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EFFECTS OF STAPHYLOCOCCAL ENTEROTOXIN B ON FUNCTIONAL AND BIOCH--ETC(U)
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6 Effects of Staphylococcal Enterotoxin B on Functional and Biochemical Changes of the Lung in Macaques^{1,2,3}.

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10 C. T./Liu, R. D./DeLauter, M. J./Griffin and C. L./Hadick⁴

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Running Head: SEB and Respiration in Monkeys

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¹In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

²The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

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Key Words. Staphylococcal enterotoxin B, pulmonary function, metabolism, pulmonary edema, blood gas tension, rhesus monkey

Abstract. A single intravenous (i.v.) injection of staphylococcal enterotoxin B (SEB) in rhesus monkeys at doses of 0.05 to 1.0 mg/kg has been shown to cause hypotension and death within 20 h. The exact cause of death is not well understood. Since others have shown pulmonary edema during SEB enterotoxemia in monkeys, it was our purpose to study pulmonary functions and arterial blood gas tension, as well as surface tension, water content, and electrolyte concentrations in the lungs of anesthetized normal and SEB-challenged rhesus monkeys. Pulmonary functions did not change during the first 5 h after SEB inoculation. However, during the hypotensive period from 6 to 11 h following SEB injection, respiratory quotient increased, while functional residual capacity, CO₂ output, O₂ consumption and expired CO₂ concentration decreased. By 11.5 h, total lung water content increased, as shown by simultaneous accumulations of extracellular Na⁺ and water. Conversely, the intracellular lung water and Na⁺ decreased. Further, the surface tension of lung extracts increased, suggesting that pulmonary surfactant contents were reduced, and the lungs might have collapsed slightly in SEB-inoculated monkeys. Although acidemia developed gradually, severe hypoxia, hypercapnia, decreased pulmonary compliance and increased airway resistance were not observed in these hypotensive monkeys until shortly before death. These results provide evidence to support a hypothesis that pulmonary dysfunction and terminal pulmonary edema contribute to death during SEB enterotoxemia in monkeys.

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Although several Staphylococcal enterotoxin B (SEB) induced physiologic changes including peripheral capillary pooling, [2, 6] intracellular dehydration, hypovolemia [16] and decreased cardiac functions [14] have been considered as possible causes of death during SEB toxemia in monkeys, the exact mechanism for induction of irreversible shock during i.v. SEB toxemia is still unknown. These changes are not a part of the gastrointestinal responses to the enteral administration of SEB to monkeys.

Previous pathologic studies revealed that pulmonary interstitial edema and increased lung weights were associated with intravenous SEB toxicity in monkeys [7, 21, 22]. This investigation was undertaken to study pulmonary function, metabolic changes, and arterial blood gas tensions, as well as lung water content, electrolyte concentrations, and surface tension in anesthetized SEB-inoculated monkeys. As in previous studies reported from this laboratory [14-16], a preparation of SEB was employed that was purified to greater than 99%. Measured values were compared between normal and SEB-challenged monkeys under identical experimental conditions. Pulmonary dysfunction and terminal pulmonary edema were present during SEB enterotoxemia, suggesting that hypoxia may be the major cause of death.

Materials and Methods

Healthy male rhesus monkeys (Macaca mulatta) weighing 3.3 - 5.9 kg were allocated into control (n = 9) and SEB-inoculated groups (n = 6). The latter group of monkeys had no detectable serum antibody against SEB prior to their use. Approximately 20 h before the experiment, unilateral polyethylene catheters (PE 190, ID = 1.19 cm, OD = 1.70 mm) were placed in the femoral artery and vein under Ketamine anesthesia. Monkeys were restrained in primate chairs for recovery from anesthesia. The femoral catheters were also flushed with heparin in saline (20 units/ml) to maintain patency. Highly purified SEB [20] at a single dose of 1 mg/kg was injected into the femoral vein of experimental monkeys, while controls received only isotonic saline.

All monkeys were sedated with Ketamine (15 mg/kg, intramuscularly) and placed in a supine position approximately 3.5 h after i.v.-SEB injection. Endotracheal and intraesophageal incubation were completed within 30 min. Various pulmonary functions, metabolic changes, and blood gas tensions were determined hourly between 6 and 11 h after SEB or saline injection. Techniques for measuring respiratory and metabolic variables in rhesus monkeys were described previously [13]. Within 15 min after completion of pulmonary studies, various tissue samples including the lower lobe of the right lung were excised from the anesthetized dying monkey. Tissue samples were collected as previously described [17, 18]. Lung samples were immediately blotted with absorbent paper to remove surface blood and prepared for determinations of surface tension, water content, total lipids,

phospholipid, and electrolytes including Na^+ , K^+ [24], Cl^- [4] and phosphate phosphorus [8].

