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Bronchoconstriction during alveolar hypocapnia and systemic hypercapnia in dogs with a cardiopulmonary bypass

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ABSTRACT

The roles of the alveolar and systemic CO_2 on the lung mechanics were investigated in dogs subjected to cardiopulmonary bypass. Low-frequency pulmonary impedance data (Z_L) were collected in open-chest dogs with an alveolar CO_2 level (FA_{CO_2}) of 0.2–7% and during systemic hypercapnia before and after elimination of the vagal tone. Airway resistance (R_{aw}), inertance (I_{aw}), parenchymal damping (G) and elastance (H) were estimated from the Z_L. The highest R_{aw} observed at 0.2% FA_{CO_2}, which decreased markedly up to a FA_{CO_2} of 2% (212 ± 24%), and remained unchanged under normo- and hypercapnia (FA_{CO_2} 2–7%). These changes were associated with smaller decreases in I_{aw} (−16.6 ± 3.7%), mild elevations in G (25.7 ± 4.7%), and no change in H. Significant increases in all mechanical parameters were observed following systemic hypercapnia; atropine counteracted the R_{aw} rises. We conclude that severe alveolar hypocapnia may contribute to minimization of the ventilation–perfusion mismatch by constricting the airways in poorly perfused lung regions. The constrictor potential of systemic hypercapnia is mediated by vagal reflexes.

1. Introduction

Numerous factors contribute to the regulation of the bronchial tone via various excitatory and inhibitory mechanisms, including direct neural control and humoral/neural mediators. Carbon dioxide (CO_2) also plays a major role in this regulation: the relaxation potential of CO_2 on the bronchial smooth muscle has been demonstrated against the bronchoconstriction induced by constrictor drugs (Astin et al., 1973; Sterling et al., 1972). Further, the bronchoconstriction resulting from temporary regional pulmonary arterial occlusions is reversed by normalizing the alveolar CO_2 partial tension (Allgood et al., 1968; Coleridge et al., 1978; Darke and Astin, 1972; Even et al., 1972; Severinghaus et al., 1961; Swenson et al., 1961; Tisi et al., 1970). In addition to these direct effects, bilateral vagotomy or cooling the vagus nerve precludes the development of bronchoconstriction subsequent to systemic hypercapnea, demonstrating that CO_2 alters the airway caliber also via indirect mechanisms mediated through the vagal reflexes (Green and Widdicombe, 1966; Nadel and Widdicombe, 1962; Parker et al., 1963).

The effects of intra-alveolar CO_2 on airway caliber have frequently been investigated in isolated lung models by altering the fraction of inspired CO_2 (FI_{CO_2}). However, in the absence of neural–humoral control of the airways, which plays an important role in the regulation of the bronchial smooth muscle tone (Chapman and Danko, 1990; Coleridge et al., 1978; Green and Widdicombe, 1966), these earlier results could hardly give a complete description of the mechanisms involved in a lung with intact nerves. More comprehensive *in vivo* investigations have altered the alveolar CO_2 concentrations by changing the breathing pattern (D'Angelo et al., 2001; Ingram, 1975). However, respiratory resistance and elastance change with varying lung volume and/or ventilation frequency (Lutchen et al., 1993). Thus, an altered ventilatory pattern itself may affect the lung mechanics so that the active effects of CO_2 in the lungs are biased. Alternatively, regional hypocapnia studied by unilateral occlusion of a pulmonary artery was shown to elevate the airway tone (Allgood et al., 1968; Coleridge et al., 1978; Darke and Astin, 1972; Even et al., 1972; Severinghaus et al., 1961; Swenson et al., 1961; Tisi et al., 1970). Nevertheless, a diminished extent of pulmonary perfusion also

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increases the systemic CO_2 level which may lead to vagally mediated bronchoconstriction (Ingram, 1975; Nadel and Widdicombe, 1962). This phenomenon may have a synergistic constrictor effect on the affected airways, which becomes indistinguishable from the direct effects of altered intra-alveolar CO_2 in the lungs. Moreover, the pulmonary arterial occlusion approach does not allow the investigation of hypercapnia and it cannot eliminate the vagal reflexes. Accordingly, none of these *in vivo* approaches allow a detailed characterization of how the different CO_2 concentrations affect the lung mechanics, i.e. the establishment of a dose–response curve. Despite the fact that the presence of a cardiopulmonary bypass (CPB) offers ideal conditions for altering both the alveolar and circulatory CO_2 levels precisely *in vivo*, without involvement of the biasing effects of the an altered ventilation pattern or pulmonary ischemia, the advantages of this approach have not been utilized for a systematic exploration of the effects of an altered CO_2 level on the airway tone.

Hence, the aims of the present study were (i) to establish a dose–response curve relating to a wide range of alveolar CO_2 level without affecting the ventilation pattern, and (ii) to characterize the differences in the regulatory role of CO_2 on the airway tone when it is delivered to the resident gas in the airways or added directly to the blood. To achieve these aims, we subjected dogs to a CPB, which allows extensive manipulation of the CO_2 level independently in the airways and in the oxygenator. While manipulation of the alveolar CO_2 level has an impact on the entire lung, alterations in the systemic blood CO_2 level most probably affect primarily the proximal airways, since they are supported by the bronchial circulation with systemic origin. Thus, the lung mechanical changes were assessed by using the low-frequency forced oscillation technique, which permits separate the evaluation of the mechanical changes in the central and peripheral lung compartments.

