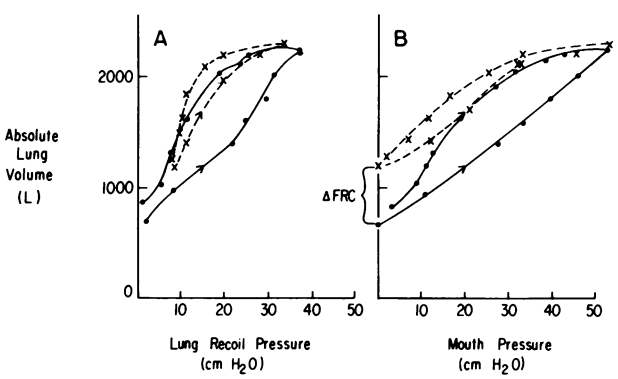

FIGURE 4 Static pressure volume curves of the lung (A) and the total respiratory system (B) are plotted. Baseline curves are shown by solid lines (O); post CNECP curves are shown by dashed lines (×). Since both curves were measured simultaneously, the increases in FRC are identical. Static compliance is reflected by the slope of inspiratory limb of these curves over the tidal range.

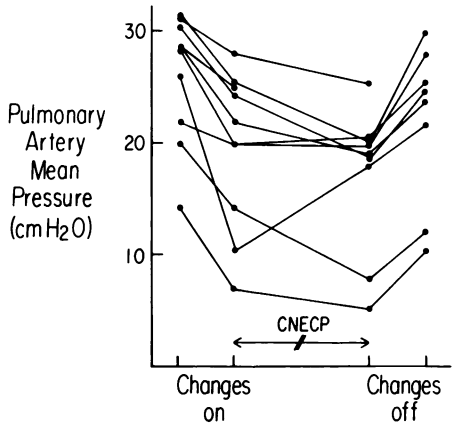

FIGURE 5 Pulmonary artery mean pressures for group III sheep before, immediately after application of CNECP, and after 3–4 h of exposure to CNECP. Significant decreases in P_{Pa} occur during CNECP; P_{Pa} increases toward control levels when CNECP is removed. $P < 0.05$.

The validity of these findings depends upon the extrapolation from lymph flow data to events occurring at the endothelial membrane. Recent studies have demonstrated that lymph is not concentrated as it drains from the lung, therefore lymph albumin concentration approximates that of filtered fluid (31–33). However, changes in lymph flow may lag behind step changes in microvascular pressures produced by CNECP. In groups II and III an excess lymph flow averaging 6 ml/h

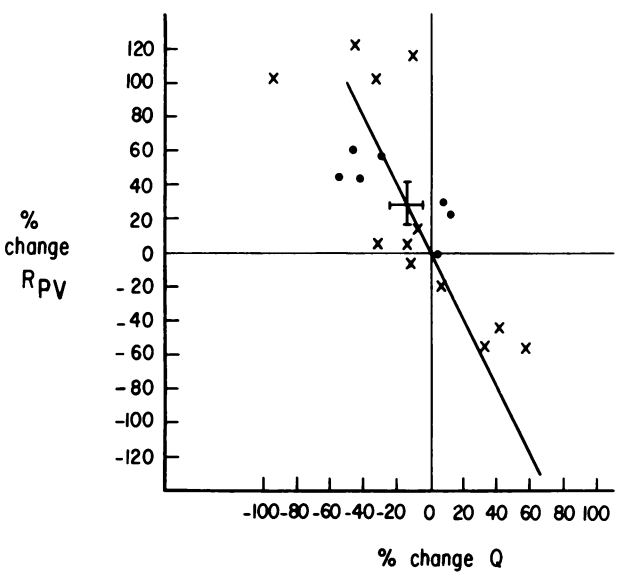

FIGURE 6 Changes in (R_{PV}) after CNECP (percentage of base-line values) are plotted vs. changes in Q after onset of CNECP (percentage of base-line values). The linear regression is plotted ($r = -0.77$, $P < 0.05$), and mean±SEM for both Q and R_{PV} as shown. ×, *Pseudomonas*-treated; ●, control.

