

Unventilated Airway Is Time-dependently Constricted in Paralyzed Dogs

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Background: Apnea has been reported to produce bronchoconstriction and to cause hypoxia, hypercapnia, and modulation of vagal afferent nerves, which also change airway tone. In this study, the authors determined the mechanism of apnea-induced bronchoconstriction.

Methods: Twenty-eight dogs anesthetized and paralyzed were assigned to four groups (n = 7 each): apnea after artificial ventilation with 50% and 100% O₂ groups (apnea-50% O₂ and apnea-100% O₂ groups, respectively), an apnea plus vagotomy group (fraction of inspired oxygen [F_{IO₂}] = 1.0), and a one-lung ventilation group (F_{IO₂} = 1.0). The trachea was intubated with a single- or double-lumen tube in the three apnea groups or the one-lung ventilation group, respectively. The bronchial cross-sectional area (BCA) was assessed by the authors' bronchoscopic method. In the apnea-100% O₂ and apnea plus vagotomy groups, a respirator was turned off for 5 min to produce apnea. In the apnea-50% O₂ group, apnea was produced for 3 min. In the one-lung ventilation group, the right lumen was blocked for 5 min, and 15 min later, the left lumen was blocked for 5 min. BCA, arterial oxygen tension (P_{aO₂}), and arterial carbon dioxide tension (P_{aCO₂}) were assessed every minute.

Results: The BCA in intact dogs time-dependently decreased by approximately 20% and 40% at 3 and 5 min after apnea started, respectively, whereas they did not in vagotomized dogs. In the apnea-50% O₂ and apnea-100% O₂ groups, bronchoconstriction could occur without hypoxemia, although hypercapnia was observed in all dogs. In the one-lung ventilation group, despite the fact that P_{aCO₂} increased by only 2 mmHg without hypoxemia, unventilated BCA time-dependently decreased by 33.6 ± 10.3%, whereas ventilated BCA did not.

Conclusion: The current study suggests that the unventilated airway may constrict spontaneously. In addition, the airway constriction could be vagally mediated but not due to hypoxia and hypercapnia.

ANESTHESIOLOGISTS often treat apnea patients in the emergency room, the intensive care unit, and the operating room. Moreover, they sometimes experience difficult ventilation during induction of anesthesia and manage one-lung ventilation during thoracic surgery. However, the influence of apnea or the absence of ventilation on the airway tone is not fully understood.

Apnea causes hypoxia, hypercapnia, and acidosis, and these modulate airway smooth muscle tone.¹⁻⁷ Several articles^{2,8,9} indicate that apnea (except hypocapnic ap-

nea) produces airway constriction. Several *in vitro* studies^{4,5} show that hypoxia impairs the contractile function of airway smooth muscle strips. However, *in vivo* studies^{2,3,7} suggest that hypoxia produces airway constriction. Similarly, hypercapnia and decrease in intracellular pH have been reported to produce airway smooth muscle relaxation *in vitro*^{5,6} and increase in pulmonary resistance or airway tone *in vivo*.^{1,7}

In addition, each inspiration and expiration also changes airway tone *via* pulmonary stretch receptors.¹⁰ Mitchell *et al.*¹⁰ reported that the major excitatory input to airway smooth muscle arises from cholinergic nerves that fire during inspiration. They also found that airway smooth muscle contraction occurs at each inspiration.⁴ In addition to slowly adapting stretch receptors, rapidly adapting stretch receptors, bronchial C fibers and pulmonary C fibers, which are vagal afferent nerves, exist in the airway and contribute to the modulation of airway tone.¹¹ Therefore, some of these afferent nerves may be involved in the mechanism of the bronchoconstriction.

