

Title : MECHANISM OF PULMONARY EDEMA IN BURN WOUND SEPSIS

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Introduction. Gram-negative sepsis is a major cause of mortality in the critical care unit. This is especially true of those forms of the syndrome manifest as low cardiac index (CI) and pulmonary edema. A previous report (1) from this laboratory described a chronic burn wound sepsis model in sheep which was found to approximate clinical sepsis. Two syndromes of sepsis were observed: 1) hyperdynamic (\uparrow CI) and 2) hypodynamic sepsis (\downarrow CI). The major difference between these two syndromes was related to an accumulation of fluid in the lungs of the hypodynamic animals which oftentimes led to their death. It was postulated that this movement of fluid from the vascular system into the lungs, and perhaps elsewhere, was responsible for the fall in CI. Thus, the purpose of the present study is to determine the mechanism of pulmonary edema (pressure or permeability induced) and to relate the fall in CI in the hypodynamic group to the movement of fluid into the lungs.

Methods. A two stage thorocotomy (one right, one left) was performed in five female range sheep over a two-week period. A silastic catheter and balloon were placed into the left atrium and the pulmonary lymphatics were cannulated. Such chronic lymph fistulas provide nearly pure lung lymph which can be used to monitor the integrity of the pulmonary vasculature (2). A flow directed, thermister-tipped catheter (7 Fr) was placed into the pulmonary artery for measurement of pulmonary arterial pressure (PAP) and cardiac output. Aortic arterial blood was withdrawn via femoral artery catheter for measurement of blood gases and protein analysis. One week later preburn controls were collected. The left atrial pressure (LAP) was elevated via balloon inflation. This allowed us to evaluate the pulmonary microvascular filtration characteristics under a pure condition of pressure edema. The next day the animals were anesthetized with halothane and a full-thickness flame burn was elicited over 40% of the body surface area. Three days later the burn eschar was seeded with *P. aeruginosa* (10^{11} organisms) and the animals were monitored for 7 days. During this time, the sheep were maintained in mobile metabolic cages with free access to food and water. Several cardiopulmonary variables were measured daily through the entire study. The permeability of the pulmonary vasculature was determined utilizing a permeability-surface area (PS) equation: $PS = LR / (1 - R)$, where L=lymph flow rate (ml/hr) and R=lymph-plasma protein ratio.

Results. Following infection the animals were separated into hyper- and hypodynamic

groups on the basis of cardiac index (1). Both responses were usually observed in the same animal on different days. As shown in the table, PS in the hypodynamic group was several times greater than in the other groups. This was associated with an increased lung lymph flow (L), a moderate rise in the lymph-plasma protein ratio (R), and an elevation in hematocrit (Hct). The pulmonary microvascular pressure (Pmv) in this group was not different than control; however, the PAP was elevated and the LAP was reduced. During a hypodynamic episode the animals routinely exhibited rales and a fall in PaO_2 . Four of the five animals died during this crisis and all four were shown to have severely edematous lungs at autopsy. The hyperdynamic group did not show a change in pulmonary vascular permeability. Moreover, L, R, and Hct were unchanged. Elevation of LAP via balloon inflation was found to more than double lymph flow rate without affecting PS.

	Preburn	Chronic Burn	Sepsis Low CI	Sepsis High CI
CI	5.11 \pm 0.44	5.50 \pm 0.60	4.34 \pm 0.37	7.53 \pm 0.42
PS	9.20 \pm 2.40	8.60 \pm 2.40	26.70 \pm 3.10	6.20 \pm 1.90
L	5.40 \pm 0.90	5.20 \pm 1.30	17.00 \pm 2.30	4.40 \pm 1.60
R	0.61 \pm 0.02	0.59 \pm 0.05	0.63 \pm 0.03	0.60 \pm 0.01
Pmv	9.80 \pm 0.80	9.40 \pm 0.70	9.00 \pm 0.40	10.20 \pm 1.40
Hct	26.00 \pm 0	24.00 \pm 1.00	28.00 \pm 2.00	24.00 \pm 1.00
LAP	3.70 \pm 0.90	2.30 \pm 1.10	-2.20 \pm 2.00	1.80 \pm 0.20
PAP	16.20 \pm 0.60	16.60 \pm 0.60	20.20 \pm 2.30	18.70 \pm 2.90

Discussion. The results indicate that the pulmonary edema associated with hypodynamic sepsis is mediated by an increased pulmonary vascular permeability. The mechanism for this is unknown. However, our studies as well as others (2) indicate that this permeability alteration is rapid and reversible. Indeed, an animal can be hypodynamic with \uparrow PS on one day and hyperdynamic with normal PS on the next. The increase in permeability with subsequent fluid loss (\uparrow Hct) may have resulted in the fall in CI. Our studies indicate that the increase in PS always precedes the fall in CI. In conclusion, an increase in permeability of unknown mechanism is responsible for pulmonary edema in sepsis and may be the predisposing factor which initiates the hypodynamic phase.

References

1. Adair TH, Thomson PD, Traber DL: Gram-negative sepsis in thermally injured sheep. *Advances in Shock Research* 2:205-218, 1979
2. Brigham KL, Woolverton WC, Black LH et al: Increased sheep lung vascular permeability caused by *Pseudomonas* bacteremia. *J. Clin Invest* 54:792-804, 1974

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