Lung tissue was homogenized in distilled water (1:10, w/v), and surface tension of the supernatant measured with a tensiometer (Model 21, Fisher Scientific Co., Pittsburgh, Pa.). Water content was determined by drying approximately 0.2 g of lung tissue to a constant weight in an oven at 110°C. The Cl^- content in the dry minced specimen was extracted for 20-24 h in 5 ml of distilled water, while Na^+ , K^+ , and phosphate phosphorus were extracted from the homogenized wet lung tissue with 5 ml of 10% trichloroacetic acid [17]. Distributions of intracellular and extracellular water and electrolytes in the lung were calculated according to the method of BENSON *et al.* [3].

Tissue phosphate extract was determined as TAS (total acid soluble) and IAS (inorganic acid soluble) fractions. The former was prepared using concentrated H_2SO_4 digestion at 310°C and the latter proceeded without acid digestion [18]. OAS (organic acid soluble) phosphate was calculated from the difference between TAS and IAS.

Total lipids in the lung were extracted with a chloroform-methanol mixture (2:1 V/V) for 20-24 h at room temperature [9]. The lung tissue was minced and a minimum of a 20:1 ratio of solvent to sample was used. The weight of total lipids in the lung was measured gravimetrically after complete evaporation of the solvent from the purified extract in a vacuum oven. Phosphorus content of phospholipid was determined by the method of BARTLETT [1]. The phospholipid concentration was obtained by multiplying the phosphorus value by a factor of 25, which is the estimated molecular weight ratio of phosphorus in phospholipid.

Values obtained from the experiments were compared using an analysis of variance with repeated measurements. The values at 6 h were used as the baselines for each monkey to test for significant changes over time. Further, differences from baselines for the control and SEB groups were also compared by an independent t-test. The Null hypothesis was rejected at the 5% level. .

Certain data were plotted as net changes from the 6-h values, which were not significantly different between control and SEB groups. However, true data for O_2 consumption and respiratory quotient (RQ) were plotted as a function of time because these values between control and SEB-inoculated monkeys were significantly different at 6 h by unpaired analyses.

Results

Pulmonary Functions and Blood Gases

Effects of i.v. SEB on tidal volume, pulmonary ventilation, and pulmonary mechanics in anesthetized rhesus monkeys breathing room air for 11 h are summarized in table 1. No significant changes were found. However, airway resistance, functional residual capacity (FRC) and expired CO₂ concentration decreased and respiratory rate increased significantly as compared to control monkeys 8-10 h after i.v. SEB injection (fig. 1, 2). Further, one monkey that died earlier (at 7.5 h) showed increased respiratory rate, dynamic pulmonary resistance and PaCO₂ while its tidal volume, dynamic pulmonary compliance, intraesophageal pressure, expired air flow, and arterial blood pH and PO₂ decreased markedly from control values approximately one half hour before death (table 2).

As compared to controls, rhesus monkeys showed significantly decreased O₂ consumption and increased RQ values at 6 h post-SEB inoculation (fig. 3). However, data on O₂ consumption and RQ remained unchanged as a function of time for 11 h after SEB inoculation. Although CO₂ output and expired CO₂ concentration were significantly decreased 9-11 h after SEB as compared with the control group of monkeys (fig. 4), arterial blood pH, PO₂, P_{CO₂}, HCO₃⁻, total CO₂, and base excess showed little or no changes during the entire 11 h experimental period (table 3).

Lung Surface Tension and Biochemical Changes

Although plasma water content and electrolytes concentrations were not altered after i.v. inoculation of SEB in anesthetized rhesus

monkeys (table 4), surface tension, OAS phosphorus, total water content, extracellular Na^+ (mEq/kg fat-free wet tissue) and total Cl^- (mEq/fatty-free dry tissue) of the lung increased significantly as compared with lungs from control monkeys (tables 4 and 5). There is also an apparent shift of intracellular lung water and Na^+ to the extracellular space in SEB-challenged monkeys (table 4). No significant changes were observed in K^+ distribution, total lipids, phospholipids, and phosphorus including IAS, and TAS of lungs 11-12 h after a lethal dose of SEB (tables 4 and 5).

Discussion

Since few changes in pulmonary functions occurred within 5 h after i.v. SEB injection in anesthetized rhesus monkeys, the present study encompassed the period 6 to 11 h after SEB. During this time, cardiovascular and hepatic functions are severely depressed [14] and body fluid volumes are significantly decreased [16]. Since SEB-challenged monkeys may survive for a few more hours beyond the 11-h experimental period, the present data only reflect changes at approximately the mid-point of SEB toxemia. According to our limited observations, a SEB-challenged monkey showed some important terminal changes including acidosis, hypoxia, hypercapnia, decreased dynamic pulmonary compliance, and increased airway resistance. The reason for presenting data from only one monkey was that all SEB-inoculated monkeys survived during the 11-h experimental period and this was the only monkey that died 7.5 h after i.v. SEB injection.

