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Study on airway smooth muscle tone using fiberoptic bronchoscopy: basic research and clinical application

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Purpose of in vivo assessment of airway smooth muscle tone

The reason why we study the in vivo effect of anesthesia-related agents on airway smooth muscle is that the anesthetic management of asthmatic patients, especially for induction of anesthesia, is still a challenge to anesthetists. A recent review article [1] demonstrates that severe perioperative bronchospasm may be life-threatening, although its incidence is relatively low in asthmatics undergoing anesthesia. In addition, we believe that in vivo data are more clinically relevant compared to the in vitro data. For example, what happen on the airway during apnea? In vitro data suggest that apnea (= hypercarbia and hypoxia) induces airways smooth muscle relaxation [2, 3]. In contrast, we found that apnea induces in vivo bronchoconstriction (Fig. 1), which is vagally mediated, in dogs [4]. For another example, clinically relevant concentration of phenylephrine has been reported to exert no effects on airway smooth muscle tone [5]. However, we found that phenylephrine worsens histamine-induced bronchoconstriction [6]. As an increase in blood pressure by phenylephrine significantly reduces endogenous catecholamine release, which counteracts histamine-induced hypotension, a decrease in endogenous epinephrine release potentiates histamine-induced bronchoconstriction (Fig. 2). We have also reported differences between in vitro and in vivo effects in several situations [7–9].

Advantage of in vivo assessment of airway smooth muscle tone

When airway caliber is assessed, indirect methods such as airway resistance, compliance, and airway pressure are commonly used, but these methods are not accurate. Thus, Brown and colleagues [10] introduced computed tomography evaluation as a direct visualization method. Although this method is precise in assessing the caliber, the system is too large to be portable. Therefore, we developed a direct visualization method using a superfine fiberoptic bronchoscope. Why are conventional indirect methods not accurate? When an asthmatic attack occurs, airway pressure increases by chemical mediator-induced airway secretion and airway smooth muscle contraction. Even if the bronchodilators completely reverse the smooth muscle contraction, airway secretions may not be immediately dissipated by the dilators. Thus, airway pressure, resistance, and compliance cannot return to the baseline, which

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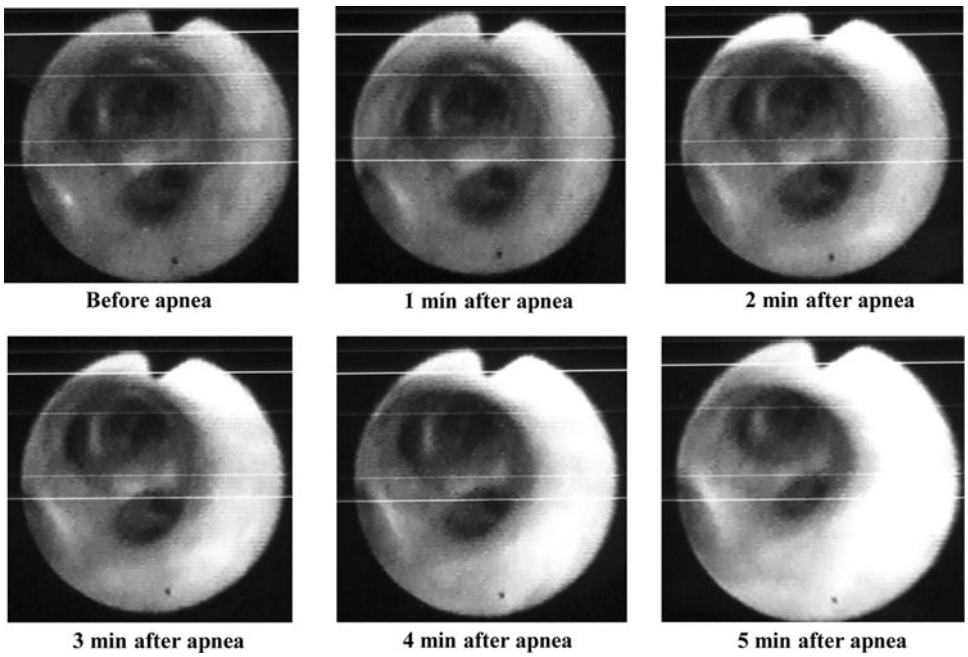

