Anesthesiology
2000; 93:95-103

Differences in Cardiovascular Response to Airway Stimulation at Different Sites and Blockade of the Responses by Lidocaine

Yoshihiro Hamaya, M.D., Ph.D., Shuji Dohi, M.D., Ph.D.†*

Background: **Mechanical stimulation of the airways elicits abrupt cardiovascular responses (CVR) in anesthetized humans. We examined a potential difference in such responses by comparing changes in heart rate (HR) and arterial blood pressure (AP) responses to mechanical stimulation of three different parts of the airways, as well as the effects of localized airway anesthesia with lidocaine on these responses.**

Methods: **After induction of general anesthesia, the larynx under laryngeal mask insertion (L, n = 20), the trachea–carina under tracheal intubation (T, n = 20), or the bronchus under bronchial intubation (B, N = 20) of each patient was mechanically stimulated in a similar manner. The same stimulation was repeated in 15 patients in each group after 5 ml of 4% lidocaine had been sprayed onto the part of the airway being stimulated. To test the systemic effect, intravenous lidocaine 1 mg/kg was given to five patients in each group, followed by the same airway stimulation. Consequent changes in HR and AP were continuously recorded and analyzed.**

Results: **Significant increases in HR and AP in response to airway tactile stimulation differed in magnitude according to the stimulated sites (L > T ≥ B). These responses were completely blocked by topical application of lidocaine and partially blocked by intravenous lidocaine.**

Conclusions: **We found that CVRs to tactile stimulation differ in their magnitude at three different sites within the airways, and localized anesthesia with lidocaine can abolish these responses in humans. The inhibition of lidocaine could be mainly due to direct blockade of the mechanoreceptors of the airways and partly to its systemic effect. (Key words: Blood pressure; heart rate; local anesthetic; neural response; respiratory tract.)**

IT is well recognized that mechanical stimulation of the respiratory tract such as that produced by tracheal intubation can elicit potent respiratory-cardiovascular reflex responses during anesthesia,[1,2] and some differences in the responses could exist between laryngotracheal stimulation and carinal stimulation.[3,4] However, the physiologic importance of airway-cardiovascular excitatory and inhibitory reflexes is not yet clear, and such reflexes could be detrimental during anesthesia.

The respiratory tracts, which anesthesiologists unavoidably must stimulate both mechanically and chemically in their routine practice, contain many receptors located in the larynx, trachea, carina, and bronchi. It has been reported that the distribution of airway receptors is richest in the larynx and more concentrated in the proximal portions of the tracheobronchial tree.[5,6] In addition, the characteristics of those receptors become more chemosensitive and less mechanosensitive in the distal portion.[7] The uneven distribution and characteristics of airway receptors may explain the different reflex responses to the two types of noxious stimuli. However, there has been no systematic attempt in humans to compare the cardiovascular responses (CVRs) evoked by stimulation of different parts of the respiratory tracts. Because most airway receptors are located just beneath the epithelium,[5] it should be possible to block them by topical application or infiltration of local anesthetics in the area stimulated.

We designed the present study to examine whether CVRs to a similar airway stimulation would differ with different parts of the respiratory tracts stimulated and whether airway anesthesia produced by topical administration of lidocaine has significant effects on CVRs to mechanical stimulation to corresponding parts of the respiratory tracts in anesthetized humans.

* Postgraduate Research Fellow, Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine. Current position: Chief of Department of Anesthesia, Gifu Social Insurance Hospital, Kani City, Gifu, Japan.

† Professor and Chair, Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine.

Received from the Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine, Gifu City, Gifu, Japan. Submitted for publication July 19, 1999. Accepted for publication February 7, 2000. Supported in part by a research grant (No. 11307027) from the Ministry of Education, Science, and Culture of Japan, Tokyo, Japan. Presented in part at the American Society of Anesthesiologists Annual Meeting, Atlanta, Georgia, October 23, 1995.