During the period of mid-toxemia of SEB, decreased FRC values were obtained. The possible cause for decreased FRC values without a simultaneous increase in tidal volume may be due to an accumulation of fluid in the lung or partial collapse of the lung. The former assumption is supported by the increased lung water content, and the latter is evidenced by the increase surface tension of the lung extract at 11-12 h. Since lung surfactant is responsible for preventing lung collapse through the mechanism of decreased pulmonary surface tension [10, 23] an increase in lung surface tension may also indicate that lung surfactant concentrations were decreased in SEB-challenged monkeys.

Metabolically, both total-body O_2 consumption and CO_2 output decreased, while RQ values increased to > 1.0 . These findings indicate that (1) cellular metabolism was depressed, although fever might be present [2, 5, 22], (2) anaerobic oxidation was involved, (3) carbohydrate (glucose) was the main fuel for energy release and utilization, and (4) a steady-state was not achieved.

Various forms of phosphorus in the lung, including phospholipid, IAS, and OAS were measured in control and SEB-inoculated macaques. Among the three categories of phosphorus, only OAS showed significant increases after SEB. Since OAS is a mixture of creatine phosphate, ATP, ADP, and AMP, it is unknown which substance(s) is affected. Further, the significance of an increased OAS in the lung during SEB toxemia remains unknown.

The SEB-induced pulmonary edema, as characterized by increase in lung weights and pathological changes of pulmonary capillary endothelial cells, has been shown by others [7, 21, 22]. Results from the present study confirm the presence of terminal pulmonary edema in monkeys following a lethal i.v. dose of SEB. This is based on the finding that extracellular water and Na^+ in lung tissue were increased at 11 h. When lungs are filled with water to a critical level, pulmonary exchanges for O_2 and CO_2 are impaired and oxygenation of vital organs is decreased, leading to death within 20 h. Such rapid death minimizes the likelihood that renal, hepatic, or gastrointestinal changes are directly involved in the lethal effect of i.v. SEB.

Results from our preliminary studies reveal that continuous positive pressure breathing (CPPB), maintained at 3-4 cm H_2O for 2 days, may prevent death in SEB-challenged macaques [15] and in Dutch

rabbits (unpublished observations). These findings indicate that CPPB is effective in preventing SEB-induced pulmonary edema, despite further decreases in cardiac output and blood pressure [11, 12]. Because SEB-challenged animals continue to survive after 2 days of treatment with CPPB, it is suggested that pulmonary capillary membranes are not critically damaged, or that capillary damage is reversible within a relatively short time.

Based upon the evidence for functional and biochemical changes in the lung during SEB toxemia, it is concluded that respiratory dysfunction, pulmonary edema, and its associated hypoxia are major contributing factors leading to death of rhesus monkeys after i.v. SEB-inoculation.

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Table 1. Effects of SEB on tidal volume, pulmonary ventilation, and pulmonary mechanics in anesthetized rhesus monkeys breathing room air compared to controls

Variable	Group ¹	Values by hours post-SEB (mean ± SEM)		
		6	7	11
Tidal volume (ml)	Control	35 ± 4	---	36 ± 4
	SEB	36 ± 5	38 ± 10	38 ± 7
Minute volume (L/min)	Control	1.36 ± 0.16	---	0.98 ± 0.13
	SEB	1.25 ± 0.17	1.16 ± 0.18 °	1.28 ± 0.17
Physiological dead space (ml)	Control	4.33 ± 1.97	---	2.52 ± 2.44
	SEB	6.56 ± 3.6	10.1 ± 5.0	12.5 ± 5.2
Intraesophageal Pressure (cm H ₂ O)	Control	-5.7 ± 0.6	---	-5.6 ± 0.8
	SEB	-4.78 ± 0.9	-5.59 ± 1.4	-5.42 ± 1.5
Transpneumotach Pressure (cm H ₂ O)	Control	1.13 ± 0.09	---	0.85 ± 0.07
	SEB	0.93 ± 0.10	0.91 ± 0.16	0.98 ± 0.12
Transpulmonary Pressure (cm H ₂ O)	Control	-4.54 ± 0.55	---	-4.75 ± 0.78
	SEB	-3.85 ± 0.85	-4.69 ± 1.22	-4.44 ± 1.42

Table I. - Continued.

