

Pulmonary Effects of Crystalloid and Colloid Resuscitation From Hemorrhagic Shock in the Presence of Oleic Acid-induced Pulmonary Capillary Injury in the Dog

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The effects of resuscitation with crystalloid and colloid solutions in the presence of increased pulmonary capillary permeability were studied. Twenty-four hours after oleic acid administration, dogs were anesthetized and bled to produce hemorrhagic shock. One hour later, resuscitation was performed with saline, 5% albumin, or 6% hydroxyethyl starch solution to restore and then maintain cardiac output at pre-oleic acid values for 6 h. Dogs were recovered and, 24 h later, were reanesthetized for final measurements. Oleic acid administration resulted in increases in pulmonary artery pressure, pulmonary vascular resistance, and extravascular lung water (EVLW). Resuscitation from hemorrhagic shock restored pulmonary hemodynamics to pre-hemorrhage levels and did not affect EVLW, P_{aO_2} , shunt fraction, dead-space-to-tidal-volume ratio, or pulmonary compliance. There were no differences in these parameters related to the choice of resuscitation fluid. Saline resuscitation markedly reduced plasma oncotic pressure and the plasma oncotic-pulmonary artery occlusion pressure gradient. Values for these two variables were markedly lower with saline than with colloid resuscitation. The authors conclude that the pulmonary effects of crystalloid and colloid solutions are similar in the presence of moderate increases in pulmonary capillary permeability. (Key words: Fluid balance. Lung: function; pulmonary edema. Measurement techniques: lung water. Protein: albumin. Shock, hemorrhagic: colloid; crystalloid; Resuscitation.)

INTRAVENOUS FLUID administration is the basis of resuscitation from hypovolemic shock. When given in sufficient quantity, all fluids will restore circulating intravascular volume. The major risk associated with fluid resuscitation is the development of pulmonary edema with subsequent compromise in pulmonary function. The importance of colloid oncotic pressure in preventing pulmonary edema remains controversial.¹ Some authors believe that maintenance of colloid oncotic pressure or the gradient between colloid oncotic pressure and pulmonary artery occlusion pressure is essential during fluid resuscitation, and that administration of crystalloid solutions will decrease colloid oncotic pressure and induce pulmonary edema.²⁻⁹ Other authors argue that colloid solutions do not decrease pulmonary

edema, and may be hazardous in the presence of altered capillary permeability.¹⁰⁻¹²

The effects of crystalloid and colloid solutions on pulmonary function have been extensively studied.^{1,8,10-27} However, there remains no consensus as to which type of fluid is clinically superior. Previous studies have not been applicable to the clinical setting, since they have lacked one or more of the following three features: hypovolemic shock with increased pulmonary capillary permeability, resuscitation according to strict hemodynamic parameters, and evaluation of the long-term (*i.e.*, 24 hours) effects of resuscitation. The present study was, therefore, designed to include these three features. We compared a crystalloid solution (0.9% sodium chloride) with two colloid solutions (5% albumin and 6% hydroxyethyl starch) for resuscitation from hemorrhagic shock in a canine model of increased pulmonary capillary membrane permeability due to previous oleic acid administration. Oleic acid produces a predictable and stable model of pulmonary edema, with the maximum effect occurring 24 h following oleic acid administration.²⁸ The accumulation of excess extravascular lung water in this model has been shown to be caused by pulmonary capillary endothelial injury, without increases in pulmonary hydrostatic pressure.²⁹⁻³⁴ During the stable phase of increased capillary permeability, hemorrhagic shock was produced. Resuscitation from hemorrhage was designed to rapidly restore normal systemic hemodynamics. The results of this study indicate that crystalloid and colloid containing solutions have equivalent effects on pulmonary function and extravascular lung water.

Materials and Methods

DAY 1: INDUCTION OF PULMONARY CAPILLARY DAMAGE

Eighteen adult mongrel dogs weighing 20-32 kg (average 25.3 kg) were anesthetized with 30 mg/kg pentobarbital, *iv*. Following tracheal intubation with a cuffed endotracheal tube, they were mechanically ventilated with 100% oxygen at a tidal volume of 15 ml/kg and a rate adjusted to maintain an end-tidal CO_2 of 38-42 mmHg. A 7.5F quadruple-lumen flow-directed thermistor-tipped pulmonary artery catheter (Ameri-

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can Edwards VIP Model 93A-131H, Santa Ana, CA) was inserted via right external jugular vein cutdown. Heart rate (HR), central venous pressure (\bar{P}_{cv}), mean pulmonary artery pressure (\bar{P}_{pa}), pulmonary artery occlusion pressure (\bar{P}_{pao}), cardiac output (\dot{Q}_t), tidal volume (TV), peak inspired airway pressure (PIP), and plasma colloid oncotic pressure (Π_p) were measured 90 min after induction of anesthesia.

Following data collection, the pulmonary artery catheter was removed and replaced by a 7F silastic catheter 15 cm in length. Two hours following induction of anesthesia, oleic acid (Eastman Kodak®), 0.09 ml/kg, was infused over 5 min through the jugular catheter. The catheter was then flushed with heparin (100 U/ml) and sealed. The animals' tracheas were extubated after recovery from anesthesia.

DAY 2: HEMORRHAGE AND FLUID RESUSCITATION

Twenty-four hours after oleic acid administration, anesthesia was again induced with 30 mg/kg pentobarbital, iv, and maintained with a continuous infusion of pentobarbital at 5–7.5 mg · kg⁻¹ · h⁻¹. The animals' tracheas were intubated, and they were mechanically ventilated as before. The respiratory rate was adjusted to achieve an initial arterial carbon dioxide tension of 38–42 mmHg. The 7.5F quadruple-lumen pulmonary artery catheter was inserted *via* femoral vein cutdown. A 5F thermistor-tipped arterial catheter designed for measurement of lung water (American Edwards Model 96-C20, Santa Ana, CA) was inserted *via* femoral artery cutdown.

Thirty minutes after catheter insertion, baseline measurements were obtained. Measured variables included HR, mean systemic arterial pressure (\bar{P}_{sa}), \bar{P}_{cv} , \bar{P}_{pa} , \bar{P}_{pao} , \dot{Q}_t , extravascular lung water (EVLW), Π_p , TV, PIP, hemoglobin, and arterial and mixed venous blood gas tensions and oxygen contents. Pulmonary compliance, shunt fraction (\dot{Q}_s/\dot{Q}_t), and dead space to tidal volume ratio (V_D/V_T) were calculated (see below). Following collection of baseline data, animals were bled 25% of their estimated blood volume (88 ml/kg) over 30 min. If \dot{Q}_t remained greater than 50% of control value (day 1), additional increments of 2.5% of estimated blood volume were withdrawn every 5 min until \dot{Q}_t was below 50% of control. One hour following completion of hemorrhage, all variables were again measured (end-shock measurement).