Address reprint requests to Dr. Dohi: Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine, 40 Tsukasamachi, Gifu City, Gifu 500-8705, Japan. Address electronic mail to: shu-dohi@cc.gifu-u.ac.jp

Table 1. Baseline Heart Rate (HR) and Systolic Arterial Blood Pressure (AP) in Patients Administered Airway or Intravenous Lidocaine

Group		HR (beats/min)		AP (mmHg)	
		Without Lidocaine	With Lidocaine	Without Lidocaine	With Lidocaine
Larynx					
Airway	n = 15	81 ± 11	75 ± 10*	117 ± 12	113 ± 11
Intravenous	n = 5	79 ± 13	77 ± 14	113 ± 13	110 ± 12
Trachea					
Airway	n = 15	78 ± 8	74 ± 8*	115 ± 14	114 ± 17
Intravenous	n = 5	79 ± 11	75 ± 12	116 ± 13	117 ± 12
Bronchus					
Airway	n = 15	78 ± 13	75 ± 14*	113 ± 11	114 ± 12
Intravenous	n = 5	78 ± 12	75 ± 13	113 ± 12	112 ± 12

Values are mean ± SD. Patients were divided into three groups according to the airway devices. Five patients in each group had intravenous lidocaine.
* $P < 0.05$ *versus* before lidocaine administration.

Materials and Methods

Sixty female patients, aged 20–65 yr and American Society of Anesthesiologists physical status 1, gave oral informed consent to their participation in the current study after it had received approval from the Human Investigation Committee of the Gifu University School of Medicine. Each patient was scheduled for elective gynecological surgery such as hysterectomy or oophorectomy. None of the patients had either a past or present cardiorespiratory disorder. Premedication with oral diazepam 10 mg and famotidine 20 mg was given 90 min prior to their arrival in the operating room.

Each patient was randomly assigned to one of three groups on the basis of the airway management and subsequent stimulation they received. The patients received laryngeal mask airway insertion with tactile stimulation of the larynx (group L, n = 20), tracheal intubation with tactile stimulation of the trachea (group T, n = 20), or endobronchial intubation with tactile stimulation of the bronchus (group B, n = 20). The airway devices used were laryngeal mask airways (size 3 or 4; Tokibo, Tokyo, Japan), endotracheal tubes (7.5 mm internal diameter; Mallinckrodt, St. Louis, MO), and left-sided endobroncheal tubes (37 French; Mallinckrodt). Positioning of each airway device was confirmed by chest auscultation and fiberoptic bronchoscopy. After insertion of an intravenous cannula, recordings of electrocardiograms, arterial blood pressure (AP, by sphygmomanometry), and oxygen saturation of arterial hemoglobin (Sp_{O_2}, by pulse oximetry) were established in each patient. General anesthesia was induced with intravenous thiopental 5 mg/kg, and the airway equipment appropriate for the type of airway management proposed was put in place with the aid of intravenous vecuronium 0.1 mg/kg. The patient was put under controlled mechanical ventilation to maintain normocapnia, which was confirmed with end-tidal carbon dioxide tension (ET_{CO_2}, by capnography). General anesthesia was maintained by inhalation of nitrous oxide (67%) in oxygen accompanied by less than 0.5 minimum alveolar concentration of isoflurane (0.6% in end-tidal concentration). Supplemental intravenous vecuronium (2–4 mg) was given, if necessary, to achieve a complete paralysis of the patient. Each patient's radial artery was cannulated for the direct measurement of AP and to obtain blood samples for analysis. Electrocardiograms, Sp_{O_2}, and ET_{CO_2} were monitored continuously.

Control Measurements

After at least 10 min of stable hemodynamic conditions (> 10 min after start of isoflurane), baseline heart rate (HR) and AP were recorded as the mean of five cardiac contractions. As a control procedure, tactile stimuli, as described later in this section, were applied to the patient's larynx (group L), trachea and carina (group T), or bronchus (group B). In a given patient, three consecutive stimuli were applied by prodding the mucosal surface of the airway with a tip of a fiberoptic bronchoscope (3 mm outer diameter, Olympus, Tokyo, Japan) for 10 s. Three tactile stimuli were given at intervals of 3 min. Evoked changes in HR and AP were continuously recorded on a thermal array recorder (Polygraph, NEC-San-ei, Tokyo, Japan). The average value obtained from each triplicate measurement was adopted as data. The stimulated portions of the larynx, trachea and carina, and bronchus were just above the vocal cords, immediately

around the carina, and 3 cm peripheral to the carina, respectively.

