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Bronchoconstriction induced by inhaled methacholine delays desflurane uptake and elimination in a piglet model

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ABSTRACT

Bronchoconstriction is a hallmark of asthma and impairs gas exchange. We hypothesized that pharmacokinetics of volatile anesthetics would be affected by bronchoconstriction. Ventilation/perfusion (V_A/Q) ratios and pharmacokinetics of desflurane in both healthy state and during inhalational administration of methacholine (MCh) to double peak airway pressure were studied in a piglet model.

In piglets, MCh administration by inhalation (100 μg/ml, $n = 6$) increased respiratory resistance, impaired V_A/Q distribution, increased shunt, and decreased paO_2 in all animals. The uptake and elimination of desflurane in arterial blood was delayed by nebulization of MCh, as determined by Micropore Membrane Inlet Mass Spectrometry (wash-in time to P50, healthy *vs.* inhalation: 0.5 min *vs.* 1.1 min, to P90: 4.0 min *vs.* 14.8 min). Volatile elimination was accordingly delayed.

Inhaled methacholine induced severe bronchoconstriction and marked inhomogeneous V_A/Q distribution in pigs, which is similar to findings in human asthma exacerbation. Furthermore, MCh-induced bronchoconstriction delayed both uptake and elimination of desflurane. These findings might be considered when administering inhalational anesthesia to asthmatic patients.

1. Introduction

The distribution of ventilation/perfusion (V_A/Q) ratios in experimentally induced bronchoconstriction (*e.g.* by methacholine, MCh) has been demonstrated to be comparable with findings in bronchial asthma (Rodriguez-Roisin et al., 1984). A characteristic finding is the bimodal shape of the distribution of perfusion with blood flow to lung units with either normal or low ventilation/perfusion (V_A/Q) ratios (Ballester et al., 1989; Kleinsasser et al., 2007; Rubinfeld et al., 1978; Wagner et al., 1978).

There are contradictory data on the relative contributions of the airways and parenchyma to MCh-induced constriction that can be attributed to the different routes of MCh delivery. Measurements

Abbreviations: MV, mechanical ventilation; V_T, tidal volume; MMIMS, micropore membrane inlet mass spectrometry; MIGET, multiple inert gas elimination technique; GC, gas chromatography; Des, desflurane; V_A/Q, ventilation-/perfusion ratio.

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Table 1
Hemodynamics, ventilation and gas exchange variables prior to and after metacholine inhalation.

Parameter	Baseline	After DES wash-in	After wash-out	During MCh inhalation	After Des wash-in with MCh	After Des wash-out with MCh
MV (l/min)	6.1 ± 0.71	6.23 ± 0.53	5.82 ± 0.53	6.06 ± 0.45	6.52 ± 0.46	6.18 ± 0.33
$etCO_2$ (mmHg)	37 ± 4	35 ± 3	35 ± 4	41 ± 8	46 ± 9*	50 ± 7*
V_T (ml)	251 ± 18	259 ± 18	244 ± 13	244 ± 12	261 ± 16	239 ± 17
PAW_{peak} (cmH_2O)	15.5 ± 1.1	15.1 ± 1.4	16.2 ± 1.7	32.6 ± 4.6*	35.7 ± 2.2*	37.7 ± 4.1*
PAW_{Mean} (cmH_2O)	8.3 ± 0.4	8.3 ± 0.4	8.4 ± 0.5	10.4 ± 2.5*	12.0 ± 1.8*	12.3 ± 2.2*
R_{tot} (cmH_2O/l/s)	5.6 ± 0.9	4.9 ± 0.6	5.9 ± 0.8	25.1 ± 5.1*	26.4 ± 4.0*	29.4 ± 6.6*
paO_2 (mmHg)	210 ± 16	204 ± 15	209 ± 19	74 ± 19*	71 ± 19*	70 ± 18*
$paCO_2$ (mmHg)	40 ± 4	36 ± 2	38 ± 2	53 ± 10*	61 ± 10*	61 ± 8*
SaO_2 (%)	100 ± 1	100 ± 1	100 ± 0	89 ± 7*	90 ± 7*	91 ± 6*
pvO_2 (mmHg)	43 ± 2	42 ± 4	42 ± 2	34 ± 4*	34 ± 6*	37 ± 6*
$pvCO_2$ (mmHg)	47 ± 4	45 ± 4	46 ± 4	61 ± 6*	68 ± 7*	67 ± 4*
HR (1/s)	118 ± 21	111 ± 11	107 ± 16	110 ± 24	109 ± 18	115 ± 24
MAP (mmHg)	96 ± 21	75 ± 22	90 ± 18	90 ± 20	79 ± 13	91 ± 19
MPAP (mmHg)	19 ± 3	17 ± 2	18 ± 3	29 ± 7*	31 ± 4*	31 ± 4*
CVP (mmHg)	6 ± 2	7 ± 1	7 ± 2	9 ± 2	10 ± 2	9 ± 3
CO (l/min)	4.0 ± 0.8	3.9 ± 0.4	3.7 ± 0.8	3.8 ± 0.8	3.6 ± 0.8	4.0 ± 0.8
PVR (dyn*s/cm^5)	282 ± 88	275 ± 31	276 ± 75	476 ± 152*	506 ± 89*	486 ± 136*
SVR (dyn*s/cm^5)	1868 ± 621	1653 ± 744	1887 ± 737	1745 ± 335	1561 ± 284	1617 ± 265