Although apnea may induce airway constriction, it remains unknown whether airway constriction occurs only during the absence of ventilation of the whole lung or in the unventilated airways even though other airways are ventilated, *e.g.*, one-lung ventilation. In this study, to determine whether the airway constriction is due to hypercapnia, hypoxemia, acidosis, or the absence of inflation of the whole lung or of some lobes (*e.g.*, one lung), we studied the effect of apnea and one-lung ventilation on bronchial tone in intact and vagotomized dogs using our previously reported bronchoscopic method.¹²⁻¹⁵

Materials and Methods

Our study protocol was approved by Animal Care and Use Committee of the University of Hirosaki School of Medicine (Hirosaki, Japan). Twenty-one adult mongrel dogs (8-12 kg) were anesthetized with intravenous pentobarbital (30 mg/kg + 2.0 mg · kg⁻¹ · h⁻¹) and were assigned to three groups: an apnea-100% O₂ group (n = 7), an apnea plus vagotomy group (n = 7), and a one-lung ventilation group (n = 7). The lungs of these dogs were ventilated with 100% O₂. The tracheas were intubated with single- or double-lumen endotracheal tubes in the apnea and apnea plus vagotomy or one-lung ventilation groups, respectively. The distal cuff of the double lumen endotracheal tube was inflated in the left lung. Neuromuscular blockade was obtained with pancuronium at 0.2 mg · kg⁻¹ · h⁻¹ for mechanical ventilation

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with oxygen using a volume-controlled respirator (Servoventilator 900C; Siemens-Elma AB, Solna, Sweden), and end-tidal carbon dioxide was maintained at 4.0–4.5%. The femoral artery was cannulated for monitoring of arterial blood pressure and blood sampling. The femoral vein was also cannulated for insertion of a double-lumen catheter through which fluid and drugs were administered. In the apnea plus vagotomy group, the vagus nerves were isolated and then cut bilaterally.

In addition, to determine whether inspiratory O₂ concentration affected the results, seven dogs were studied with the same protocol as the apnea-100% O₂ group, except that apnea was produced after ventilation with 50% O₂ plus 50% N₂ (apnea-50% O₂ group). In this group, we measured airway tone not only during apnea but also after ventilation was restarted.

In all groups, the bronchial cross-sectional area (BCA) of the third bronchial bifurcation in the right lung was monitored *via* a superfine fiberoptic bronchoscope (2.2 mm OD, AF type 22A; Olympus, Tokyo, Japan) to assess bronchial tone as reported previously.¹²⁻¹⁵ Briefly, the image of the third bifurcation was printed out with a video printer (VY-170; Hitachi, Tokyo, Japan) during the end-expiratory pause and then was taken into a Macintosh computer (Power Macintosh 7100/80 AV; Apple Computer Inc, Cupertino, CA) by the scanner (ScanJet 4c; Hewlett Packard Co., Singapore) to measure the BCA using image-analyzing software (MacSCOPE 2.56; Mitani Co., Fukui, Japan). This image processing was performed by an investigator who was blinded to the study protocol.

In the apnea-100% O₂ and apnea plus vagotomy groups, a respirator was turned off at the end-expiratory pause to produce apnea for 5 min. However, in the apnea-50% O₂ group, the respirator was turned off only for 3 min because we preliminarily found that apnea for more than 3 min causes hypoxemia (< 60 mmHg). In the one-lung ventilation group, the right-sided lumen was blocked for 5 min to cause an absence of ventilation of the right lung, and 15 min later, the left-sided lumen was blocked for 5 min to cause only right-lung ventilation. The BCA was assessed before and 1, 2, and 3 min after the ventilator was turned off (at the end-expiratory pause) and on again in the apnea-50% O₂ group, and it was assessed before and 1, 2, 3, 4, and 5 min after absence of ventilation began in the other groups. When the ventilator was turned off or one-lung ventilation was started, the lumen of the endotracheal tube was occluded by the clamp. In addition, arterial blood (1 ml) was simultaneously sampled to assess arterial oxygen tension (PaO₂), arterial carbon dioxide tension (PaCO₂), and pH.

