Inhaled and intravenous methacholine evoke differential effects on bronchial blood flow and 3rd generation airway dimensions in awake sheep

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Evolution and natural selection of specific mechanisms in mammals has ensured that airway absorption of inhaled atmospheric molecules normally presents a limited threat to homeostasis. Indeed there is evidence (Charan *et al.*, 1998) suggesting nebulized cholinoceptor agonists have limited capacity to traverse the airway wall. If they could, the bronchi may constrict and the bronchovascular bed dilate, two actions which when combined would cause airway obstruction. Other evidence suggests inhaled β-adrenergic agonists inhibit vagal constrictor tone in both airway wall and the bronchovascular bed, two actions in opposition which clinically prevent airway obstruction. However, whether autonomic agonists, and antagonists, selectively affect airway wall structures by either inhaled or vascular route is not defined.

In order to examine the hypothesis that inhaled cholinergic agonists and antagonists do have selective access to wall structures in high airflow resistance 3rd generation bronchi, six sheep were instrumented at left thoracotomy under general anaesthesia (i.v. propofol 5 $mg.kg^{-1}$, 2-3% isoflurane – oxygen) each with pulsed-Doppler blood flow transducers mounted on the single bronchial artery, and sonomicrometer probes (AIDA, Bishop *et al.*, 2007) mounted on the 3rd generation lingular lobe bronchus. The instruments permit continuous measurement of bronchial blood flow (Q_{br}) and conductance (C_{br}), plus bronchial hemi-circumference ($CIRC_{br}$) and wall thickness (WALL TH_{br}). Dose-response studies were performed in the recovered, standing awake sheep using i.v. methacholine (MCh: 0.125, 0.25, 0.5, 1.0, 2.0 $\mu g.kg^{-1}$), and nebulized MCh inhaled through a mask, (1, 2, 4, 8, 16, 32 $mg.kg^{-1}$), to compare selectivity of access to airway wall structures and effects on lower airway dimensions. MCh i.v. at the highest dose (2 $\mu g.kg^{-1}$) caused a 233% rise in Q_{br} from control ($P<0.05$), and 286% rise in C_{br} ($P<0.05$). $CIRC_{br}$ fell to 90% of control ($P<0.05$); WALL TH_{br} did not change. Inhaled MCh at the highest dose (32 $mg.kg^{-1}$) caused a rise in ventilation, and a proportional rise in aortic pressure and Q_{br} ; $CIRC_{br}$ fell to 91% ($P<0.05$); C_{br} and WALL TH_{br} did not change. Thus MCh caused similar reductions in $CIRC_{br}$ when given i.v. or when inhaled, but bronchovascular dilatation only when MCh was given i.v., and not when inhaled.

It is concluded that at very high concentrations of inhaled cholinoceptor agonists there is selective contraction of the airway wall smooth muscle, because at these concentrations no effects occur in the bronchial circulation. By contrast, at much lower intravascular MCh concentrations the effects are non-selective, suggesting that the same circumferential wall shortening is accompanied by bronchovascular dilatation presumably due to endothelial NO release. A new hypothesis is that the lymphatics are normally a major physiological factor coping with bronchovascular fluid extravasation to the interstitial space during circumferential shortening of the airway.

Charan NB, Carvalho P, Johnson SR, Thompson WH, Lakshminarayan S. (1998) Effect of aerosolized acetylcholine on bronchial blood flow. *Journal of Applied Physiology* **85:** 432-436.

Bishop R, McLeod D, McIlveen S, Blake R, Gunther R, Davis J, Talken L, Cottee D, Quail A, Parsons G, White S. (2007) Effects of graded exercise on bronchial blood flow and airway dimensions in sheep. *Pulmonary Pharmacology & Therapeutics* **20,** 178- 189.