MV: minute ventilation, V_T: tidal volume, Paw : airway pressure, R_{tot}: total respiratory resistance, pa: arterial partial pressure, SaO_2: oxygen saturation in arterial blood, pv: venous partial pressure, HR: heart rate, MAP: mean arterial pressure, MPAP: mean pulmonary arterial pressure, CVP: central venous pressure, CO: cardiac output, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance.

* $p < 0.05$, as compared with the healthy state, $n = 6$.

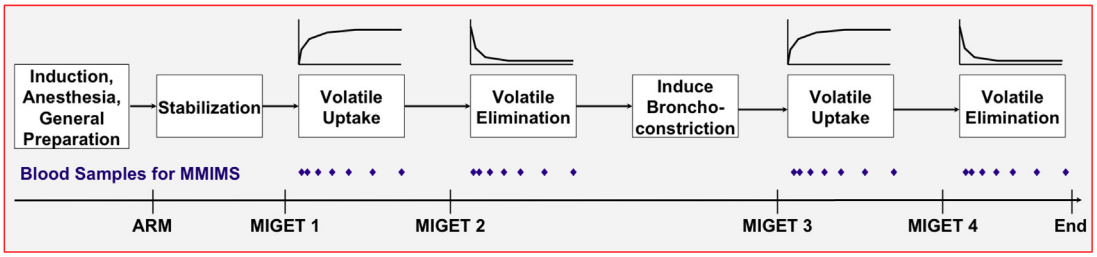

Fig. 1. Experimental Workflow. *Abbr.*: ARM, Alveolar Recruitment Maneuver; MMIMS, Micropore Membrane Inlet Mass Spectrometry; MIGET, Multiple Inert Gas Elimination Technique.

with different resident gases (air *vs.* neon-oxygen mixture (Lutchen et al., 1996) in rat lungs indicate that the intravenous challenge of MCh is a result of tissue inhomogeneity. However, this study could not distinguish alveolar parenchymal effects from patchy airway effects. Inhalation administration might also have involved real tissue contractions *via* selective stimulation of muscarinic receptors (McLeod et al., 2012). Thus, nebulized MCh seems to have greater effects on the airways (Petak et al., 1997).

The alveolar and blood concentrations of inhalational anesthetics depend first on inspiratory partial pressure and alveolar ventilation but secondary on diffusion of the volatile agent from the alveoli into the pulmonary capillary blood, the distribution of pulmonary perfusion, and mixed venous concentrations (Eger and Saidman, 2005).

The potential changes of uptake and elimination of a volatile based on uneven distribution of ventilation and/or pulmonary perfusion have not been demonstrated yet. Clinical experience suggests a delayed induction and emergence from anesthesia in patients suffering from obstructive pulmonary diseases (Seigne et al., 2000). These conditions decrease alveolar ventilation, and pulmonary ventilation-/perfusion-(V_A/Q) mismatch may occur. As a result, uptake and elimination of volatile anesthetics might also be impaired.

The prevalence of obstructive lung diseases is growing; thus, understanding of the pharmacokinetics of inhalation anesthetics in different pulmonary pathologies has become increasingly important. The inspiratory fraction of the agent is routinely adjusted in relation to the clinical parameters of the patient. The differences in recovery time from desflurane anesthesia are frequently related to cardiopulmonary changes, such as decrease in cardiac output, arterial hypotension and alveolar hypoventilation as a result of atelectasis formation, which may be potentiated by desflurane. Whether there would be some clinically relevant differences in the pharmacokinetics of the agent due to the alterations in V_A/Q distributions, is usually not considered. Hence, additional investigations are needed to include effects of ventilation/perfusion distribution mismatch on pharmacokinetics of inhalational anesthetics.

The objective of this experimental study is therefore to test two hypotheses in a porcine model: (I) Inhaled methacholine causes patchy—asthma-like—bronchoconstriction, indicated by an inhomogeneous V_A/Q distribution, and (II) MCh inhalation delays desflurane uptake and elimination.

2. Materials and methods

The present experiment was scheduled as a prospective, controlled, animal study in a single cohort of juvenile piglets. The Animal Ethics Committee of Uppsala University (Sweden) approved the study protocol. The care and handling of animals were in accordance with National Institutes of Health guidelines for ethical animal treatment (National Research Council (US) Committee on Regulatory Issues in Animal Care and Use, 2000).

2.1. Animals

Six healthy, 2.5-month-old piglets, weight 26.8 ± 1.9 kg, of mixed Yorkshire/Norwegian country breeds obtained from a local