Statistical Analysis

All data are expressed as mean \pm SD. The BCA is presented as percent of basal BCA. Data were appropri-

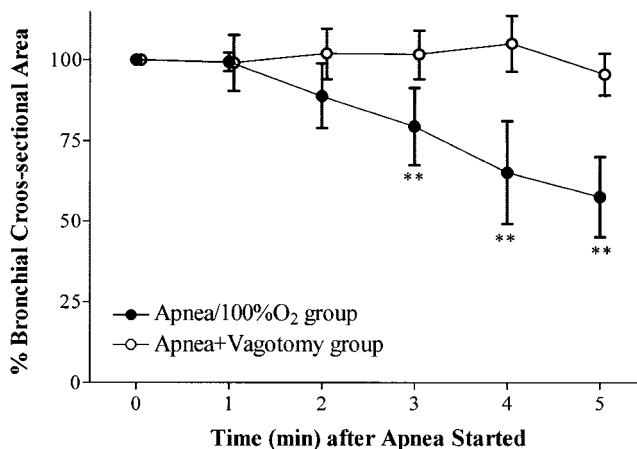


Fig. 1. Changes in percent of bronchial cross-sectional area after apnea started. Apnea-100% O₂ group: apnea after inhalation of 100% O₂; * $P < 0.05$, ** $P < 0.01$ versus apnea-100% O₂ group. All values are presented as mean \pm SD.

ately analyzed with one-way or two-way repeated-measures analysis of variance followed by Student-Newman-Keuls test using Sigma Stat for Windows (Jandel Scientific Software, Chicago, IL). $P < 0.05$ was considered significant.

Results

Effects of Apnea on the Airway Tone

In the apnea plus vagotomy group, vagotomy increased the basal BCA by $10.3 \pm 9.7\%$. After the start of apnea, BCA decreased time-dependently in the apnea-100% O₂ group, whereas it did not in the apnea plus vagotomy group (fig. 1). In the apnea-50% O₂ group, BCA was reduced time-dependently, similar to the apnea-100% O₂ group. In addition, the reduction in BCA rapidly returned to baseline after ventilation was restarted (fig. 2).

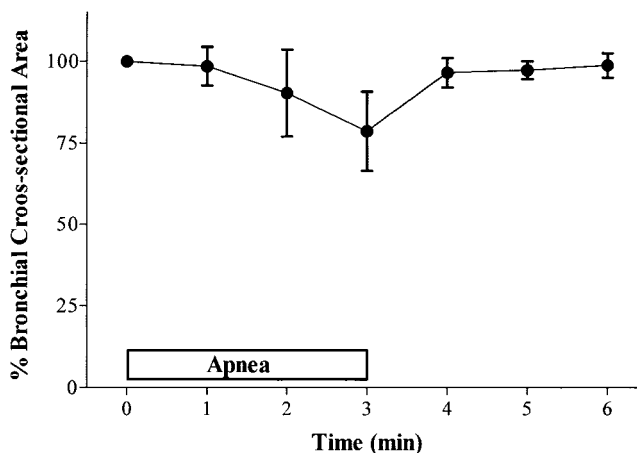


Fig. 2. Changes in percent of bronchial cross-sectional area during apnea and after rebreathing was started. The lungs were ventilated with 50% O₂ and 50% N₂ before and after apnea (apnea-50% O₂ group). All values are presented as mean \pm SD.

Table 1. Changes in pH, PaCO₂, and PaO₂ during Apnea after Ventilation with 100% O₂

Groups	Time after Apnea Started (min)					
	0	1	2	3	4	5
pH						
Apnea-100% O ₂	7.37 ± 0.05	7.30 ± 0.04†	7.27 ± 0.04†	7.25 ± 0.05†	7.22 ± 0.05†	7.20 ± 0.04†
Apnea + vagotomy	7.35 ± 0.06	7.27 ± 0.05†	7.23 ± 0.05†	7.20 ± 0.05†	7.18 ± 0.05†	7.16 ± 0.06†
PaCO₂ (mmHg)						
Apnea-100% O ₂	40 ± 5	50 ± 6†	55 ± 7†	60 ± 7†	64 ± 8†	68 ± 8†
Apnea + vagotomy	43 ± 4	55 ± 3†	61 ± 4†	66 ± 4†	70 ± 4†	74 ± 4†
PaO₂ (mmHg)						
Apnea-100% O ₂	493 ± 49	469 ± 40	416 ± 90	334 ± 132†	237 ± 176†	178 ± 168†
Apnea + vagotomy	452 ± 71	420 ± 81	324 ± 108†	231 ± 131†	156 ± 148†	120 ± 158†

All data are expressed as mean ± SD.