Animals were then randomized to resuscitation with 0.9% saline, 5% human albumin (Cutter) or 6% hydroxyethyl starch (Hetastarch; American Critical Care). The fluid chosen was given in 100-ml increments every 5 min until \dot{Q}_t was greater than 90% of control value (day 1). Initial resuscitation was considered complete

when \dot{Q}_t remained at this level for 10 min. Data measurements were made following the completion of initial resuscitation and 1, 2, and 6 h later. \dot{Q}_t was measured every 20 min for the first 2 h following initial resuscitation, and then hourly for the next 4 h. If the \dot{Q}_t fell below 90% of control value (day 1), resuscitation was continued as outlined above, *i.e.*, 100 ml of fluid every 5 min until \dot{Q}_t remained above 90% of control level for 10 min.

Following the 6-h post-resuscitation measurement, the pentobarbital infusion was discontinued and monitoring catheters were removed. Mechanical ventilation was discontinued following resumption of adequate spontaneous ventilation. The animals' tracheas were extubated following recovery from anesthesia.

DAY 3: FINAL DATA COLLECTION

Twenty-four hours following initial fluid resuscitation, the animals were anesthetized, tracheally intubated, and mechanically ventilated as on day 2. Arterial and pulmonary artery catheters were placed by cutdown as before, and all measurements were repeated. Animals were then anticoagulated with 10,000 U heparin, iv, and killed by an intravenous bolus of 20 meq potassium chloride. The endotracheal tube was clamped, the thorax was opened, and the lungs were isolated and removed. Gravimetric analysis for extravascular lung water was performed by the technique of Pearce *et al.*³⁵ as described by Mihm *et al.*³⁶ In the last animal of each group, samples of the upper and lower lobes were fixed in glutaraldehyde and processed for electron microscopy.

MEASUREMENT TECHNIQUES

Intravascular pressures were measured at end-expiration using Hewlett-Packard® quartz transducers (model 1290A) and a four-channel strip-chart recorder. EVLW was measured in triplicate by the thermal-dye double-indicator dilution technique³⁷ using 10 ml of iced saline containing 0.2 mg/ml indocyanine green. Simultaneous with injection, blood was withdrawn through the femoral artery catheter at a rate of 30 ml/min and passed through an in-line densitometer cuvette (Waters D 402A). Withdrawn blood was returned to the animals after each measurement. The Edwards Laboratories Model 9310 Lung Water Computer was used to determine the transit times of the thermal and dye indicators and to calculate EVLW. \dot{Q}_t was measured in triplicate by thermodilution technique with 10 ml iced saline using the Edwards Laboratories Cardiac Output Computer 9520A. When both \dot{Q}_t and EVLW were measured, the injection of 10 ml iced saline with indocyanine green was used for both measurements. Π_p was

TABLE 1. Cardiac Output, Pulmonary Vascular Resistance, and Compliance

	Q _c				PVR				Compliance			
	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL
Day 1	3.7 ± 0.2	3.7 ± 0.4	3.5 ± 0.1	3.7 ± 0.1*	162 ± 18	156 ± 32	200 ± 31	173 ± 15*	62 ± 18	64 ± 11	82 ± 16	69 ± 9*
Baseline (day 2)	3.0 ± 0.2	2.9 ± 0.4	3.2 ± 0.4	3.0 ± 0.2†	335 ± 21	323 ± 56	299 ± 135	319 ± 26†	24 ± 4	26 ± 2	25 ± 1	25 ± 1†
Post-hemorrhage	1.8 ± 0.1	1.8 ± 0.2	2.0 ± 0.2	1.9 ± 0.1**†	473 ± 51	446 ± 67	410 ± 54	443 ± 32**†	24 ± 3	27 ± 1	23 ± 1	24 ± 1†
Resuscitation (0 h)	3.6 ± 0.1	3.8 ± 0.4	4.0 ± 0.3	3.8 ± 0.2*	260 ± 51	243 ± 40	248 ± 57	250 ± 11‡	24 ± 3	28 ± 2	23 ± 1	25 ± 1†
Resuscitation (1 h)	3.4 ± 0.1	3.8 ± 0.4	3.7 ± 0.3	3.6 ± 0.2*	294 ± 35	248 ± 39	230 ± 21	257 ± 19†	24 ± 3	29 ± 2	23 ± 1	25 ± 1†
Resuscitation (2 h)	3.5 ± 0.2	3.6 ± 0.4	3.8 ± 0.2	3.6 ± 0.2*	274 ± 27	214 ± 27	220 ± 24	236 ± 15§	23 ± 3	28 ± 1	23 ± 1	25 ± 1†
Resuscitation (6 h)	3.6 ± 0.1	3.8 ± 0.3	3.7 ± 0.3	3.7 ± 0.1*	342 ± 42	280 ± 30	330 ± 58	317 ± 25†	25 ± 4	28 ± 2	22 ± 1	25 ± 2†
Day 3	3.9 ± 0.4	3.8 ± 0.4	3.6 ± 0.3	3.8 ± 0.2*	312 ± 44	265 ± 59	270 ± 90	283 ± 20†	28 ± 5	30 ± 3	27 ± 2	28 ± 2†

Values are means ± SEM. Q_c = cardiac output (l · min⁻¹); PVR = pulmonary vascular resistance (dynes · sec · cm⁻⁵); Compliance = dynamic lung-thorax compliance (ml · cm H₂O⁻¹); SAL = saline resuscitation group (n = 6); ALB = albumin resuscitation group (n = 6); HES = hydroxyethyl starch resuscitation group (n = 6); ALL = all three

resuscitation groups combined (n = 18).

* P < 0.01 compared to baseline (day 2).

† P < 0.01 compared to day 1.

‡ P < 0.05 compared to day 1.

§ P < 0.05 compared to baseline (day 2).

measured using a IL186 Weil Oncometer (Instrumentation Laboratory). Blood gases were measured on a Corning 168 pH/blood gas analyzer. Hemoglobin (Hb) and hemoglobin saturation were measured on an IL282 Co-Oximeter (Instrumentation Laboratory) calibrated for canine hemoglobin. Blood oxygen contents were calculated as percent saturation × Hb × 1.34 + .0031 × P_{O₂}. Dynamic pulmonary compliance was calculated as tidal volume divided by peak inspiratory pressure. For measurement of dead-space-to-tidal-volume-ratio (V_D/V_T), 3 l of expired gas were collected for measurement of mixed expired carbon dioxide tension (Puritan Bennett/Datex CO₂ Monitor). V_D/V_T was calculated using the Enghoff modification of the Bohr equation. Shunt fraction (Q_s/Q_c) was calculated by standard formula.