TABLE VII
Lymph Flow and Protein Transport during CNECP

	Q_L*	Protein transport	Lymph to plasma albumin concentration
	ml/h	*g albumin/h*	
Controls			
Group I (6)			
Base line	16.1±2.5	0.254±0.026	0.617±0.034
CNECP	14.2±1.8	0.233±0.025	0.658±0.051
P value	NS	NS	NS
Group II (6)			
Base line	8.1±2.3	0.142±0.014	0.702±0.053
CNECP	4.1±0.8	0.083±0.013	0.678±0.051
P value	<0.05	<0.05	NS
Pseudomonas			
Group I (6)			
Base line	26.1±4.5	0.449±0.015	0.755±0.037
CNECP	23.1±5.4	0.389±0.021	0.734±0.017
P value	NS	NS	NS
Group III (10)			
Base line	11.8±2.0	0.248±0.039	0.725±0.026
CNECP	8.1±1.5	0.139±0.022	0.717±0.034
P value	<0.05	<0.05	NS

Values are mean±SEM.
* Q_L for group I is reported for the entire period of CNECP, since this data did not differ from steady-state flow data; Q_L for Groups II and III is reported for steady-state period only (Table V).

occurred during the first hour of CNECP compared to eventual steady-state Q_L. We speculate that this "lymph surplus" resulted from a decrease in the volume of the interstitial compartment during CNECP. Q_L might have decreased if edema formation occurred during steady-state condition; however, no evidence of intrapulmonary lymphatic dilation (Fig. 7) or unusual increase in extravascular lung water/dry weight ratio (Fig. 8) occurred during CNECP. Fluid did not appear to be sequestered in the lungs during CNECP. Q_L might also have fallen if mechanical obstruction of the lymph cannula occurred during CNECP. However, in this event an immediate fall in Q_L would be expected rather than the gradual decrease we observed. These findings support our conclusion that the falls in Q_L and Q_p do reflect decreases in fluid and protein transport occurring at the endothelium.

It is very unlikely that CNECP would cause an immediate "structural" change in the vessel wall. The falls in Q_L and Q_p might result from either a reduction in the convective force driving transvascular flux, or a reduction in the total surface area available for solute and water exchange. We documented a decrease in pulmonary blood volume in all animals where this parameter was measured. This might be expected in a setting where P_{Pa} and P_{La} fall, and P_{TV} remains constant (Table V, 34). Total vascular surface area should decrease as blood volume decreases. The method we used to measure PBV is flow dependent, therefore changes in PBV might be due to changes in Q or P_{Pa}. However, since it is improbable that bulk flow occurs in nonperfused vessels, we consider that all the PBV involved in fluid-filtration was measured.

In three animals, Q increased and R_{PV} fell (Fig. 6). In these animals a greater fraction of the pulmonary

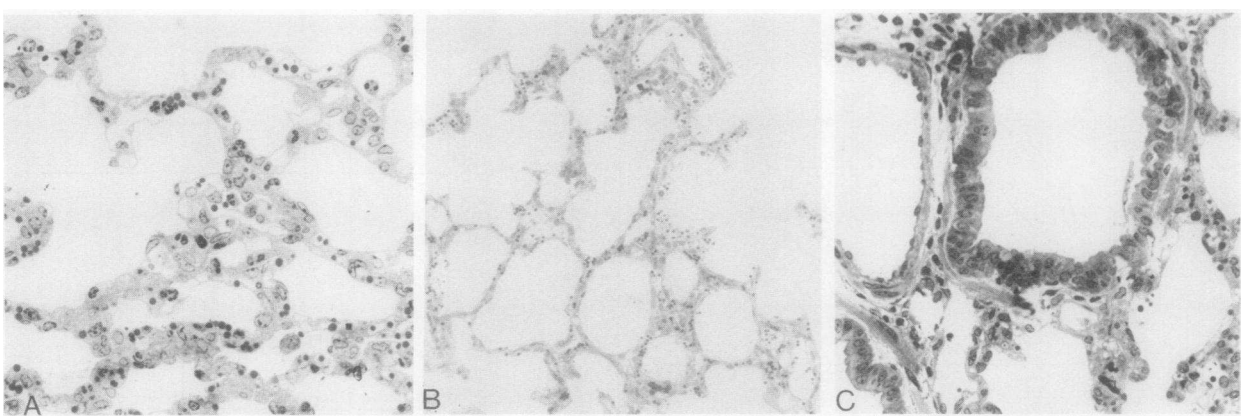

FIGURE 7 Sheep lung after *Pseudomonas* bacteremia and CNECP. (A) S-12-78. Lung removed from chest and perfused with 2.5% glutaraldehyde via the pulmonary artery at 20 cm H_2O pressure. There is no evidence of peribronchial "cuffing" or increase in the volume of peribronchial connective tissue secondary to edema formation. ×250. (B) Lung fixed by transthoracic needle puncture and local instillation of 2.5% glutaraldehyde in indocyanine green dye while on CNECP. The lung is essentially normal. The absence of septal thickening, or hyaline membrane formation is apparent. ×40. (C) S-6-78. Fixed as in A immediately after CNECP. The lung is essentially normal. Apparent increase in septal thickness is due to lung being fixed at a lower FRC off of CNECP. ×250.