† $P < 0.01$ compared with 0. No significant differences between groups in all variables in table.

PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension; Apnea-100% O₂ = intact dogs group; apnea + vagotomy = vagotomized dogs group.

Apnea also significantly decreased PaO₂ and pH and increased PaCO₂ in the apnea-50% O₂, apnea-100% O₂, and apnea plus vagotomy groups (tables 1 and 2). However, hypoxemia (< 60 mmHg) was not seen in all dogs of the apnea-50% O₂ group. In the apnea-100% O₂ group, no dogs showed hypoxemia until 4 min after apnea started, but 6 of 14 dogs did 5 min after apnea started. In addition, PaO₂ rapidly returned to baseline after ventilation was restarted in the apnea-50% O₂ group (table 2).

Effects of One-lung Ventilation on the Airway Tone

In the one-lung ventilation group, the BCA of the unventilated lung decreased time dependently, whereas the area of the ventilated lung did not change (fig. 3). PaCO₂ slightly increased from 44 ± 7 to 46 ± 5 mmHg 5 min after one-lung ventilation was started. In addition, although PaO₂ significantly decreased from 468 ± 59 to 131 ± 158 mmHg, hypoxemia was seen in only 1 of 12 dogs (PaO₂ = 59 mmHg; table 3).

Discussion

In the current study, during apnea, BCA decreased in a time-dependent manner with a decrease in PaO₂ and an increase in PaCO₂. Several factors should be considered

to understand the mechanism of apnea-induced bronchoconstriction.

Apnea causes hypoxia and hypercapnia. Previous *in vitro* studies⁴⁻⁶ show that these attenuate contraction of airway smooth muscles. In contrast, *in vivo* studies^{1-3,7} suggest that these may induce airway constriction. Iscoe and Fisher⁷ showed that pulmonary resistance in response to hypoxia (fraction of inspired oxygen [FiO₂] = 0.1) and to hypercapnia (inhalation of 5% CO₂) increased by 49% and 59%, respectively, in decerebrate cats. In the current study, although hypercapnia and respiratory acidosis occurred in all dogs, bronchoconstriction was observed even without hypoxia. Therefore, hypoxia may not be a main contributor to apnea-induced airway constriction.

The report of Iscoe and Fisher⁷ suggests that the airway constriction may occur by means of hypercapnia and that it could be abolished by atropine or vagotomy, similar to the current study showing that vagotomy abolished apnea-induced bronchoconstriction. However, in the one-lung ventilation group, despite the fact that PaCO₂ increased by only 2 mmHg 5 min after one-lung ventilation was started, the BCA of unventilated lung time-dependently decreased. Therefore, it is unlikely that hypercapnia is a main factor for apnea-induced airway constriction.

It is known that absorption atelectasis easily occurs by means of a high inspired O₂ concentration.¹⁶ In addition,

Table 2. Changes in pH, PaCO₂, and PaO₂ during Apnea after Ventilation with 50% O₂ and after Rebreathing

	Pre	Time after Apnea Started (min)			Time after Rebreathing Started (min)		
		1	2	3	1	2	3
pH	7.45 ± 0.04	7.36 ± 0.04†	7.32 ± 0.04†	7.30 ± 0.04†	7.37 ± 0.04†	7.39 ± 0.05†	7.40 ± 0.05†
PaCO ₂ (mmHg)	35 ± 6	46 ± 8†	50 ± 8†	53 ± 8†	43 ± 8†	41 ± 6†	40 ± 6†
PaO ₂ (mmHg)	309 ± 13	245 ± 20†	134 ± 40†	69 ± 11†	287 ± 22†	300 ± 14†	298 ± 17†

All data are expressed as mean ± SD.

† $P < 0.01$ compared with 0.

PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension.