Fig. 1 Changes in bronchial cross-sectional images after apnea

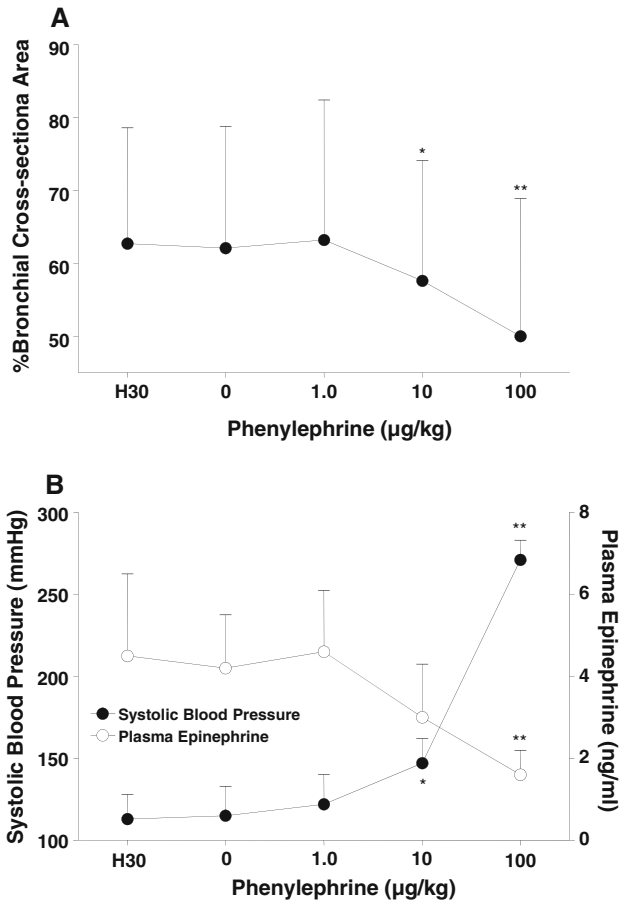

Fig. 2 Effects of i.v. phenylephrine on bronchial cross-sectional area (**a**) and systolic blood pressure and plasma epinephrine (**b**) under histamine continuous infusion. *H30*, 30 min after histamine infusion at 10 μg/kg/min, mean ± SEM

means that the relaxant effects of the bronchodilators are underestimated.

How to assess airway caliber using a fiberoptic bronchoscope

The trachea is intubated with a Univent tube, which has two lumens; the smaller one is for insertion of a bronchial blocker when one lung is ventilated. From this lumen, we put a superfine fiberoptic bronchoscope (outer diameter, 2.2 mm; Fig. 3) into the right bronchus to monitor a bronchial cross-sectional area between the second and third bifurcation. The bronchial cross-sectional area image on the monitor was put into a computer, and the area was analyzed with computer software (NIH image or Macscope) [4, 6–9, 11, 15–18].

Validation of a direct visualization method using a superfine fiberoptic bronchoscope

To validate a direct visualization method using a superfine fiberoptic bronchoscope, we compared the percent (%) bronchial cross-sectional area with percent (%) airway resistance and percent (%) dynamic compliance in a histamine–bronchoconstriction model [11]. Epinephrine dose-dependently decreased and increased airway resistance and dynamic compliance, respectively. However, these indirect variables could not return to the baseline. In contrast, %bronchial cross-sectional area increased more than the baseline (Fig. 4a). As the bronchial smooth muscle has a

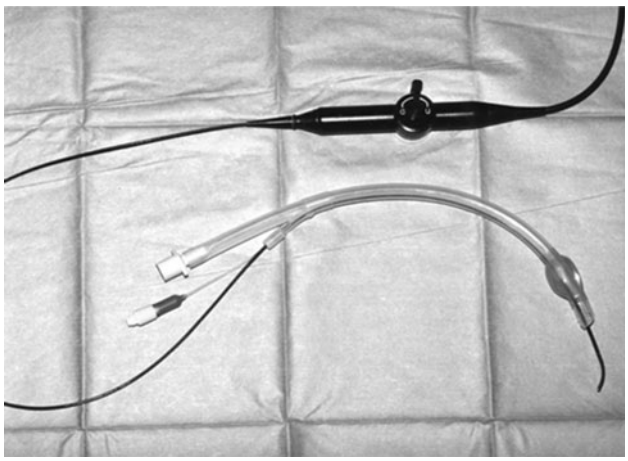

Fig. 3 Univent tube with a superfine fiberoptic bronchoscope (OD, 2.2 mm)

