

Title : BRADYKININ AND LUNG LYMPH PROTEIN AND FLUID FLOW

Authors : L.M. Pang, M.D., S.A. Stalcup, M.D., H.O'Brodivich, M.D., J.S. Lipset, M.S., and R.B. Mellins, M.D.

Affiliation : Departments of Anesthesiology and Pediatrics, College of Physicians and Surgeons, Columbia University, New York, New York 10032.

**Introduction.** The effects of bradykinin (BK), a potent endogenous vasodilator and edema-producing substance, on lung fluid movement have not been defined. Bradykinin is known to be elevated in such pathophysiologic states as acidosis, sepsis, hypotension, severe hypertension and profound hypothermia. Since acute hypoxia inhibits converting enzyme activity (CEA)<sup>1</sup> and hence BK degradation, we hypothesized that an elevated blood concentration of BK produced during acute hypoxia would increase lung microvascular permeability to proteins and water.

**Methods.** Through bilateral thoracotomies, catheters were placed in the pulmonary artery, left atrium, aorta, jugular vein and efferent duct of the caudal mediastinal lymph node<sup>2</sup> in anesthetized sheep weighing between 25-35 kg. Three days later, 0.6-1.2 ug/kg/min BK was infused intravenously into 7 unanesthetized sheep with chronic lymph fistulas during normoxia and hypoxia (PaO<sub>2</sub>=30-40 torr). At 15 min intervals, simultaneous blood samples from the pulmonary artery and aorta were obtained for radioimmunoassay of BK and lymph fluid was obtained for volume and protein determinations.

**Results.** During normoxia when CEA was normal and only BK concentration in the pulmonary artery (BK pA) was elevated to  $2.9 \pm 1.1$  ng/ml there was an increase in lung lymph fluid flow ( $1.8 \pm 0.3$  to  $2.7 \pm 0.4$  ml/hr) and lung lymph protein flow ( $7.7 \pm 1.3$  to  $11.7 \pm 2.0$  mg/hr). When CEA was inhibited by acute hypoxia and both BK pA and BK concentration in the aorta (BK Ao) were elevated ( $25$  ng/ml) there was a greater than 200% increase from baseline for both lung lymph protein ( $25.3 \pm 8.0$  mg/hr) and fluid flow ( $6.6 \pm 2.1$  ml/hr). The greatest increase in microvascular hydrostatic pressure during that period was 6.3 torr. During hypoxia alone lung lymph protein and fluid flow returned to baseline levels. A significant correlation between lung lymph protein flow and BK pA ( $r=0.85$ ,  $p=0.01$ ) and BK Ao ( $r=0.83$ ,  $p=0.01$ ) was found. Figure 1 shows the relation of BK and oxygen on physiologic changes during one sheep experiment.

**Discussion.** The results show that there is a bradykinin concentration related increase in lung lymph protein and fluid flow. Since the changes in microvascular hydrostatic pressures were too small to account for the large increases in lung lymph protein and fluid flow<sup>3</sup>, our results suggest that BK produces an increase in pulmonary vascular permeability to proteins and water. This change is dependent on the interaction between O<sub>2</sub>, CEA and BK concentration.

# References.

1. Stalcup SA, Lipset JS, Legant PM, Leuenberger PM, Mellins RB: Inhibition of converting enzyme activity by acute hypoxia in dogs. J Appl Physiol: Respirat. Environ and Exercise Physiol 46:227-234, 1979.
2. Staub NC, Bland RD, Brigham KL, Demling R, Erdmann AJ III, Woolverton WC: Preparation of chronic lung lymph fistulas in sheep. J Surg Res 19:315-320, 1975.
3. Erdmann AJ III, Vaughan TR Jr, Brigham KL, Woolverton WC, Staub NC: Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circ Res 37:271-284, 1975.

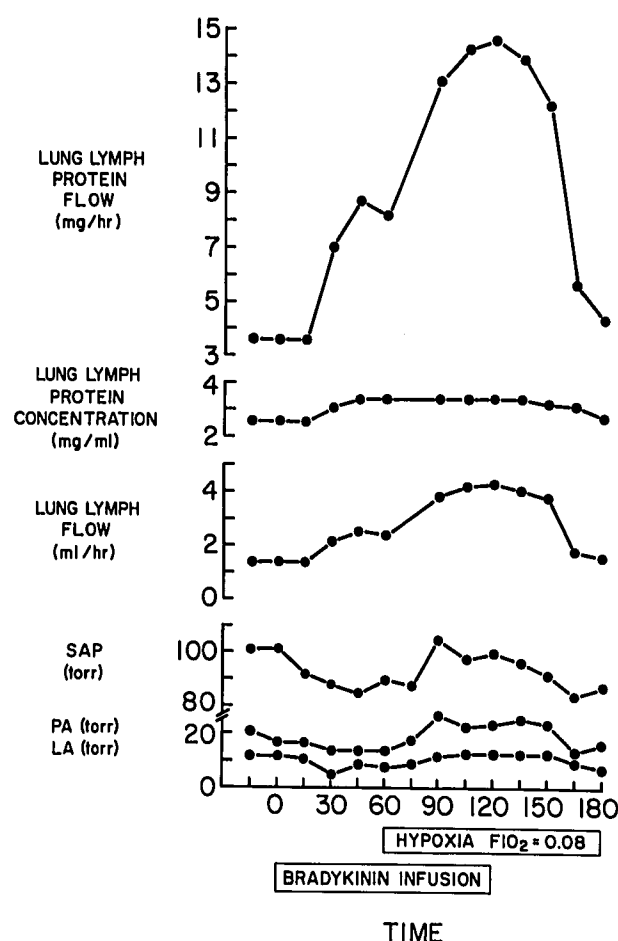


Fig. 1: The relation between bradykinin and oxygen on systemic arterial (SAP), pulmonary arterial (PA) and left atrial (LA) pressures and lung lymph protein and fluid flow is shown.