Maximum Expiratory flow (ml/sec)	Control	66.6 ± 6.1	---	56.9 ± 8.7	61.9 ± 7.5
	SEB	60.6 ± 10	59.6 ± 11	66.2 ± 11	61.8 ± 10
Maximum inspiratory flow (ml/sec)	Control	64.0 ± 5.1	---	48.4 ± 3.7	59.5 ± 6.8
	SEB	52.8 ± 6	51.3 ± 9	55.6 ± 7	51.1 ± 5
Dynamic pulmonary Compliance (ml/cm H ₂ O)	Control	8.2 ± 0.9	---	9.4 ± 1.8	7.9 ± 1.7
	SEB	8.6 ± 1.7	7.1 ± 1.1	9.1 ± 1.9	6.8 ± 1.5
Specific compliances [(compliance/FRC) × 10 ⁻³]	Control	72 ± 9	---	83 ± 14	52 ± 7
	SEB	77 ± 18	71 ± 13	101 ± 22	113 ± 48

1 Controls, n = 9; SEB, n = 6 monkeys.

Table II. Changes in pulmonary functions and arterial blood pH, PO₂ and PCO₂ during terminal SEB enterotoxemia (0.5 h before death)

Variable	Values (mean ± SEM)		
	Control (n = 9)	SEB (n = 1)	
Tidal volume (ml)	38 ± 15	19	
Respiratory rate (cycle/min)	33 ± 5	57	
Dynamic pulmonary compliance (ml/cm H ₂ O)	8.3 ± 4.3	1.8	
Dynamic pulmonary resistance (cm H ₂ O/L/sec)	31 ± 7	168	
Intraesophageal pressure (cm H ₂ O)	-6.3 ± 0.7	-15.7	
Expired airflow (ml/sec)	62 ± 2	47	
Arterial Blood	pH	7.375 ± 0.008	7.318
	PO ₂ (mm Hg)	88.6 ± 4.9	33.3
	PCO ₂ (mm Hg)	29.0 ± 2.7	38.8

Table III. Effects of SEB on arterial blood pH, gas tensions, total CO₂ and base excess in anesthetized rhesus monkeys breathing pure O₂

Variable	Group ¹	Values by hours post-SEB (mean ± SEM)			
		6	7	9	11
pH	Control	7.374 ± 0.009	----	7.362 ± 0.008	7.365 ± 0.01
	SEB	7.373 ± 0.015	7.394 ± 0.020	7.383 ± 0.017	7.378 ± 0.021
PO ₂ (mm Hg)	Control	367 ± 32	----	389 ± 23	411 ± 16
	SEB	413 ± 17	413 ± 24	392 ± 17	399 ± 30
PCO ₂ (mm Hg)	Control	33.4 ± 2.4	----	33.0 ± 2.8	31.3 ± 2.6
	SEB	34.2 ± 3.3	33.3 ± 2.7	32.1 ± 3.0	29.2 ± 3.5
HCO ₃ ⁻ (mmol/L)	Control	19.1 ± 1.5	----	19.0 ± 1.7	18.1 ± 1.7
	SEB	18.1 ± 2.0	18.9 ± 1.9	16.4 ± 1.7	15.9 ± 2.2
Total CO ₂ (mmol/L)	Control	20.4 ± 1.5	----	20.6 ± 1.7	19.6 ± 1.6
	SEB	21.5 ± 1.5	21.9 ± 1.3	20.5 ± 1.6	19.0 ± 2.5
Base excess (mmol/L)	Control	-3.7 ± 1.3	----	-4.2 ± 1.4	-5.0 ± 1.4
	SEB	-4.7 ± 1.2	-3.9 ± 1.3	-5.9 ± 1.2	-6.5 ± 2.0

¹ Controls, n = 9, SEB, n = 6.

Table IV - Changes in water and electrolyte in plasma and the lung of SEB-inoculated rhesus monkeys

Sample	Variable	Values (mean \pm SEM)	
		Control (n = 4)	SEB (n = 7)
Plasma	H ₂ O (g/100 ml)	93.0 \pm 0	93 \pm 0.1
	Na ⁺ (mEq/L)	143 \pm 2	143 \pm 3
	K ⁺ (mEq/L)	3.57 \pm 0.22	3.65 \pm 0.19
	Cl ⁻ (mEq/L)	113 \pm 4	108 \pm 4
	Total H ₂ O (H ₂ O) _T (g/kg FFWT ¹)	807 \pm 8	841 \pm 9 ⁵
Lung	Extracellular H ₂ O (H ₂ O) _E (g/kg FFWT)	386 \pm 53 ³	512 \pm 31 ⁴
	(H ₂ O) _T - (H ₂ O) _E (H ₂ O) _I (g/kg FFWT)	421 \pm 60 ³	329 \pm 36 ⁴
	Total Na (mEq/kg FFWT)	81.9 \pm 2.6	76.3 \pm 5.8
	Total Na (mEq/kg FFDT ²)	429 \pm 26	457 \pm 44
	Intracellular Na (mEq/kg intracellular H ₂ O)	62.8 \pm 3.0 ³	34.8 \pm 9.1 ⁴
	Extracellular Na (mEq/kg FFWT)	46.5 \pm 3.0 ³	66.6 \pm 3.1 ^{4,6}
	Total K (mEq/kg FFWT)	63.3 \pm 4.3	53.0 \pm 5.7
	Total K (mEq/kg FFDT)	326 \pm 21	311 \pm 38
	Intracellular K (mEq/kg intracellular H ₂ O)	161 \pm 16	162 \pm 22
	Extracellular K (mEq/kg FFWT)	1.46 \pm 0.27	1.80 \pm .17

Table IV - Continued.