2. Materials and methods

2.1. Animal preparation

After approval from the Institutional Animal Care and Use Committee of the University of Szeged, eight adult mongrel dogs (23.7 ± 5.0 kg) were anesthetized (30 mg/kg pentobarbital, iv). Analgesia was provided by iv injections of fentanyl (5–10 μg/kg). Muscle relaxation was achieved with an iv bolus of pipecuronium bromide (0.1 mg/kg). The dogs were then intubated with an 8–9-mm-internal diameter cuffed endotracheal tube (Portex, Hythe, UK) and ventilated with a Siemens Servo 900C Ventilator (Solna, Sweden) in volume-controlled mode. A tidal volume of 10 ml/kg and a positive end-expiratory pressure (PEEP) of 5 cmH_2O were applied, and the frequency was set to maintain a normal arterial CO_2 level (40 mmHg) in the pre-bypass period. The anesthesia was maintained by continuous iv infusion of propofol (50 μg/kg/min) and the muscle relaxant was administered as needed. After opening of the chest by midline sternotomy, anticoagulant (heparin, 3 mg/kg) was administered. The ascending aorta and the inferior and superior vena cava were then cannulated, and the CPB was achieved by means of a roller pump (Pemco, Inc., Cleveland, OH, USA) with non-pulsatile blood flow at 100 ml/kg/min and use of a membrane oxygenator (Spiral Gold Buxter Healthcare Irvine, CA, USA). A left vent was introduced into the left ventricle through the right upper pulmonary vein. During total CPB, the pulmonary circulation was ceased and the lungs were ventilated with a gas mixture of 50% O_2 in air with controlled concentration of CO_2 added to this gas mixture from a cylinder attached to the low-pressure gas input of the respirator. The end-tidal partial pressure of CO_2 (PET_{CO_2}) and FI_{CO_2} were monitored (Datex, Oscar Helsinki, Finland). Arterial blood gas samples were analyzed (model 505, Acid Base Laboratory, Copenhagen, Denmark).

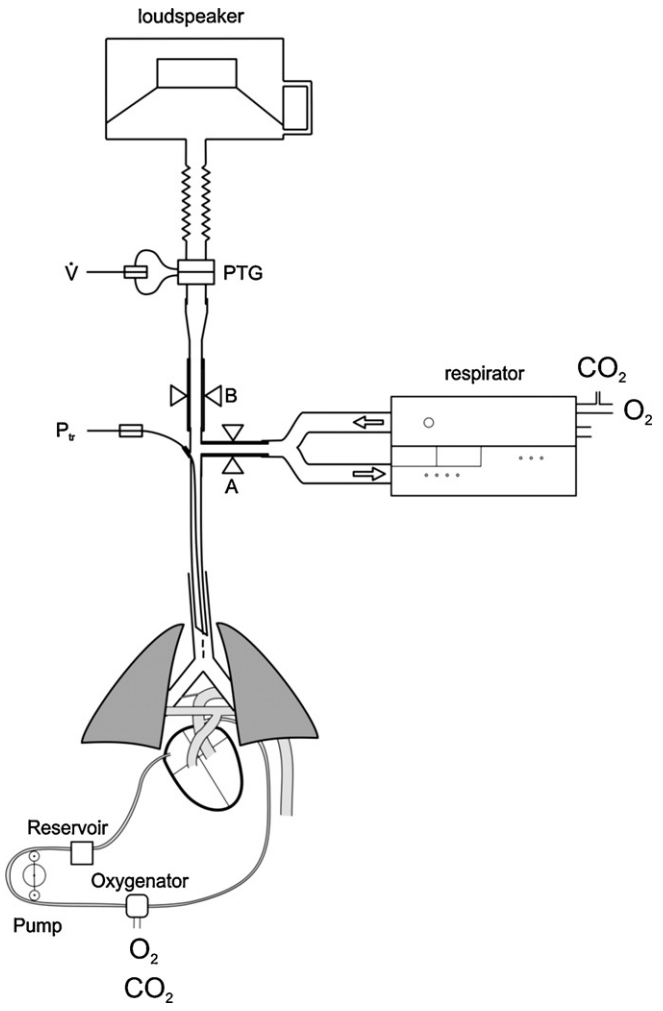

Fig. 1. Schematic illustration of the measurement set-up. A and B denote collapsible latex tube segments. PTG, pneumotachograph; P_{tr}, tracheal pressure; $\dot{V}$, tracheal flow.

2.2. Measurement of airway and parenchymal mechanics

The measurement system for the collection of the forced oscillatory input impedance spectra of the pulmonary system (Z_L) was similar to that described in detail previously (Babik et al., 2003; Hantos et al., 1992, 1995; Kaczka et al., 2009). The set-up used for impedance measurements during short intervals of suspended mechanical ventilation is shown schematically in Fig. 1. Two collapsible latex tube segments (A and B) were clamped alternately to switch the endotracheal tube from the respirator to the oscillatory device and back, as follows. During mechanical ventilation, segment A was open and segment B was closed. Following a few ventilatory cycles, the respirator was stopped at end-expiration and its tubing was detached from segment A. Segment B was then opened and segment A was clamped. In this apneic period, small-amplitude (1.5 cmH_2O peak-to-peak) pseudorandom pressure excitations were delivered by the loudspeaker into the trachea. The forcing signal contained 30 integer-multiple frequency components between 0.2 Hz and 6 Hz; the 15-s long recordings included 3 complete cycles of the periodic forcing signal. Tracheal flow ($\dot{V}$) was measured with a 28-mm ID screen pneumotachograph connected to a differential pressure transducer (ICS Model 33NA002D; ICSensors, Miltipas, CA). To exclude endotracheal tube impedance from the measurements, tracheal pressure (P_{tr}) was measured with an identical pressure transducer through a 1.5-mm-OD polyethy-