resting tension by vagal activity, epinephrine could diminish the basal vagal tone. There is a significant correlation between bronchial cross-sectional area and airway resistance or dynamic compliance (Fig. 4b). Therefore, a direct visualization method using a superfine fiberoptic bronchoscope may be more sensitive to assess airway caliber than conventional indirect methods.

Application of the direct visualization method to clinical practice and bronchodilating effects of phosphodiesterase III (PDEIII) inhibitors

It has been reported that the therapeutic benefits of aminophylline, a nonselective PDE inhibitor, for asthmatic patients are dubious [12]. In addition, theophylline dosage must be individually decided with measurement of serum theophylline concentration to optimize the treatment because of its narrow therapeutic range [13]: overdose induces severe adverse reactions such as life-threatening arrhythmias, convulsion, and hypotension. PDEI–V isoforms have been identified in the lung, and PDEIII activity is prominent in alveolar macrophages, endothelial cells, platelets, and airway smooth muscle cells [14]. We found that PDEIII inhibitors could produce more potent bronchodilating effects than aminophylline did in dogs [15–17]. We also found that relaxant effects of aminophylline could be the result of endogenous epinephrine release as aminophylline-induced bronchodilation was fully reversed by propranolol, a β-blocker, while relaxant effects of PDEIII inhibitor were not [16, 17]. Therefore, we had considered use of PDEIII inhibitors as bronchodilators in clinical practice, which may be safer than aminophylline. To determine our hypothesis, after approval of our university ethical committee, we assessed the efficacy of olprinone, a

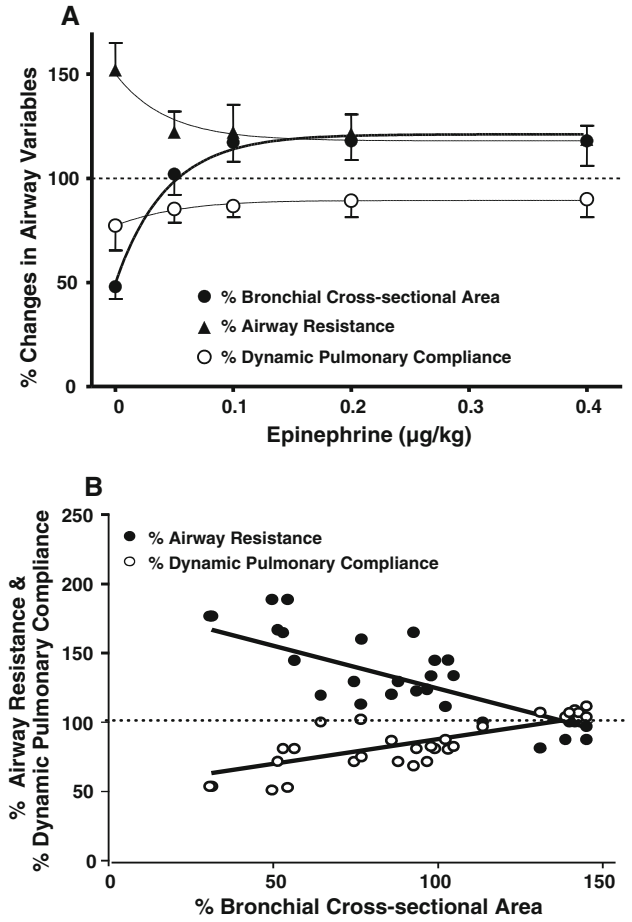

Fig. 4 **a** Effects of epinephrine on histamine-induced bronchoconstriction assessed by % bronchial cross-sectional area, % airway resistance, and % dynamic pulmonary compliance. **b** Significant correlations between % bronchial cross-sectional area and % dynamic pulmonary compliance ($r = 0.720$, $P < 0.0001$) and % airway resistance ($r = 0.727$, $P < 0.0001$). (Figure modified from Otomo et al. [11] with the publisher's permission)

PDEIII inhibitor for treatment of patients showing asthmatic attack under oral theophylline medication, by our direct visualization method using a superfine fiberoptic bronchoscope. Although we had only one case during the research period, we confirmed that olprinone could produce a potent bronchodilation and that this direct visualization method may be more sensitive to determine relaxant effects of olprinone than peak airway pressure [18] (Fig. 5).