Total Cl (mEq/kg FFWT)	54.8 ± 5.7	64.2 ± 2.7¹
Total Cl (mEq/kg FFDI)	290 ± 31	389 ± 16^{4,5}

¹ FFWT = fat free wet tissue.

² FFDI = fat free dry tissue.

³ n = 3.

⁴ n = 6.

⁵ By independent t-test, P < 0.05.

⁶ By independent t-test, P < 0.01.

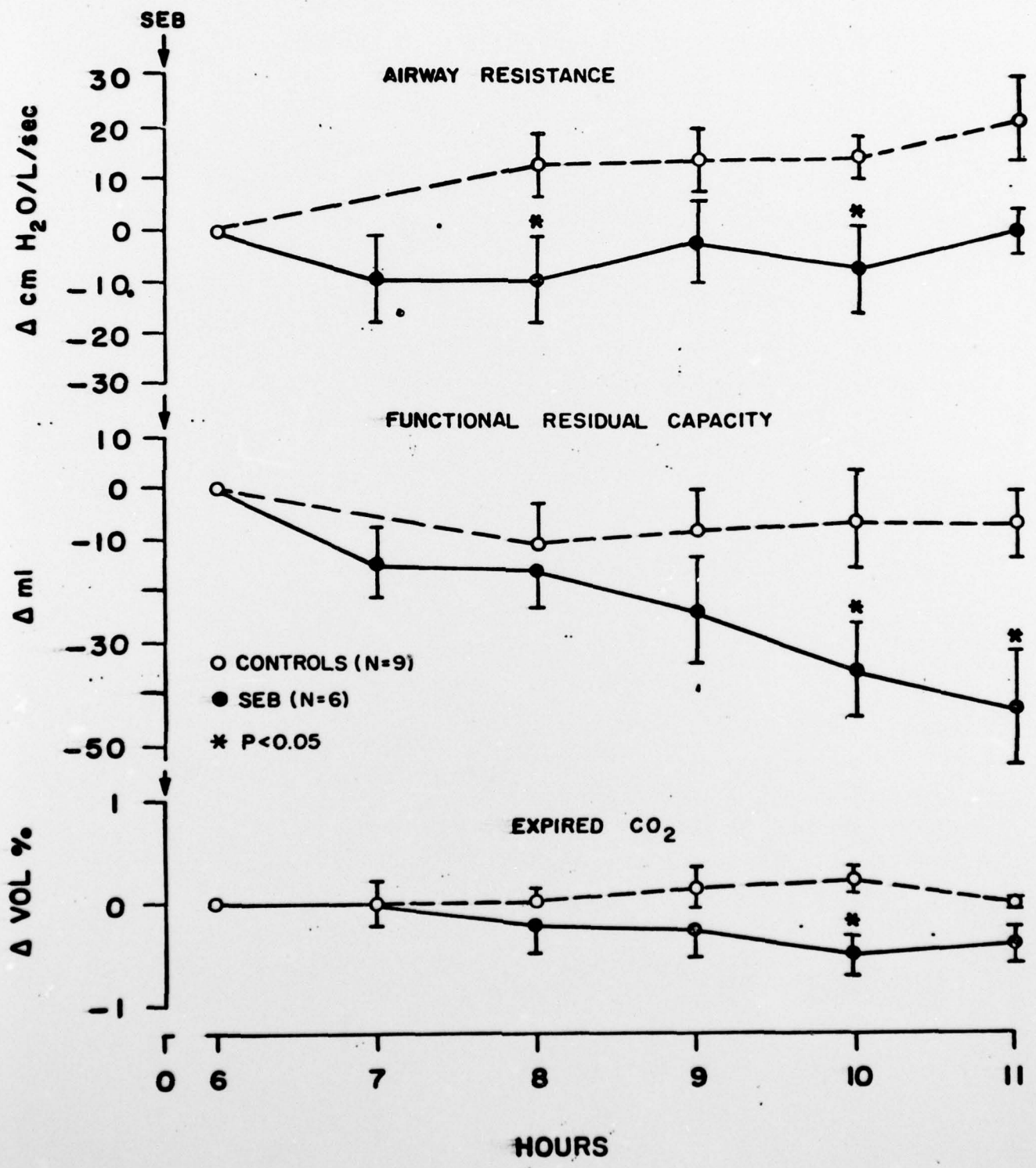
Table V - Changes in surface tension, total acid-soluble phosphorus (TAS), inorganic acid-soluble phosphorus (IAS), organic acid-soluble phosphorus (OAS), total lipids, and phospholipids in the lungs of control and SEB-inoculated monkeys