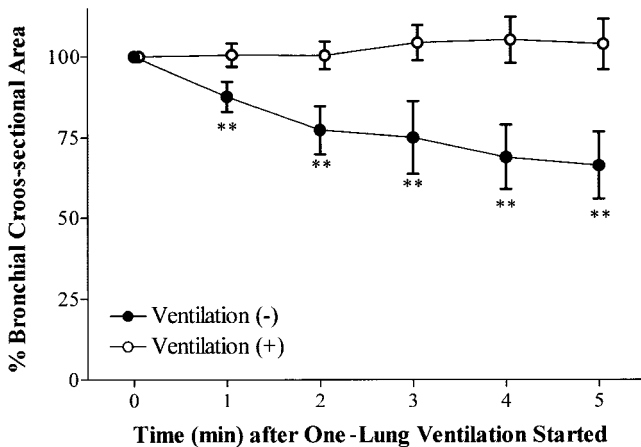


Fig. 3. Changes in percent of bronchial cross-sectional area of right lung after one-lung ventilation was started. Ventilation (+): right lung was ventilated; ventilation (-): right lung was not ventilated; * $P < 0.05$, ** $P < 0.01$ versus ventilation (+). All values are presented as mean \pm SD.

as apnea substantially decreases the ventilation-perfusion ratio,¹⁶ lung collapse is likely to occur and may reflect reduction in BCA. However, it is also known that a lower inspired O₂ concentration causes lung collapse more slowly.¹⁶ However, in the current study, reduction in BCA in the apnea-50% O₂ group was not less than that in the apnea-100% O₂ group. In addition, the reduction was not observed even after ventilation with 100% O₂ in vagotomized dogs. Therefore, the passive collapse is not involved in bronchoconstriction.

An *in vitro* study reported by Fredberg *et al.*¹⁷ clearly showed that tidal stretch of airway smooth muscles attenuates active force or muscle stiffness. Such stretching of airway smooth muscle during tidal breathing may contribute to attenuation of bronchoconstriction. In fact, the airways in normal humans and dogs do not constrict to closure even when maximally stimulated.¹⁸ In contrast, maximal stimulation can produce airway closure in isolated lobes and bronchial segments.¹⁸ Thus, in the absence of tidal stretch, such as apnea, airway narrowing may easily occur. However, Fredberg *et al.*¹⁷ reported that the attenuation of active force or muscle stiffness by tidal stretch may not be neurally mediated because tetrodotoxin did not affect the results. The current study shows that because vagotomy abolished ap-

nea-induced airway narrowing, tidal stretch may not be involved in the mechanism.

The fact that vagotomy completely abolished apnea-induced bronchoconstriction suggests involvement of the neural reflex. Similarly, Brown *et al.*¹⁹ also reported that breath holding after ventilation with 100% O₂ produces airway narrowing, which can be antagonized by atropine pretreatment. It is known that activation of airway afferent nerve fibers results in reflexes that serve to protect the airways.¹¹ Because vagotomy or atropine abolished the bronchoconstriction during apnea, the afferent neurons of the vagus nerve should be involved in the mechanism of apnea-induced bronchoconstriction. The afferent neurons have been classified into four subclasses: slowly adapting stretch receptors, rapidly adapting stretch receptors (irritant receptors), pulmonary C fibers, and bronchial C fibers.¹¹ Therefore, some of these vagal afferent nerves may be involved in apnea-induced bronchoconstriction.

The slowly adapting stretch receptors are located in the tracheobronchial tree but are concentrated in the large conducting airway and have an important role in the Hering-Breuer reflex.¹¹ In addition, the activation of these units decreases parasympathetic drive to the airway and leads to airway smooth muscle relaxation during inflation.¹¹ Therefore, it is possible that as a consequence of reduction of the slowly adapting stretch receptors by apnea, an increase in the parasympathetic drive may lead to bronchoconstriction. The current data showing that vagotomy abolished bronchoconstriction support this hypothesis.

The rapidly adapting receptors are located in circumference of the entire tracheobronchial tree but are concentrated in the large airway.¹¹ These receptors respond to mechanical stimulation with a burst of action potential during the dynamic phase and then rapidly adapt during the static phase of stimuli, although the activity of these receptors is not coordinated with inspiration or expiration of normal tidal breathing.¹¹ Relatively large changes in transmural pressure, evoked by either distention or collapse of the airway, are required to activate the rapidly adapting receptors.¹¹ In addition, activation of some of these fibers is known to produce cough, bronchoconstriction, and secretion, and these fibers are