STATISTICS

Measured variables are reported as the mean ± SEM of the six dogs in each group. Data were analyzed by

two-factor repeated-measures analysis of variance (resuscitation fluid × time), followed by the Newman-Keuls' multiple range test.³⁸ When appropriate, data from the three groups were combined for statistical analysis.

Results

There were no significant differences among the three resuscitation groups (saline, albumin, hydroxyethyl starch) for any variable prior to oleic acid administration (tables 1–3). With the exception of P_i and the gradient between colloid oncotic pressure and pulmonary artery occlusion pressure (P_i – P_{pao}), there were no significant differences among the three groups in any variable at any time point throughout the experiment (tables 1–5). We have, therefore, combined the data from the three groups for discussion of all other variables.

Oleic acid administration resulted 24 h later in significant pulmonary and hemodynamic changes. For all

TABLE 2. Mean Pulmonary Artery Pressure, Pulmonary Artery Occlusion Pressure, and Central Venous Pressure

	P _{pa}				P _{pao}				P _{cv}			
	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL
Day 1	11 ± 1	11 ± 2	12 ± 1	11 ± 1*	3.5 ± 0.4	3.7 ± 1.1	2.8 ± 0.5	3.3 ± 0.4	1.7 ± 0.7	2.8 ± 0.7	1.7 ± 0.8	2.3 ± 0.4
Baseline (day 2)	15 ± 1	13 ± 2	14 ± 1	14 ± 1†	2.2 ± 0.7	2.2 ± 1.1	2.3 ± 0.5	2.2 ± 0.5	1.7 ± 1.1	0.7 ± 1.5	1.0 ± 1.2	1.1 ± 0.8
Post-hemorrhage	10 ± 1	10 ± 1	10 ± 2	10 ± 1*	-0.5 ± 0.9	0.0 ± 1.2	0.3 ± 0.9	-0.1 ± 0.6**‡	0.7 ± 1.4	0.3 ± 1.2	0.7 ± 1.0	0.6 ± 0.7‡
Resuscitation (0 h)	14 ± 1	13 ± 2	15 ± 2	14 ± 1†	2.2 ± 1.2	2.0 ± 1.3	2.2 ± 1.3	2.1 ± 0.8	3.3 ± 0.9	1.2 ± 1.4	2.3 ± 1.2	2.3 ± 0.7
Resuscitation (1 h)	14 ± 1	14 ± 2	13 ± 2	14 ± 1†	2.2 ± 1.2	2.7 ± 1.1	2.7 ± 1.2	2.5 ± 0.7	3.3 ± 1.1	2.5 ± 1.6	1.5 ± 1.3	2.4 ± 0.8
Resuscitation (2 h)	14 ± 1	12 ± 2	13 ± 2	13 ± 1†	2.5 ± 1.4	2.8 ± 1.0	2.8 ± 0.9	2.7 ± 0.6	3.8 ± 1.0	1.5 ± 1.2	2.2 ± 1.1	2.5 ± 0.8
Resuscitation (6 h)	15 ± 2	13 ± 1	15 ± 2	14 ± 1†	3.0 ± 1.3	3.3 ± 1.0	3.0 ± 1.2	3.1 ± 0.7	3.8 ± 1.4	2.0 ± 1.1	2.7 ± 1.3	2.8 ± 0.8§
Day 3	14 ± 1	13 ± 2	12 ± 2	13 ± 1	3.2 ± 0.9	3.0 ± 1.0	2.3 ± 0.6	2.0 ± 0.5	3.5 ± 0.7	2.2 ± 1.0	1.2 ± 0.9	2.3 ± 0.5

Values are means ± SEM. P_{pa} = mean pulmonary artery pressure (mmHg); P_{pao} = pulmonary artery occlusion pressure (mmHg); P_{cv} = central venous pressure (mmHg); SAL = saline resuscitation group (n = 6); ALB = albumin resuscitation group (n = 6); HES = hydroxyethyl starch resuscitation group (n = 6); ALL = all three resuscitation

groups combined (n = 18).

* P < 0.01 compared to baseline (day 2).

† P < 0.05 compared to day 1.

‡ P < 0.01 compared to day 1.

§ P < 0.05 compared to baseline (day 2).

TABLE 3. Plasma Colloid Oncotic Pressure and the Plasma Colloid Oncotic Pressure-pulmonary Artery Occlusion Pressure Gradient

	Π_p			$\Pi_p - \bar{P}_{pao}$		
	SAL	ALB	HES	SAL	ALB	HES
Day 1	16.4 ± 0.6	16.7 ± 0.3	16.6 ± 0.8	12.9 ± 0.6	13.0 ± 1.1	13.6 ± 0.9
Baseline (day 2)	15.2 ± 0.8	15.4 ± 0.2	16.8 ± 0.5	13.1 ± 1.0	13.2 ± 1.3	14.4 ± 0.9
Post-hemorrhage	12.6 ± 0.7*†	13.8 ± 0.4*	14.2 ± 0.8*†	13.1 ± 1.3	13.8 ± 1.4	14.2 ± 1.7
Resuscitation (0 h)	8.6 ± 0.8*†	15.2 ± 0.3‡	14.3 ± 0.6*†‡	6.5 ± 1.8*†	13.1 ± 1.4‡	12.9 ± 1.5‡
Resuscitation (1 h)	8.2 ± 1.1*†	15.6 ± 0.4‡	14.7 ± 0.6†‡§	6.1 ± 2.0*†	13.0 ± 1.4‡	12.3 ± 1.9‡
Resuscitation (2 h)	8.2 ± 0.9*†	14.4 ± 0.5‡§	14.2 ± 0.7*†‡	5.7 ± 2.1*†	11.6 ± 1.2‡	11.8 ± 1.5‡
Resuscitation (6 h)	8.3 ± 1.0*†	14.1 ± 1.0‡§	14.9 ± 0.5†§¶	5.4 ± 2.1*†	11.6 ± 1.5‡	12.5 ± 1.4‡
Day 3	10.7 ± 0.6*†	16.5 ± 0.8‡	14.4 ± 0.4*†‡	7.6 ± 1.0*†	13.6 ± 1.5‡	12.4 ± 0.7‡

Values are means ± SEM. Π_p = plasma colloid oncotic pressure (mmHg); \bar{P}_{pao} = pulmonary artery occlusion pressure; SAL = saline resuscitation group (n = 6); ALB = albumin resuscitation group (n = 6); HES = hydroxyethyl starch resuscitation group (n = 6).
* P < .01 compared to day 1.