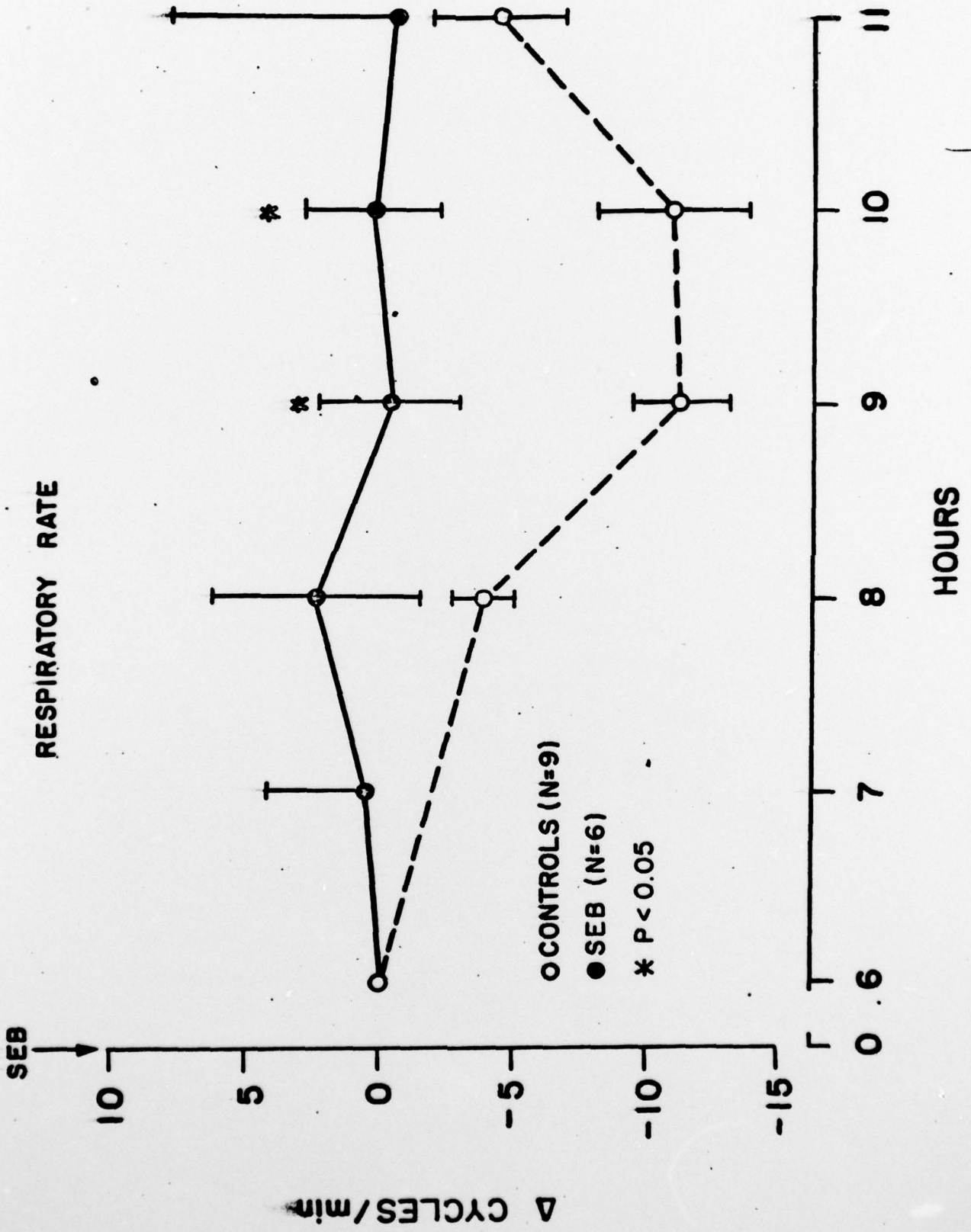
Variable	Values (mean \pm SEM)	
	Control (n = 4)	SEB (n = 6)
Surface tension ¹ (dyne/cm)	42.70 \pm 0.95	52.07 \pm 2.02 ²
TAS (mM/kg FFWT ³)	102.9 \pm 10.4	132.2 \pm 11.2
IAS (mM/kg FFWT ³)	50.3 \pm 9.9	40.7 \pm 4.0
OAS (mM/kg FFWT)	52.6 \pm 7.4	93.6 \pm 12.6 ²
Total lipids (g/kg)	21.36 \pm 3.76	15.27 \pm 1.73
Phospholipids (g/100 g)	1.80 \pm 0.27	1.48 \pm 0.11