Lidocaine Administration to the Airways

For 15 patients in each group, anesthesia of the respiratory tract was produced by spraying a 5 ml of 4% lidocaine solution on the area. One of the authors sprayed the appropriate portion of the airways with the lidocaine solution *via* a specially designed spray tube; this tube was 550 mm long and had multiple microholes over a length of 35 mm at the tip (No. 10 550 mm R100, Hakko, Tokyo, Japan). Spray was applied to the larynx (group L), trachea and carina (group T), or one main bronchus (either left [n = 8] or right [n = 7]; group B) under direct visual control with the aid of a fiberoptic bronchoscope. Airway stimulation to the lidocaine-applied portion was repeated 5–10 min after lidocaine application in the same manner as the control measurements.

Intravenous Lidocaine Administration

Intravenous lidocaine, 1 mg/kg, was given to five patients in each group, and airway proddings to the appropriate areas using the tip of the fiberoptic bronchoscope were applied 5 min later in the same manner as in the control measurements.

Arterial Blood Samples

In each patient, arterial blood was sampled before and 5, 10, 15, 20, and 60 min after the lidocaine administration, and the serum concentration of lidocaine in each sample was determined by a fluorescence polarization immunoassay.[8,9] Arterial blood gas tensions, pH, and electrolytes were measured 5 min after lidocaine administration in all patients.

Statistical Analyses

Results are reported as mean ± SD. A one-way factorial analysis of variance was applied to test the difference between groups, followed by the Scheffé test for *post hoc* comparisons. To assess differences produced by lidocaine administration in a given group, a paired Student *t* test was used. *P* values less than 0.05 were considered statistically significant.

Results

Baseline Heart Rate and Arterial Blood Pressure

Baseline HR before and after administration of lidocaine did not differ among the groups, but there were

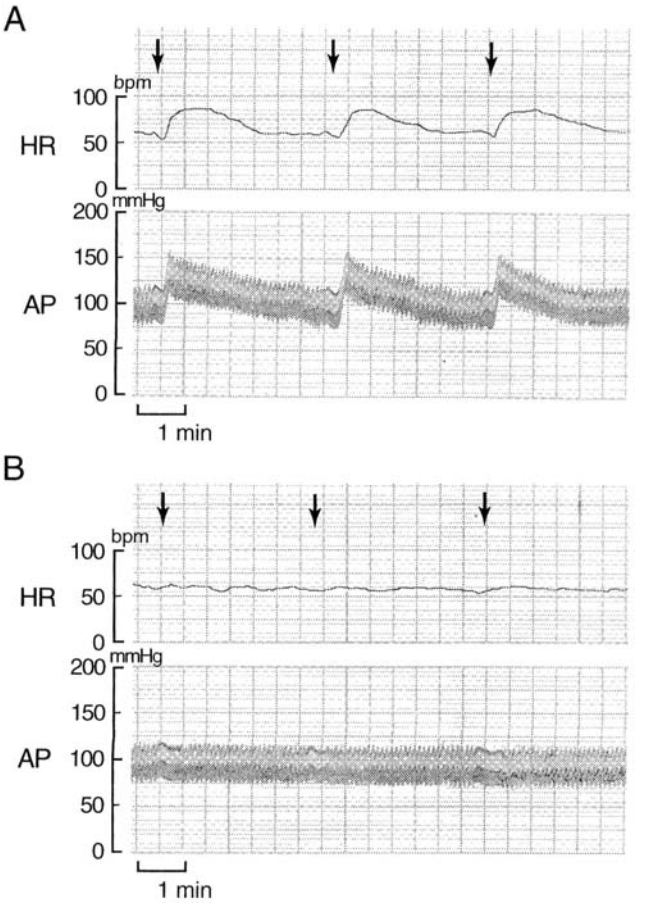

Fig. 1. Tracings of heart rate (HR) and arterial blood pressure (AP) of a patient in group L showing responses to airway stimuli. Records (*A*) before and (*B*) after the topical application of lidocaine (4%, 5 ml). Three consecutive proddings (arrow) were applied to the mucosal surface of the larynx with the tip of a fiberoptic bronchoscope.

within-group differences in all groups ($P < 0.05$; table 1) except the patients given intravenous lidocaine. Baseline AP did not show between- and within-group differences (table 1).