† P < .01 compared to baseline (day 2).
‡ P < .01 compared to corresponding saline value.
§ P < .05 compared to day 1.
¶ P < .05 compared to baseline (day 2).

three groups combined, dynamic pulmonary compliance decreased 69%, \bar{P}_{pa} increased 21%, \dot{Q}_t decreased 19%, and pulmonary vascular resistance increased 84% (tables 1, 2). Average EVLW on day 2 was 14.5 ml/kg (table 4), significantly higher than the normal values of 5–9 ml/kg reported by multiple investigators using the double indicator dilution thermal-green dye technique.^{16,19,36,39-47} Shunt fraction was also significantly higher than normal values (table 5).^{48,49}

There were no significant changes in EVLW at any time point from 24 h post-oleic acid administration (baseline day 2) through completion of the experiment. As mentioned above, the three groups did not differ significantly in EVLW at any time point. Consistent with the experimental design, \dot{Q}_t which was decreased at 24 h post-oleic acid administration decreased further with hemorrhage and returned to baseline values throughout resuscitation (table 1); \dot{Q}_t remained at baseline values 24 h after completion of initial resuscitation. \bar{P}_{pa} decreased with hemorrhage and returned to post-oleic acid values (which were significantly higher than day 1 baseline) with resuscitation (table 2); \bar{P}_{pa} re-

mained at these elevated values for the duration of the experiment. \bar{P}_{pao} decreased with hemorrhage and returned to pre-hemorrhage values with resuscitation (table 2); \bar{P}_{pao} remained at this level for the remainder of the experiment. \bar{P}_{cv} decreased from day 1 baseline values with hemorrhage and returned to baseline values with resuscitation (table 2). \bar{P}_{sa} decreased with hemorrhage and remained at this level for the duration of the study (table 4). Pulmonary compliance which was decreased 24 h after oleic acid administration remained at this decreased level for the remainder of the study (table 1). There were no changes in V_D/V_T , \dot{Q}_v/\dot{Q}_t , or Pa_{O_2} from post-oleic acid values throughout the duration of the study (tables 4, 5).

Π_p was not significantly affected by oleic acid administration (table 3). In the albumin and hydroxyethyl starch groups, there were only small changes in Π_p throughout the remainder of the study. In the saline group, Π_p decreased to 52% of pre-hemorrhage value (57% of post-oleic acid value) during initial resuscitation and remained decreased throughout the duration of the experiment. Π_p in the saline group was significantly

TABLE 4. Extravascular Lung Water, Arterial Oxygen Tension, and Mean Systemic Arterial Pressure

	EVLW				Pa_{O_2}				\bar{P}_{sa}			
	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL
Baseline (day 2)	15.9 ± 4.9	12.8 ± 0.9	14.9 ± 3.1	14.5 ± 1.7	323 ± 77	374 ± 38	334 ± 56	344 ± 33	122 ± 7	133 ± 8	125 ± 7	127 ± 4
Post-hemorrhage	15.5 ± 4.0	12.3 ± 1.0	15.6 ± 3.0	14.5 ± 1.6	342 ± 85	423 ± 25	341 ± 75	369 ± 36	104 ± 7	126 ± 4	105 ± 11	112 ± 4*
Resuscitation (0 h)	13.2 ± 3.3	11.9 ± 1.0	15.4 ± 3.7	13.5 ± 1.6	354 ± 73	446 ± 8	350 ± 58	383 ± 27	109 ± 8	126 ± 4	113 ± 10	116 ± 4*
Resuscitation (1 h)	14.1 ± 3.8	12.2 ± 1.0	15.4 ± 3.1	13.9 ± 1.5	326 ± 72	411 ± 31	305 ± 62	347 ± 32	110 ± 8	121 ± 3	107 ± 11	113 ± 4*
Resuscitation (2 h)	14.3 ± 3.9	12.5 ± 1.0	16.3 ± 3.8	14.4 ± 1.7	324 ± 73	406 ± 24	316 ± 60	349 ± 30	103 ± 9	114 ± 3	105 ± 11	107 ± 5*
Resuscitation (6 h)	13.9 ± 3.3	12.0 ± 0.7	16.2 ± 4.1	14.0 ± 1.6	328 ± 74	417 ± 16	294 ± 54	346 ± 28	113 ± 11	102 ± 3	100 ± 10	105 ± 5*
Day 3	14.7 ± 4.7	14.9 ± 1.6	16.6 ± 2.8	15.4 ± 1.7	372 ± 89	341 ± 64	408 ± 69	374 ± 43	103 ± 8	116 ± 4	99 ± 12	106 ± 5*

Values are means ± SEM. EVLW = extravascular lung water (mL · kg⁻¹); Pa_{O_2} = systemic arterial oxygen tension (mmHg); \bar{P}_{sa} = mean systemic arterial pressure (mmHg); SAL = saline resuscitation group (n = 6); ALB = albumin resuscitation group (n = 6); HES

= hydroxyethyl starch resuscitation group (n = 6); ALL = all three resuscitation groups combined (n = 18).

* P < 0.01 compared to baseline (day 2).