Problems of the direct visualization method using a superfine fiberoptic bronchoscope

This system using a superfine fiberoptic bronchoscope for in vivo assessment of airway caliber has several problems, as follows. This system cannot provide real airway caliber, although it can monitor relative changes. When the tip of

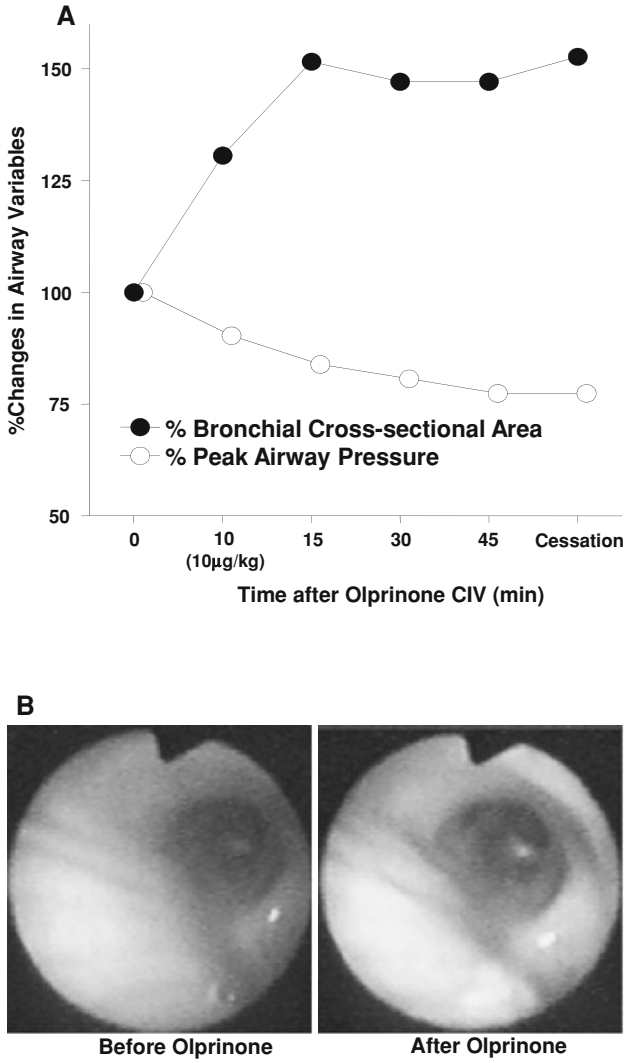

Fig. 5 Continuous i.v. infusion of olprinone improved asthmatic attack during anesthesia. **a** Changes in % bronchial cross-sectional area and % peak airway pressure. **b** Bronchial cross-sectional image before and after olprinone infusion at 10 μg/kg/10 min + 0.3 μg/kg/h. (Figure modified from Hirota et al. [18] with the publisher's permission)

the bronchoscope is moved, the target size is also changed. Moreover, when airway discharge sticks to the tip of the bronchoscope, the assessment cannot continue.

New direct visualization method using a fiberoptic bronchoscope

Quantitative assessment is impossible as the bronchoscope provides an image but not quantitative data. Therefore, we have asked the Olympus Medical Systems Corporation to develop a new bronchoscopy system with measuring ability. This new bronchoscope has two independent lenses at the tip and enables measuring the distance using a principle of triangulation. However, this bronchoscope still has several problems, as follows. Each picture is small consequent to the two-lens system. Technically, it requires more careful manipulation because of its extended hard distal end. We will show the usefulness of a new bronchoscope that can perform quantitative assessment of airway caliber and solve the problems in the near future.

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