TITLE: COMPLEMENT MODERATION OF CARDIOPULMONARY RESPONSE TO BACTEREMIA IN SHEEP

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Complement system and neutrophil activation are important cofactors in sepsis-induced acute respiratory failure.[1] Complement depletion by pretreatment with cobra venom factor (CVF) in a bacteremic pig model lessened the pulmonary hypertension, hypoxemia, accumulation of extravascular lung water, and neutropenia. However, complement depletion in an endotoxic sheep model was not beneficial.[2] Resident macrophages in the pulmonary capillaries of both sheep and pigs phagocytize infused bacteria primarily in the lung.[2] CVF pretreatment was performed in sheep, who then were infused with live *Ps. aeruginosa*, to determine if complement depletion is beneficial with bacterial challenge.

Thirteen sheep were prepared with chronic hemodynamic and lung lymphatic catheters under halothane anesthesia one week before study. The CVF+*Ps.* group (n=6) received 100 U/kg of *Na/e ha/e* CVF 48 hr before femoral vein infusion with live *Ps. aeruginosa* (5×10^7 *Ps.*/min until mean pulmonary artery pressure was 40 mmHg, or up to 1 hr). The *Ps.* only group (n=7) received just the bacteria. Statistical differences were determined by analysis of variance with $p \leq 0.05$.

Equivalent total bacterial loads were infused: CVF+*Ps.*= 9.8 ± 2.5 X 10^8 and *Ps.* only = 5.6 ± 1.2 X 10^8 bacteria. CVF did not impair the efficient phagocytosis of bacteria in the lung. Mean pulmonary artery pressure initially doubled with persistent, equivalent pulmonary hypertension. The permeability index (PI = lymph flow X Lymph/Plasma protein ratio) was increased in both groups from 1.5–24 hrs, but the increase was significantly less from 16-24 hr in CVF+*Ps.* Equivalent cardiovascular depression occurred from 3-6 hr, with decreased cardiac index (CI) and elevated mean arterial pressure (MAP) and systemic vascular resistance (SVR). A hyperdynamic circulation with increased CI and decreased MAP and SVR occurred from 20-24 hr in *Ps.* only, but only mild hypotension occurred in CVF+*Ps.*

Complement depletion shortened the pulmonary permeability response and prevented the hyperdynamic circulation in bacteremic sheep, supporting a role for complement. The interactions between complement, neutrophils, and macrophages are complex, vary in different animal models, and direct activation of C5 could have occurred during bacteremia, since *Na/e ha/e* CVF only depletes C3.

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	0	4	12	20 hr
		PI (ml•hr^{-1})		
CVF+*Ps.*	4.3 ± 0.7	21.9 ± 5.5*	14.8 ± 5.2*	10.2 ± 2.1*
Ps. only	4.0 ± 0.3	23.0 ± 4.2*	25.8 ± 4.1*	19.5 ± 3.4*§
		CI (L•m^{-1}•m^{-2})		
CVF+*Ps.*	6.6 ± 0.5	4.3 ± 0.4*	7.0 ± 0.7	6.4 ± 0.5
Ps. only	6.4 ± 0.4	5.0 ± 0.4*	6.9 ± 0.7	8.4 ± 0.7*§
		MAP (mmHg)		
CVF+*Ps.*	91 ± 5	100 ± 5	77 ± 5*	85 ± 5
Ps. only	104 ± 4	101 ± 4	86 ± 6*	85 ± 5*

* = $p \leq 0.05$ within § = $p \leq 0.05$ between

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TITLE: THE ANTICONVULSANT AND PULMONARY EFFECT OF ENDOTRACHEALLY-ADMINISTERED MIDAZOLAM IN A MODEL OF STATUS EPILEPTICUS.

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Midazolam's (M) success as an anticonvulsant has prompted interest in its use for the treatment of status epilepticus. In status epilepticus, endotracheal intubation is performed to ensure adequate ventilation and oxygenation, as well as to provide access for the administration of emergency drugs. Endotracheally-administered (ETA) diazepam (D) is effective in ameliorating seizures; however, pathologic lung damage has been noted. The purpose of this study was twofold: 1) to evaluate the efficacy of ETA-M in terminating seizures, and 2) to determine the degree, if any, of ETA-M-induced pathologic lung damage.

In the first experiment, 25 male Sprague-Dawley rats were anesthetized with ketamine and acepromazine. After exposing the skull, screw electrodes for EEG were placed. Anesthesia was maintained with halothane 0.6% and pancuronium. Baseline EEG's were recorded. The animals were then given intraperitoneal pilocarpine 300mg/kg, to induce seizures. At the onset of epileptiform seizure activity, the animals were randomly given 10mg/kg of: (1)IM-D, (2)IM-M, (3)ETA-saline, (4)ETA-D, (5)ETA-M. Doses were repeated every 15 minutes x 2. 15 minutes after the final injection, the rats were euthanized. Data from this study appears in Table 1. ETA-M was noted to have a rapid onset of action with no seizure recurrences noted during the experimental time period.

TABLE 1: EFFECT OF THERAPY ON EEG EPILEPTIFORM ACTIVITY

Treatment		#1			#2			#3		
Group	Route	NR	P	C	NR	P	C	NR	P	C
Diazepam	IM	0	1	4	0	1	4	0	1	4
Midazolam	IM	0	2	3	0	1	4	0	0	5
Saline	ETA	5	0	0	4	1	0	4	1	0
Diazepam	ETA	0	4	1	0	0	5	0	0	5
Midazolam	ETA	0	0	5	0	0	5	0	0	5

NR:No response
P:Partial response (diminished spiking)
C:Complete response

The second experiment was then performed to assess the degree of ETA-M-induced lung damage. 8 cats were anesthetized with ketamine and xylozine, and randomly given ETA-M 1mg/kg or 10mg/kg. The cats were subsequently awakened, extubated and returned to the vivarium for 48 hours. They were then euthanized, the lungs fixed in vivo and excised. Specimens were reviewed by a pathologist blinded to the nature of the study. Microscopic examination revealed no evidence of chemical pneumonitis, edema, or alveolar infiltrates. Lungs of 2 cats (one ETA-M, 1mg/kg; one, 10mg/kg) revealed a moderate inflammation confined to the bronchial or bronchiolar walls.

Our results indicate that ETA-M is as effective in abolishing seizures in the pilocarpine-induced seizure model, and does so with minimal lung damage.