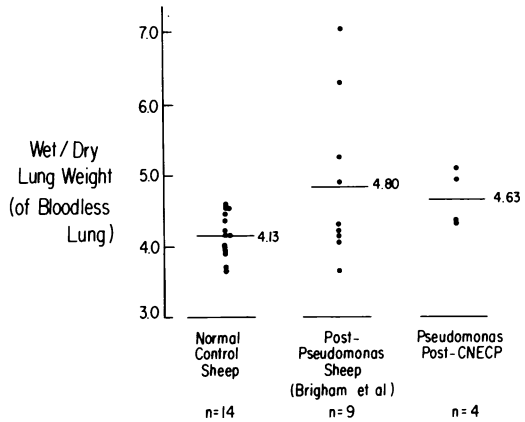

FIGURE 8 Gravimetric determination of extravascular lung water, expressed as fraction of dry lung weight, for normal sheep studied in our laboratory, for *Pseudomonas*-treated sheep reported by Brigham et al. (48), and for four *Pseudomonas*-treated sheep from group III after exposure to CNECP for 4 h. Extravascular lung water/dry weight ratios for the *Pseudomonas*-treated groups were identical; both were slightly increased compared to normal sheep. Exposure to CNECP did not increase lung water.

capillary bed, and therefore a larger cross-sectional area of vessels must have been perfused (35). In these three animals, Q_L and Q_p fell despite this increase in surface area available for fluid and protein transport.

In the lung, transvascular solute flux is impelled by both convective and diffusive forces. In the presence of an injured capillary endothelium and increased pulmonary vascular permeability, transvascular fluid, and protein transport is determined to a greater extent by hydrostatic pressure gradients across the vessel and to a lesser extent by oncotic forces (30). MacNamee and Staub (36) have recently presented evidence that even under conditions of normal vascular permeability, convection predominates. After *Pseudomonas* infusion, microvascular hydrostatic pressure is usually elevated, whereas the concentration gradient for macromolecules is normal or decreased (30). A mechanical drop in P_{Pa} produced by application of CNECP should therefore decrease both solvent and solute flow across the endothelium.

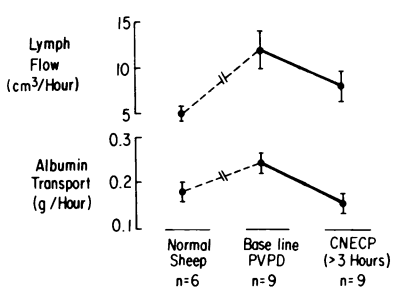

FIGURE 9 Mean±SEM (bars) data for lymph flow and protein transport are shown for normal control sheep (group II) under baseline conditions, and for *Pseudomonas*-treated sheep after the induction of a PVPD in group III sheep, before and after CNECP. $P < 0.05$ for all changes.

How does CNECP produce a fall in vascular perfusion pressures? CNECP may alter vascular pressures by direct transmission of more negative pleural pressure to pulmonary vessels. The decrease in pleural pressure during CNECP was completely transmitted to P_{Pa} in 9 of 26 studies; in another 13 of 26 studies P_{Pa} decreased by more than P_{pl}. In the latter sheep the decrease in P_{TV} implies that mechanisms in addition to the direct transmission of P_{Pl} to P_{Pa} must be present. At a higher end expiratory lung volume, CNECP conceivably could lower R_{PV} by recruitment or distention of vessels so that for a given cardiac output P_{Pa} would fall (37). Our observations suggest vascular interdependence during lung inflation (38, 39). In addition CNECP could reduce Q and therefore reduce P_{Pa} for a given R_{PV}. In any specific study a combination of these factors could be operational.

Lynch et al. (40) reported that changes in intrapulmonary shunting in dogs with pulmonary edema after oleic acid administration varied directly with changes in Q. They attributed this to the possibility that vessels injured by oleic acid might have a lower compliance and thus be derecruited preferentially when perfusion pressures fell. This suggests a mechanism by which the falls in P_{Pa} observed during CNECP in our group III animals might shift pulmonary blood flow from injured to more normal vessels. P_{Pa} fell during application of CNECP in all sheep, even though Q increased in three.