Tactile Stimulation of the Airways

Mechanical stimulation of the airways using the tip of a fiberoptic bronchoscope initially caused HR and AP to decrease slightly in some patients, and then caused significant increases in HR and AP in all patients studied in the absence of lidocaine (fig. 1). These changes returned to the baseline within 2 min. The changes from baseline values are referred to as ΔHR and ΔAP. The maximal values of ΔAP following stimulation of the larynx were significantly greater ($P = 0.0178$, fig. 2) than those re-

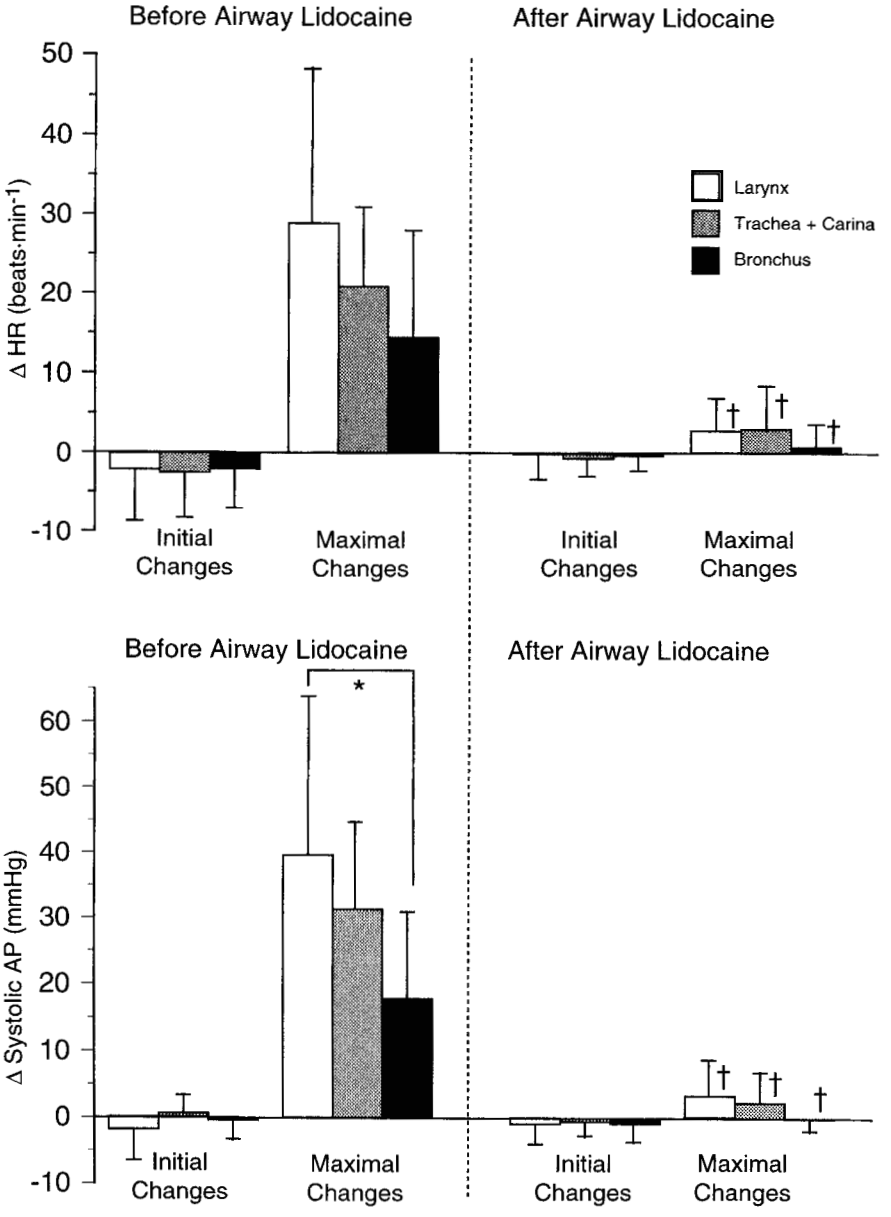

Fig. 2. Changes in heart rate (HR) and systolic arterial blood pressure (AP) from baseline values in groups L, T, and B, before and after airway application of lidocaine. Values are mean ± SD. The "initial changes" indicate the cardiovascular responses immediately after the application of tactile stimuli to the airway, and the "maximal changes" indicate the maximal cardiovascular responses to the same stimuli. *$P < 0.05$ *versus* group B; †$P < 0.001$ *versus* before lidocaine administration.