TABLE 5. Shunt Fraction, Dead-space-to-tidal-volume Ratio, and Hemoglobin

	\dot{Q}_s/\dot{Q}_t				V_D/V_T				Hgb			
	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL	SAL	ALB	HES	ALL
	Baseline (day 2)	29 ± 4	28 ± 2	26 ± 4	28 ± 2	0.63 ± 0.01	0.63 ± 0.05	0.64 ± 0.02	0.63 ± 0.02	12.9 ± 0.8	13.4 ± 0.4	13.8 ± 0.7
Post-hemorrhage	22 ± 4	20 ± 4	19 ± 4	20 ± 2	0.66 ± 0.03	0.60 ± 0.02	0.66 ± 0.02	0.63 ± 0.01	13.7 ± 0.8	14.3 ± 0.5	14.4 ± 0.8	14.1 ± 0.4
Resuscitation (0 h)	22 ± 4	25 ± 4	28 ± 2	25 ± 2	0.65 ± 0.03	0.62 ± 0.03	0.63 ± 0.02	0.63 ± 0.02	8.8 ± 1.2	9.3 ± 0.3	11.0 ± 1.1	9.7 ± 0.5*
Resuscitation (1 h)	28 ± 3	27 ± 2	30 ± 3	28 ± 2	0.69 ± 0.02	0.65 ± 0.04	0.65 ± 0.02	0.66 ± 0.01	8.8 ± 1.3	8.6 ± 0.4	10.4 ± 1.0	9.3 ± 0.5*
Resuscitation (2 h)	27 ± 3	27 ± 4	26 ± 3	27 ± 2	0.68 ± 0.03	0.63 ± 0.03	0.65 ± 0.02	0.65 ± 0.02	8.5 ± 1.2	7.9 ± 0.4	9.5 ± 1.0	8.6 ± 0.5*
Resuscitation (6 h)	27 ± 3	26 ± 4	27 ± 3	27 ± 2	0.66 ± 0.04	0.65 ± 0.02	0.67 ± 0.02	0.66 ± 0.02	7.8 ± 0.7	7.0 ± 0.5	8.9 ± 1.3	7.9 ± 0.5*
Day 3	25 ± 4	30 ± 5	21 ± 2	25 ± 2	0.60 ± 0.05	0.62 ± 0.03	0.63 ± 0.03	0.62 ± 0.02	8.3 ± 1.0	9.4 ± 0.4	9.3 ± 1.1	9.0 ± 0.5*

Values are means ± SEM. \dot{Q}_s/\dot{Q}_t = shunt fraction (%); V_D/V_T = dead-space-to-tidal-volume ratio; Hgb = hemoglobin (gm · dl⁻¹); SAL = saline resuscitation group (n = 6); ALB = albumin resuscitation group (n = 6); HES = hydroxyethyl starch resuscitation group (n = 6); ALL = all three resuscitation groups combined (n = 18).

* $P < 0.01$ compared to baseline (day 2).

lower than in the other two groups at all resuscitation time points and at 24 h after resuscitation. The $\Pi_p\text{-}\bar{P}_{pao}$ gradient was not affected by oleic acid administration or by hemorrhage (table 3). In the albumin and hydroxyethyl starch groups, there were no changes in $\Pi_p\text{-}\bar{P}_{pao}$ throughout the study. In the saline group, $\Pi_p\text{-}\bar{P}_{pao}$ decreased to 50% of pre-hemorrhage values during initial resuscitation, and remained decreased throughout the duration of the study. $\Pi_p\text{-}\bar{P}_{pao}$ values in the saline group were significantly lower than in the other two groups at all resuscitation time points and at 24 h after initial resuscitation.

The total volume of fluid required for resuscitation was significantly greater in the saline group (140 ± 26 ml/kg) than in the albumin group (35 ± 4 ml/kg; $P < 0.001$) or the hydroxyethyl starch group (24 ± 6 ml/kg; $P < 0.001$).

Gravimetric analysis of absolute EVLW correlated with immediate pre-termination thermal-dye lung water measurements ($r = 0.88$, $P < 0.001$). There were no significant differences in gravimetric EVLW among the three groups (10.8 ± 3.6 ml/kg in the saline group, 11.4 ± 1.1 ml/kg in the albumin group, and 12.4 ± 1.1 ml/kg in the hydroxyethyl starch group), and gravimetric EVLW in each group was higher than the normal value of approximately 6 ml/kg.^{35,36,40,41,50,51} There were no significant differences in the ratio of gravimetric EVLW to extravascular dry weight (5.69 ± 1.14 in the saline group, 5.20 ± 0.46 in the albumin group, and 5.56 ± 0.58 in the hetastarch group); these values are significantly higher than the normal values of approximately 4 in multiple other studies.^{8,28,41,47,50,52-54}

Electron microscopy demonstrated abnormalities in the lungs of all three dogs studied. The degree of injury varied both among animals and among sections from the same animal. In the sections showing the least degree of abnormalities, there were increased numbers of polymorphonuclear leukocytes in the capillaries and some edema fluid in the alveoli. In two of the three dogs, there was severe capillary damage with exudation of the capillary contents (leukocytes, red blood cells, fibrin, and fluid) into the alveoli. In the areas of severest damage, there was complete loss of capillary structures with no recognizable endothelial or epithelial cells (fig. 1).

Discussion

In this study, oleic acid administration resulted in increased pulmonary vascular resistance, increased extravascular lung water, decreased dynamic pulmonary compliance, and increased \dot{Q}_s/\dot{Q}_t . As suggested by other studies²⁹⁻³⁴ and by the electron micrographs, these changes were likely due to pulmonary capillary injury. Subsequent hemorrhage and resuscitation with