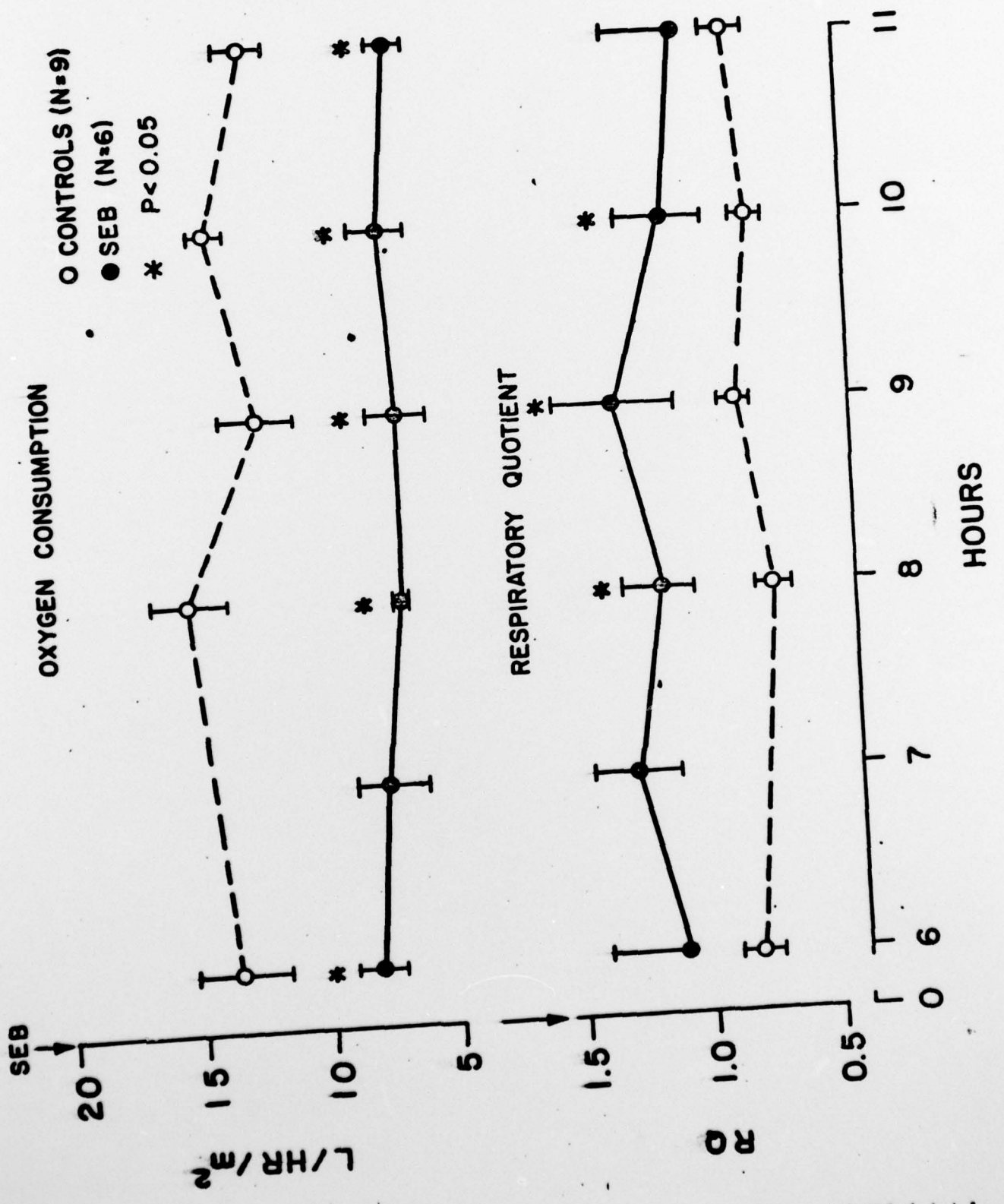
¹Control, n = 3, SEB, n = 7.