sponses following bronchial stimulation, although maximal response of HR did not differ ($P = 0.0784$) between laryngeal stimulation and bronchial stimulation. The responses to stimulation of the trachea and carina were less than the responses to laryngeal stimulation, but the differences did not reach significance. The responses in systolic AP and HR to trachea-carinal stimulation tended to be greater than those to bronchial stimulation but did not reach statistical significance. Airway anesthesia, produced by application of 4% lidocaine to the area stimulated, abolished all of the airway CVRs; the maximal ΔHR and the maximal ΔAP each showed a significant difference when responses before and after lidocaine administration were compared ($P < 0.001$; fig. 2). No clinically significant bradycardia or hypotension was observed in response to tactile airway stimulation to any part of the airways before or after administration of lidocaine.

Intravenous administration of lidocaine also attenuated the increases in HR and AP provoked by tactile stimuli of the airways ($P \leq 0.01$; fig. 3). However, the responses

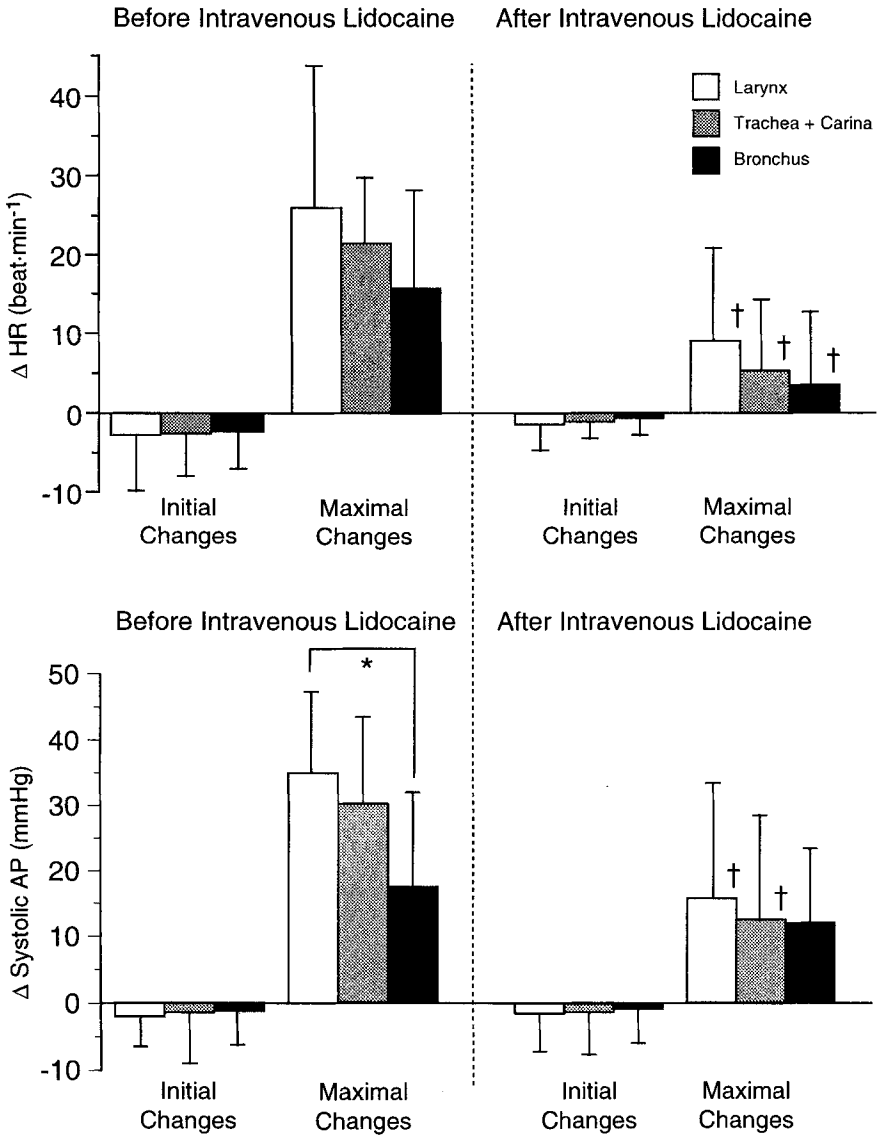

Fig. 3. Changes in heart rate (HR) and systolic arterial blood pressure (AP) from baseline values in groups L, T, and B before and after intravenous administration of lidocaine. Values are mean − SD. The "initial changes" indicate the cardiovascular responses immediately after the application of tactile stimuli to the airway, and the "maximal changes" indicate the maximal cardiovascular responses to the same stimuli. *$P < 0.05$ *versus* group B; †$P < 0.01$ *versus* before lidocaine administration.

