Influence of Endogenous Endothelial and Neural Nitric Oxide on the Bronchial Vasculature*

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To test whether endogenous nitric oxide (NO) influences baseline bronchial vascular tone and mediates acetylcholine (ACh)-induced bronchial vascular dilation, and to determine the importance of NO as a neurally derived modulator of ovine bronchial vascular smooth muscle, we studied anesthetized, ventilated, open-chested sheep and measured bronchial blood flow (QBr) using a transonic flow probe.

In six sheep, we measured the response of QBr to the dose of ACh required to produce 50% of the maximal increase in QBr at baseline during infusion of the NO synthase inhibitor Nω-nitro-L-arginine (10^{-2} M) (L-NNA), and of the vasoconstrictor phenylephrine in a dose sufficient to decrease baseline QBr to the same extent as seen with L-NNA. Infusion of L-NNA decreased both the baseline QBr (28±13 to 8±2 mL/min, p<0.01) and the ACh-induced increase in QBr from the baseline value (84±42 to 33±18 mL/min, p<0.05). We concluded from this study that endothelial-derived NO maintains baseline bronchial vascular caliber and mediates vasodilation. Using a similar preparation, we investigated the importance of NO as a neurally derived modulator of ovine bronchial vascular smooth muscle. In nine anesthetized, ventilated, open-chested sheep, we measured the response of QBr to vagal stimulation during a control period; during infusion of the α-agonist phenylephrine (to reduce baseline QBr by the same amount as would be produced by infusion of L-NNA), and during infusion of L-NNA (10^{-2} M). L-NNA and phenylephrine reduced baseline blood flow to the same extent (16±7 to 9±6 mL/min, and 16±7 to 8±2 mL/min, respectively). Vagal stimulation increased QBr from 16±7 to 34±12 mL/min; although baseline flow was decreased, the vasodilatation produced by vagal nerve stimulation was not significantly attenuated during L-NNA or phenylephrine infusion (8±1 to 21±4 mL/min and 9±6 to 17±9 mL/min, respectively). The bronchial vascular dilation induced by vagal nerve stimulation was completely blocked after administration of atropine (1.5 mg/kg) (11±5 to 12±5 mL/min).

We concluded from this study that bronchial vasodilation caused by stimulation of the vagus nerve is due to the release of ACh but is not mediated through ACh-induced secondary release of NO.

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Lung Injury After Heavy Exercise at Altitude*

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Exposure to high altitude imposes a risk of developing high altitude pulmonary edema (HAPE). The etiology of HAPE is not completely understood but appears to be due to an increase in lung capillary permeability, often associated with exercise. We investigated the potential of heavy exercise at altitude to cause pulmonary vascular damage and pulmonary capillary leak in humans by monitoring postexercise gas exchange, plasma levels of E-selectin, and bronchoalveolar cell counts and T cell phenotypes.

MATERIALS AND METHODS

Five healthy volunteers were studied at the White Mountain Research Station (3,810 meters) in California. The subjects exercised on a cycle ergometer at 85% maximum for 5 min, with a 5 min recovery at 30% maximum, repeating this three times. Radial artery blood samples and gases were drawn at rest, during exercise, at 15, 30, 60, 90, and 120 min, and 24 h postexercise. At 120 min and 24 h postexercise, bronchoalveolar lavages (BAL) were performed. The BAL fluid samples were analyzed for cell count and protein concentration. The harvested T cells were analyzed by flow cytometry for expression of γδ TCR as a marker of epithelial injury. Plasma was analyzed by enzyme-linked immunosorbent assay (ELISA) for soluble E-selectin (sE).

RESULTS

Blood gas data showed that the P(A-a)O2 gradient widens with exercise and then returns to baseline by 90 min, but widens to 16.9±4.0 (p=0.02) at 120 min. The BAL at 120 min showed 5.46X104 RBC and 5.84X104 WBC with 525 γδ T cells. At 24 h, the cell counts increased to 15.58X104 RBC (p=0.03), 10.72X104 WBC (p=0.08), and 1,600 γδ T cells. sE concentration (ng/mL) significantly increased (p<0.05) from 28.7±8.9 pre-exercise to 39.4±14.2 at 24 h postexercise. All data are presented as mean±SD.

DISCUSSION

Pulmonary γδ T cells are typically found in the epithelium, where they are in intimate association with epithelial cells. The role of γδ T cells is not well defined, but they appear to monitor epithelial cells for signs of damage and play an important role in inflammation and tissue repair by secreting chemokines. The appearance of γδ T cells in the BALF is suggestive of epithelial injury. Since E-selectin is an inducible adhesion molecule only expressed on activated endothelium, the