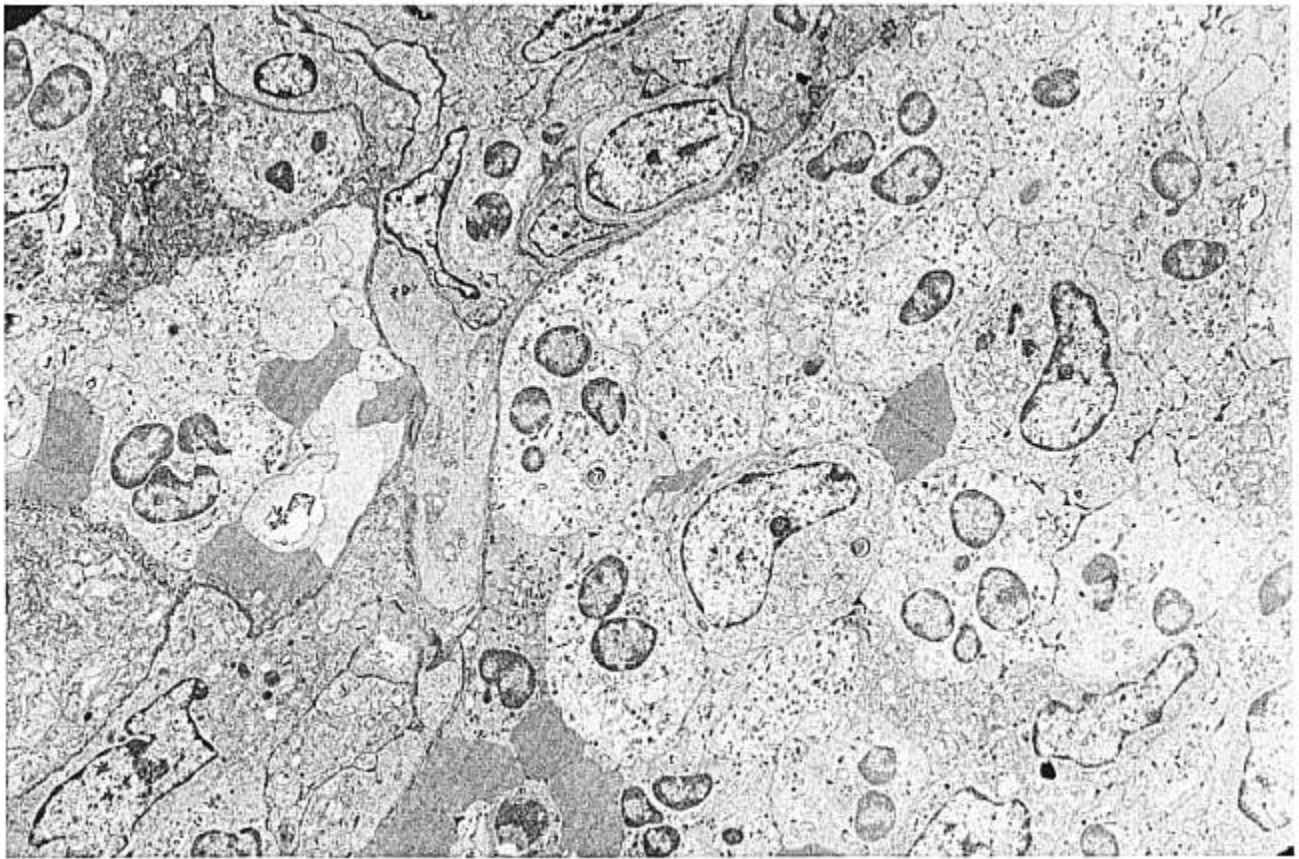


FIG. 1. Electron microscopy demonstrates severe injury throughout this section of lung. There is loss of normal capillary structures and the alveoli are filled with polymorphonuclear leukocytes (recognizable by multilobed nuclei), red blood cells, fibrin, and fluid.

saline, albumin, or hydroxyethyl starch caused no further changes in EVLW or pulmonary function either during the acute period of resuscitation or 24 h later; the absence of differences in EVLW among the three groups was confirmed by gravimetric analysis at 24 h. Hemodynamic variables were similar among the three groups. Crystalloid resuscitation resulted in marked decreases in Π_p and $\Pi_p - \bar{P}pao$; colloid resuscitation had little effect on these variables. Our results suggest that when volume resuscitation is performed according to appropriate hemodynamic criteria, there is no difference in pulmonary effects between crystalloid and colloid solutions.

Our results and those of other investigators are best understood in terms of the forces which govern fluid movement across the capillary membrane.⁵⁵ Factors which promote net fluid movement include a decrease in capillary membrane integrity, an increase in pulmonary capillary pressure, and a decrease in the colloid oncotic pressure gradient between plasma and the interstitium. Net lung water accumulation is affected not only by capillary fluid filtration, but also by fluid removal *via* pulmonary lymph flow. Previous studies have

demonstrated that the lung is partially protected from interstitial fluid accumulation by increases in pulmonary lymphatic flow.^{56,57}

In the current experiment, resuscitation was performed on the basis of strict hemodynamic criteria (restoration of normal cardiac output) to simulate clinical practice. $\bar{P}pao$ was similar among the three groups, but Π_p and $\Pi_p - \bar{P}pao$ were markedly decreased in the saline compared to the colloid groups. However, there were no differences in lung water accumulation among the three groups. There are two possible explanations for these findings. First, net fluid movement across the pulmonary capillaries may have been equal among the three groups. Oleic acid results in pulmonary capillary injury with marked decreases in σ , the protein reflection coefficient. The reflection coefficient σ is an index of the impermeability of the capillary membrane to protein, and varies from 0 (completely permeable) to 1 (impermeable).⁵⁸ Subsequent colloid administration to increase plasma colloid oncotic pressure will also increase interstitial colloid oncotic pressure as colloid moves across the abnormal capillary membrane.^{18,19,59} Thus, the transmembrane difference in colloid oncotic

pressure may only marginally increase after colloid administration. Crystalloid administration will similarly decrease both plasma and interstitial colloid oncotic pressure, so the transmembrane gradient will remain relatively constant.^{60,61} Furthermore, as a result of the decrease in the protein reflection coefficient, the contribution of colloid oncotic pressure may have been small in both the crystalloid and colloid groups. The second possible explanation for the failure of colloid administration to decrease lung water accumulation in our experiment is that pulmonary lymph flow may have been greater in the crystalloid group.^{57,62,63}

Several studies have claimed that resuscitation with colloid solutions produces less pulmonary dysfunction than resuscitation with crystalloid solutions.^{8,13-17} However, these studies have had major methodologic problems, including lack of direct assessment of extravascular lung water and pulmonary function, lack of randomization, and resuscitation according to non-hemodynamic criteria so that significant differences in pulmonary artery occlusion pressure occurred among the groups. Several studies demonstrate a correlation between pulmonary dysfunction and reductions in colloid oncotic pressure or the colloid oncotic pressure-pulmonary artery occlusion pressure gradient.²⁻⁶ These studies may be explained on the basis that critically ill patients are prone to develop both pulmonary dysfunction and low colloid oncotic pressures, but that the two are not causally related. Albumin administration to increase Π_p does not reduce lung water⁴³ or improve outcome,⁶⁴ and the relationship between lung water accumulation and Π_p or $\Pi_p - \bar{P}_{pao}$ has been refuted in several other studies.^{23,65-67}

In contrast to the above studies, which have claimed an advantage of colloid over crystalloid solutions, many studies have demonstrated equivalent pulmonary effects of the two solutions.²¹⁻²⁷ Criticisms of these studies have focused on the degree of pulmonary capillary injury (either none or too severe), the assessment of EVLW and pulmonary function, the quantity of fluid administered, and the duration of the experiment. Our study was designed to meet these criticisms. We induced a moderate degree of pulmonary capillary injury as assessed by extravascular lung water and pulmonary function. We bled at least 25% of estimated blood volume to allow resuscitation with large enough fluid volumes to reduce Π_p by 50% in the crystalloid group. We continued our resuscitation for 6 h and obtained a final set of measurements at 24 h, thus allowing us to evaluate long-term pulmonary changes from fluid resuscitation. We conclude that crystalloid and colloid solutions have equivalent pulmonary effects when used for resuscitation from hemorrhagic shock in the presence of

moderate pulmonary permeability injury due to oleic acid administration. Furthermore, in this oleic acid model, resuscitation from hemorrhagic shock when performed according to hemodynamic criteria does not adversely affect pulmonary function or extravascular lung water.