were not suppressed as much as those with the topical administration of lidocaine.

Serum Concentrations of Lidocaine

The serum concentration of lidocaine increased significantly after each topical administration of this agent (fig. 4). The peak level (7.2 ± 4.1 μg/ml) in the bronchial application was higher than those attained following laryngeal (2.7 ± 1.6 μg/ml) or tracheal (5.7 ± 1.6 μg/ml) applications (at 5 or 10 min after the application, respectively; $P \leq 0.0019$; fig. 4). There were no significant differences between groups T and B from 10 to 60 min after lidocaine administration. The mean serum lidocaine concentrations for the group L were always lower than those for groups T and B from 10 to 20 min ($P \leq 0.0039$; fig. 4).

The maximum value (4.3 ± 2.5 μg/ml) obtained after intravenous injection of lidocaine was at 5 min, followed by a steep decline of the mean serum concentration (fig. 4). The peak level was significantly lower than that in group B ($P = 0.020$).

Other Data

The patients' demographic data showed no significant differences among the groups (table 2). Arterial blood gas tensions, pH, plasma electrolyte concentrations, and

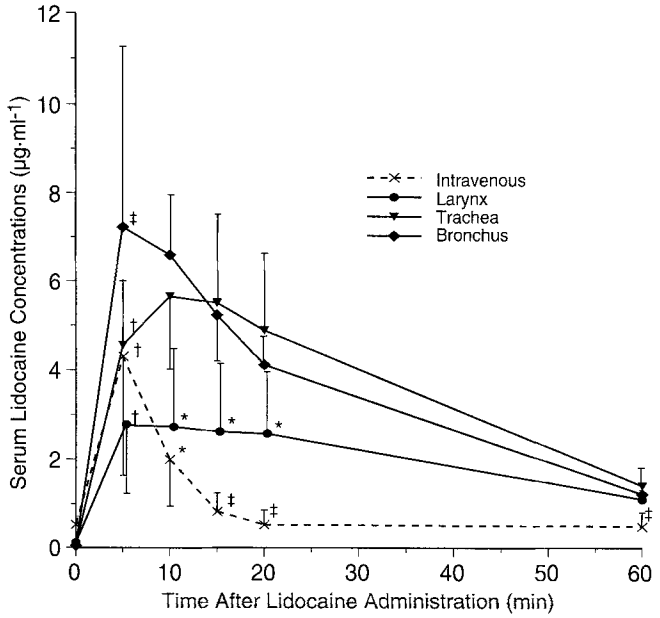

Fig. 4. Changes in serum lidocaine concentrations after 5 ml of lidocaine solution had been sprayed onto a site with the airway, or after intravenous injection of 1 mg/kg lidocaine. Values are mean ± SD. *$P < 0.05$ *versus* groups T and B; †$P < 0.05$ *versus* group B; ‡$P < 0.05$ *versus* other groups.

rectal body temperature were also similar among the groups (table 3).