Table 3. Effects of One-lung Ventilation on pH, P_{aCO₂}, and P_{aO₂}

	Time (min) after One-lung Ventilation Started					
	0	1	2	3	4	5
pH	7.36 \pm 0.02	7.35 \pm 0.04	7.34 \pm 0.04*	7.34 \pm 0.03†	7.34 \pm 0.04†	7.34 \pm 0.04†
P _{aCO₂} (mmHg)	44 \pm 7	45 \pm 7	45 \pm 7	46 \pm 7*	46 \pm 6.0*	46 \pm 5*
P _{aO₂} (mmHg)	469 \pm 59	465 \pm 54	398 \pm 66	273 \pm 100†	160 \pm 151†	131 \pm 158†

All data are expressed as mean \pm SD.

* $P < 0.05$, † $P < 0.01$ compared with 0.

P_{aCO₂} = arterial carbon dioxide tension; P_{aO₂} = arterial oxygen tension.

found in the large airway.¹¹ The current study shows that volumes of the large airway may not change for 5 min of apnea because BCA did not change in the vagotomized dogs. Therefore, unchanged volume in the large airway may not lead to bronchoconstriction, *i.e.*, the rapidly adapting stretch receptors may not be involved.

The classification of pulmonary and bronchial C fibers are based on their location in the peripheral airways (J receptors) and the large airways, respectively.¹¹ Both C fibers are mechanically sensitive, and stimulation of these fibers results in defensive pulmonary reflexes, such as cough, apnea, bronchoconstriction, and mucous secretion.¹¹ Both C fibers are stimulated by hyperinflation of the lung but not by deflation.¹¹ In addition, a considerable increase in P_{aCO_2} stimulates bronchial C fibers.¹¹ However, bronchoconstriction was observed without a considerable increase in P_{aCO_2} in the one-lung ventilation group. Therefore, both C fibers may be uninvolved in apnea-induced bronchoconstriction.

Pentobarbital *per se* has been reported to attenuate the airway reflex.⁷ However, because vagotomy increased BCA by 10% during pentobarbital anesthesia in the current study, the dose of pentobarbital used could not inhibit the reflex completely. Similarly, using high-resolution computed tomography, Brown *et al.*¹⁹ reported that 0.2 mg/kg atropine caused an increase in baseline airway area to $115 \pm 5\%$ during thiopental anesthesia in dogs. The bronchodilation could be due to blockade of parasympathetic drive to the airway by vagotomy or atropine.

Pancuronium was used to prevent spontaneous breathing during apnea in the current study. Cembela *et al.*²⁰ showed that a clinical concentration of pancuronium inhibits muscarinic receptor subtype M2 rather than M1 or M3. Okanlami *et al.*²¹ also reported that a small dose of pancuronium produces M2 antagonistic effects and M3 effects predominantly at the larger dose. Because M2 activation inhibits the release of acetylcholine,²² M2 antagonism by pancuronium is likely to potentiate vagally mediated bronchoconstriction.^{21,23} Therefore, apnea-induced bronchoconstriction may also be potentiated by pancuronium.

In the current study, we used a fiberoptic bronchoscopy method to assess airway caliber. Although airway caliber has classically been assessed with indirect measurement methods, such as airway resistance and compliance, direct methods are more specific than the indirect ones that Brown *et al.*²⁴ reported. Therefore, we have developed a portable direct method using a fiberoptic bronchoscope.¹² To validate our method, we previously compared changes in BCA with percent of dynamic pulmonary compliance ($\%C_{dyn}$) and percent of airway resistance ($\%R_{aw}$) in a histamine bronchoconstriction model. We observed that the $\%BCA$ completely returned to the prehistamine value by means of intravenous epinephrine, yet $\%C_{dyn}$ and $\%R_{aw}$ did not.¹² In addition, there was a significant correlation between

$\%BCA$ and $\%C_{dyn}$ or $\%R_{aw}$.¹² Therefore, the bronchoscopic method can assess airway caliber more specifically than indirect ones can.¹²

In conclusion, the current study shows that the unventilated airway constricts spontaneously. This constriction could be vagally mediated (maybe slowly adapting stretch receptors) but is not due to hypoxia and hypercapnia. Further studies are required to elucidate the mechanism.

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