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References

1. Shoemaker WC, Hauser CJ: Critique of crystalloid versus colloid therapy in shock and shock lung. *Crit Care Med* 7:117-124, 1979
2. Weil MH, Henning RJ, Puri VK: Colloid oncotic pressure: Clinical significance. *Crit Care Med* 7:113-116, 1979
3. Rackow EC, Fein IA, Siegel J: The relationship of the colloid osmotic-pulmonary artery wedge pressure gradient to pulmonary edema and mortality in critically ill patients. *Chest* 82:433-437, 1982
4. Weil MH, Henning RJ, Morissette M, Michaels S: Relationship between colloid osmotic pressure and pulmonary artery wedge pressure in patients with acute cardiorespiratory failure. *Am J Med* 64:643-649, 1978
5. Puri VK, Weil MH, Michaels S, Carlson RW: Pulmonary edema associated with reduction in plasma oncotic pressure. *Surg Gynecol Obstet* 151:344-348, 1980
6. Da Luz PL, Shubin H, Weil MH, Jacobson E, Stein L: Pulmonary edema related to changes in colloid osmotic and pulmonary artery wedge pressure in patients after acute myocardial infarction. *Circulation* 51:350-357, 1975
7. Stein L, Beraud JJ, Morissette M, Da Luz P, Weil MH, Shubin H: Pulmonary edema during volume infusion. *Circulation* 52:483-489, 1975
8. Cooper JD, Maeda M, Lowenstein E: Lung water accumulation with acute hemodilution in dogs. *J Thorac Cardiovasc Surg* 6:957-965, 1975
9. Klancke KA, Assey ME, Kratz JM, Crawford FA: Postoperative pulmonary edema in postcoronary artery bypass graft patients. *Chest* 84:529-534, 1983
10. Holcroft JW, Trunkey DD: Pulmonary extravasation of albumin during and after hemorrhagic shock in baboons. *J Surg Res* 18:91-97, 1975
11. Goodwin CW, Dorethy J, Lam V, Pruitt BA: Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. *Ann Surg* 197:520-529, 1983
12. Holcroft JW, Trunkey DD: Extravascular lung water following hemorrhagic shock in the baboon: Comparison between resuscitation with Ringer's lactate and Plasmanate. *Ann Surg* 180:408-415, 1974
13. Rackow EC, Falk JL, Fein IA, Siegel JS, Packman MI, Haupt MT, Kaufman BS, Putnam D: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 11:839-850, 1983
14. Skillman JJ, Restall S, Salzman EW: Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. *Surgery* 78:291-303, 1975