Although P_{Pa} fell in every animal during CNECP, P_{pl} also fell, so that no significant change in P_{TV} occurred. Is P_{TV} the relevant pressure to consider when discussing vascular distention and transvascular fluid flux at the exchanging vessels in lung? Permutt (34) has recently reviewed data that demonstrates that P_{TV} is both the luminal distending pressure and the force driving fluid filtration in extra-alveolar vessels. Although several authors have shown that fluid can be filtered from the pulmonary circulation at extra-alveolar sites (41, 42), and Pietra et al. (43) have demonstrated increased permeability of the bronchial circulation during endotoxin shock, the majority of capillary surface available for fluid exchange in the pulmonary vascular bed lies within the alveolus. It is these vessels that have been shown to have increased permeability after endotoxin administration (43). The alveolar capillary bed is influenced less by P_{TV} than by $P_{Pa} - P_{alv}$. Woolverton et al. (14) studied the effects of PEEP on lung fluid balance in sheep with chronic lung lymph fistulas, and reported that increases in P_{alv} were almost completely transmitted to P_{Pa} (14). Although the lung was maintained in zone III by raising P_{La}, they found no increase in fluid filtration after P_{Pa} was increased by

PEEP. They concluded that increased P_{alv} was transmitted to the perimicrovascular fluid surrounding exchanging vessels so that no change in hydrostatic forces across the alveolar capillary occurred. In contrast to PEEP, during application of CNECP, P_{Pa} falls, whereas P_{alv} remains atmospheric, thereby producing a decrease in convective forces across septal microvessels.

Could decreases in P_{pl} caused by CNECP lower interstitial pressures in the lung? This is likely only when airway obstruction is present. Airway patency appears to be an important factor in preventing transmission of negative pleural pressures to the perimicrovascular mileau (44–46). Increases in FRC during application of CNECP should open previously closed airways, decreasing the extent to which negative P_{pl} effects fluid exchange at the alveolus. The decrease in A-aDO_2 we noted during CNECP supports the idea that airways were splinted open at increased FRC in our sheep.

In previous studies, we reported that Q decreased to a lesser extent during CNECP than during PEEP. We attributed this difference to the impedance of venous return caused by the higher intrathoracic pressures seen during PEEP. However, Q decreased in 13 of 17 of our present studies. This fall in Q was due to the effects of the higher inflation pressure observed during tidal breathing while on CNECP (compared to baseline periods). Chest wall compliance decreased in all sheep probably as a result of impingement of the cuirass on the chest wall. This stiffening of the chest wall contributed to an increase in peak inflation pressures in many sheep (Fig. 4). We did not attempt to adjust the Δ FRC or the V_T delivered by the ventilator during CNECP to optimize Q (in a manner analogous to best PEEP [47]), nor did we attempt to defend Q by increasing vascular volume to offset the reduction in venous return, caused by higher inflating pressures. These maneuvers would be relevant to the clinical application of CNECP in patients with ARDS.

Other interventions have been shown to result in decreases in Q_L and Q_p in sheep: pulmonary artery infusion of isoproterenol, aminophylline, diphenhydramine, and prostaglandin E_1 all decrease lung lymph and protein clearance (48–50). The mechanisms of action of these agents are unknown; however, each produces pulmonary vasodilation and reduces P_{Pa}. In patients with ARDS, Zapol and Snider (51) have found that elevated P_{Pa} is a poor prognostic sign. Fluid restriction to lower pulmonary artery and pulmonary capillary wedge pressures has been found to be a useful management strategy in ARDS patients (2, 3, 5, 6). Unfortunately, the side effects of the previously mentioned pharmacologic agents are potentially harmful to critically ill patients, and the strategy of fluid restriction in ARDS patients is often limited by renal and cerebral hypoperfusion (5–7). CNECP offers a simple mechanical alternative to these approaches. Like PEEP, CNECP increases FRC, but CNECP also decreases P_{Pa} and PBV. These changes are associated with decreased surface area for fluid exchange and decreased convective flux of water in the microvessels; both will decrease the rate of edema formation in the lung. These unique physiologic advantages of CNECP may benefit patients with ARDS.

ACKNOWLEDGMENTS

This work was supported by the Veterans Administration and by a grant from the American Lung Association. The authors acknowledge the assistance of John Gould during sheep surgery, Curtis Williams, Martinez Veterans Administration Medical Center, for performance of most of the protein assays, and of Elaine Yeager and Bette Laccoarce for manuscript preparation.

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