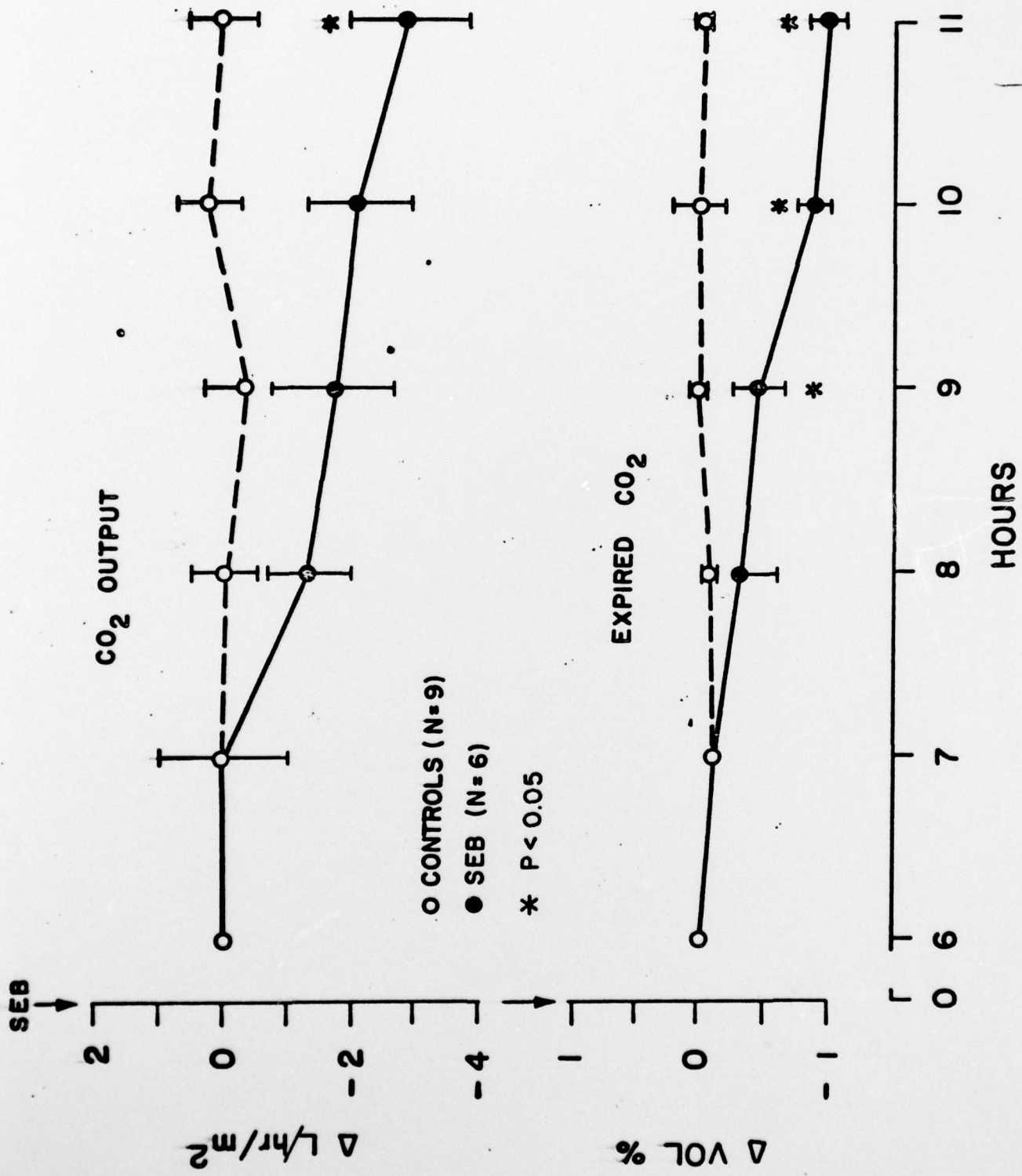
²By independent t-test, P < 0.05.

³Fat-free wet tissue.









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19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Staphylococcal enterotoxin B Rhesus monkey Pulmonary function Metabolism Pulmonary edema Blood gas tension		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A single intravenous (i.v.) injection of staphylococcal enterotoxin B (SEB) in rhesus monkeys at doses of 0.05 to 1.0 mg/kg has been shown to cause hypotension and death within 20 h. The exact cause of death is not well understood. Since others have shown pulmonary edema during SEB enterotoxemia in monkeys, it was our purpose to study pulmonary functions and arterial blood gas tension, as well as surface tension, water content, and electrolyte concentrations in the lungs of anesthetized normal and SEB-challenged rhesus monkeys. Pulmonary functions did not change during the first 5 h after SEB inoculation. (Cont'd)		

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However, during the hypotensive period from 6 to 11 h following SEB injection, respiratory quotient increased, while functional residual capacity, CO_2 output, O_2 consumption and expired CO_2 concentration decreased. By 11.5 h, total lung water content increased, as shown by simultaneous accumulations of extracellular Na^+ and water. Conversely, the intracellular lung water and Na^+ decreased. Further, the surface tension of lung extracts increased, suggesting that pulmonary surfactant contents were reduced, and the lungs might have collapsed slightly in SEB-inoculated monkeys. Although acidemia developed gradually, severe hypoxia, hypercapnia, decreased pulmonary compliance and increased airway resistance were not observed in these hypotensive monkeys until shortly before death. These results provide evidence to support a hypothesis that pulmonary dysfunction and terminal pulmonary edema contribute to death during SEB enterotoxemia in monkeys.

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