15. Boutros AR, Ruess R, Olson L, Hoyt JL, Baker WH: Comparison of hemodynamic, pulmonary, and renal effects of use of three types of fluids after major surgical procedures on the abdominal aorta. *Crit Care Med* 7:9-13, 1979
16. Finch JS, Reid C, Bandy K, Fickle D: Compared effects of selected colloids on extravascular lung water in dogs after oleic acid-induced lung injury and severe hemorrhage. *Crit Care Med* 11:267-270, 1983
17. Brinkmeyer S, Safar P, Motoyama E, Stezoski W: Superiority of colloid over electrolyte solution for fluid resuscitation (severe normovolemic hemodilution). *Crit Care Med* 9:369-370, 1981
18. Sturm JA, Carpenter MA, Lewis FR Jr, Graziano C, Trunkey DD: Water and protein movement in the sheep lung after septic shock: Effect of colloid versus crystalloid resuscitation. *J Surg Res* 26:233-248, 1979
19. Peitzman AB, Shires T III, Illner H, Shires T: Pulmonary acid injury. Effects of positive end-expiratory pressure and crystalloid vs colloid fluid resuscitation. *Arch Surg* 117:662-667, 1982
20. Staub NC: Pulmonary edema due to increased microvascular permeability to fluid and protein. *Circ Res* 43:143-151, 1978
21. Virgilio RW, Smith DE, Zarins CK: Balanced electrolyte solutions: Experimental and clinical studies. *Crit Care Med* 7:98-106, 1979
22. Moss GS, Lowe RJ, Jilek J, Levine HD: Colloid or crystalloid in the resuscitation of hemorrhagic shock: A controlled clinical trial. *Surgery* 89:434-438, 1981
23. Virgilio RW, Rice CL, Smith DE, James DR, Zarins CK, Hobelmann CF, Peters RM: Crystalloid vs. colloid resuscitation: Is one better? *Surgery* 85:129-139, 1979
24. Lowe RJ, Moss GS, Jilek J, Levine HD: Crystalloid vs. colloid in the etiology of pulmonary failure after trauma: A randomized trial in man. *Surgery* 81:676-683, 1977
25. Metildi LA, Shackford SR, Virgilio RW, Peters RM: Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. *Surg Gynecol Obstet* 158:207-212, 1984
26. Shires GT III, Peitzman AB, Albert SA, Illner H, Silane MF, Perry MO, Shires GT: Response of extravascular lung water to intraoperative fluids. *Ann Surg* 197:515-518, 1983
27. Horton J, Landreneau R, Truggle D: Cardiac response to fluid resuscitation from hemorrhagic shock. *Surg Gynecol Obstet* 160:444-452, 1985
28. Luce JM, Robertson T, Huang T, Colley PS, Gronka R, Nessly ML, Cheney FW: The effects of expiratory positive airway pressure on the resolution of oleic acid-induced lung injury in dogs. *Am Rev Respir Dis* 125:716-722, 1982
29. Hara N, Furukawa T, Yoshida T, Motohiro A, Inokuchi K: Effect of free fatty acid on pulmonary transvascular fluid and protein exchange. *Res Exp Med (Berl)* 184:41-48, 1984
30. Motohiro A, Furukawa T, Yasumoto K, Inokuchi K: Mechanisms involved in acute lung edema induced in dogs by oleic acid. *Eur Surg Res* 18:50-57, 1986
31. Sugeran HJ, Blocher CR, Hirsch JI, Strash AM, Tatum JL: Failure of various agents to decrease oleic acid pulmonary albumin leak. *J Surg Res* 34:456-462, 1983
32. Saul GM, Feeley TW, Mihm FG: Effect of graded administration of PEEP on lung water in noncardiogenic pulmonary edema. *Crit Care Med* 10:667-669, 1982
33. Derks CM, Jacobovitz-Derks D: Embolic pneumopathy induced by oleic acid. *Am J Pathol* 87:143-151, 1977
34. King EG, Wagner WW, Ashbaugh DG, Latham LP, Halsey DR: Alterations in pulmonary microanatomy after fat embolism. *Chest* 59:524-530, 1971
35. Pearce ML, Yamashita J, Beazell J: Measurement of pulmonary edema. *Circ Res* 16:482-488, 1965
36. Mihm FG, Feeley TW, Rosenthal MH, Lewis F: Measurement of extravascular lung water in dogs using the thermal-green dye indicator dilution method. *ANESTHESIOLOGY* 57:116-122, 1982
37. Lewis FR Jr, Elings VI: Microprocessor determination of lung water using thermal-green dye double indicator dilution. *Surg Forum* 29:182-184, 1978
38. Winer BF: *Statistical Principles in Experimental Design*. Boston, McGraw-Hill, 1971, pp 518-539
39. Sivak ED, Tita J, Meden G, Ishigami M, Graves J, Kavlich J, Stowe NT, Magnusson MO: Effects of furosemide versus isolated ultrafiltration on extravascular lung water in oleic acid-induced pulmonary edema. *Crit Care Med* 14:48-56, 1986
40. Enderson BL, Rice CL, Moss GS: Effect of positive-end expiratory pressure on accuracy of thermal-dye measurements of lung water. *J Surg Res* 38:224-230, 1985
41. Gray BA, Beckett RC, Allison RC, McCaffree DR, Smith RM, Sivak ED, Carlile PV Jr: Effect of edema and hemodynamic changes on extravascular thermal volume of the lung. *J Appl Physiol* 56:878-890, 1984
42. Carlile PV, Gray BA: Type of lung injury influences the thermal-dye estimation of extravascular lung water. *J Appl Physiol* 57:680-685, 1984
43. Jing DL, Kohler JP, Rice CL, Moss GS: Albumin therapy in permeability pulmonary edema. *J Surg Res* 33:482-488, 1982
44. Peitzman AB, Corbett WA, Shires GT III, Lynch NJ, Shires GT: The effect of increasing end-expiratory pressure on extravascular lung water. *Surgery* 90:439-445, 1981
45. Miller WC, Rice DL, Unger KM, Bradley BL: Effect of PEEP on lung water content in experimental noncardiogenic pulmonary edema. *Crit Care Med* 9:7-9, 1981
46. Hill SL, Elings VB, Lewis FR: Changes in lung water and capillary permeability following sepsis and fluid overload. *J Surg Res* 28:140-150, 1980
47. Oppenheimer L, Elings VB, Lewis FR: Thermal-dye lung water measurements: Effects of edema and embolization. *J Surg Res* 26:504-512, 1979
48. Prewitt RM, McCarthy J, Wood LDH: Treatment of acute low pressure pulmonary edema in dogs. Relative effects of hydrostatic and oncotic pressure, nitroprusside, and positive end-expiratory pressure. *J Clin Invest* 67:409-418, 1981
49. Ali J, Chernicki W, Wood LDH: Effect of furosemide in canine low-pressure pulmonary edema. *J Clin Invest* 64:1494-1504, 1979
50. Schwartz JS, Konopka RG, Spragg RG: Effect of histamine and propranolol on extravascular lung water. *Am J Physiol* 246:H69-H73, 1984
51. Noble WH, Severinghaus JW: Thermal and conductivity dilution curves for rapid quantitation of pulmonary edema. *J Appl Physiol* 32:770-775, 1972
52. Huchon CJ, Lipavsky A, Pangburn P, Hoeffel JM, Jibelian G, Murray JF: Factors affecting tissue volume measurements in normal and edematous dog lungs. *J Appl Physiol* 59:1548-1554, 1985
53. Helbert C, Paskanik A, Bredenberg CE: Effect of positive end-expiratory pressure on lung water in pulmonary edema caused by increased membrane permeability. *Ann Thorac Surg* 36:42-48, 1983
54. Snashall PD, Weidner WJ, Staub NC: Extravascular lung water

- after extracellular fluid volume expansion in dogs. *J Appl Physiol* 42:624-629, 1977
55. Levine OR, Mellins RB, Senior RM, Fishman AP: The application of Starling's law of capillary exchange to the lungs. *J Clin Invest* 46:934-944, 1967
 56. Staub NC: "State of the art" review. Pathogenesis of pulmonary edema. *Am Rev Respir Dis* 109:358-372, 1974
 57. Zarins CK, Rice CL, Peters RM, Virgilio RW: Lymph and pulmonary response to isobaric reduction in plasma oncotic pressure in baboons. *Circ Res* 43:925-930, 1978
 58. Staub NC: Pulmonary edema. *Physiol Rev* 54:678-811, 1974
 59. Civetta JM: A new look at the Starling equation. *Crit Care Med* 7:84-91, 1979
 60. Demling RH, Duy N, Manohar M, Proctor R: Comparison between lung fluid filtration rate and measured Starling forces after hemorrhagic and endotoxic shock. *J Trauma* 20:856-861, 1980
 61. Demling RH, Manohar M, Will JA, Belzer FO: The effect of plasma oncotic pressure on the pulmonary microcirculation after hemorrhagic shock. *Surgery* 86:323-328, 1979
 62. Harms BA, Kramer GC, Bodai BI, Demling RH: Effect of hypoproteinemia on pulmonary and soft tissue edema formation. *Crit Care Med* 9:503-508, 1981
 63. Kramer GC, Harms BA, Gunther RA, Renkin EM, Demling RH: The effects of hypoproteinemia on blood-to-lymph fluid transport in sheep lung. *Circ Res* 49:1173-1180, 1981
 64. Grundmann R, Heistermann S: Postoperative albumin infusion therapy based on colloid osmotic pressure. A prospectively randomized trial. *Arch Surg* 120:911-915, 1985
 65. Rafferty TD, Ljungquist R, Firestone L, Curtis A, Raven C, Hui S, Barash PG: Plasma colloid oncotic pressure-pulmonary artery occlusion pressure gradient. A poor predictor of pulmonary edema in surgical intensive care unit patients. *Arch Surg* 118:841-843, 1983
 66. Bongard FS, Lewis FR: Crystalloid resuscitation of patients with pulmonary contusion. *Am J Surg* 148:145-149, 1984
 67. Tranbaugh RF, Lewis FR, Christensen JM, Elings VB: Lung water changes after thermal injury: The effects of crystalloid resuscitation and sepsis. *Ann Surg* 192:479-488, 1980