Discussion

In the current study, we found in anesthetized humans that the CVRs to airway stimulation, which appeared to be sympathetic in nature, differed in magnitude depending on the site stimulated within the respiratory tract. The increases in HR and AP could be ranked according to the location of the stimulation site in descending order: larynx, trachea and carina, and bronchus. The current results also indicate that topical administration of lidocaine to the mucosal surface of the larynx, the trachea and carina, or the bronchus can block the airway-cardiovascular reflexes evoked by mechanical stimulation of the same part of the respiratory tract. Because intravenous lidocaine also partly suppressed the CVRs associated with the airway stimulation, and because plasma concentrations of lidocaine administered in the localized area of the three different parts of the airways were considerably high, the suppressive effect of lidocaine topically administered could be due to the systemic effect of absorbed lidocaine as well as to direct blockade of the mechanoreceptors in the corresponding part of the airway.

Although the physiologic importance of airway-cardiovascular reflexes is not yet clearly understood, it is well known that airway manipulations can elicit potent CVRs in both awake and anesthetized humans. These potent CVRs to airway stimulation can be suppressed or attenuated by numerous means, such as deepening the level of anesthesia[10]; administration of intravenous lidocaine,[11] supplementary opioids,[12] α_2-adrenoceptor agonists,[13] β-adrenergic blockers,[14] or other antihypertensive agents[15]; and sympathetic blockade *via* a cervical epidural block.[4] This is the first systematic attempt to study the effects of localized stimulation and anesthesia of different sections of the airway on CVRs in humans. There are three main types of sensory receptor in the respiratory tract: rapidly adapting chemoreceptors and mechanoreceptors with small-diameter myelinated fibers, slowly adapting stretch receptors with large-diameter myelinated fibers, and polymodal endings of nonmyelinated nerve fibers.[6,16,17] Although there may be considerable species differences among CVRs to mechanical and chemical stimuli, it is generally assumed that lower down the airway the receptor population becomes more chemosensitive and less mechanosensitive, and slower to adapt to repeated stimuli, at least in animals.[7] Mechanical stimulation of a given site in the airways could activate receptors in that locality (predominantly rapidly adapting chemoreceptors and mechanoreceptors but also slowly adapting stretch receptors), which are considered to be served primarily by vagal afferents[5,6] and partly by sympathetic afferents.[18] The rapidly adapting chemoreceptors and mechanoreceptors located around the circumference of the trachea and the main bronchi are concentrated in the more proximal airways[6] and thus may play an important role in the CVRs to mechanical stimulation, especially tactile stimulation with a bronchoscope, of those parts of the airways. The evoked CVRs in cats differ in intensity depending on the sites of the airway stimulated,[18] presumably because the uneven distribution and characteristics of airway receptors yielded the different reflex responses.

One might argue that the presence of the airway devices, namely the inflated balloons and the endotracheal tubes, could be considered ongoing stimuli that might evoke some kinds of airway-cardiovascular reflexes or modulate the responses to additional stimuli by causing adaptation and thus could have made the basal condition of the patients in a given group different from the pa-

Table 2. Patients' Demographic Data

Group		Age (yr)	Height (cm)	Weight (kg)
Larynx				
Airway	n = 15	44 ± 11	156.3 ± 5.8	51.7 ± 7.0
Intravenous	n = 5	46 ± 12	158.6 ± 6.3	52.3 ± 7.5
Trachea				
Airway	n = 15	46 ± 11	155.5 ± 7.0	51.8 ± 4.6
Intravenous	n = 5	46 ± 12	155.9 ± 6.1	52.5 ± 6.1
Bronchus				
Airway	n = 15	44 ± 11	156.4 ± 4.3	52.0 ± 5.7
Intravenous	n = 5	41 ± 12	157.9 ± 5.8	51.6 ± 6.6

Values are mean ± SD.

tients in other groups. The slowly adapting stretch receptors, which are mainly distributed in the airway smooth muscle,[5] could be activated by the stretching stimuli from the balloon or balloons of the airway devices, and the rapidly adapting chemoreceptors and mechanoreceptors may have been activated by the tactile stimulation from the balloon or balloons. However, the airway devices are unlikely to have significantly affected the present results, because the baseline HR and AP did not differ among the groups (table 1). Additionally, the order of the response intensity (L > T ≥ B) is consistent with the report of the respiratory reflex responses in the patients with a laryngeal mask airway whose larynx, trachea, and bronchi were stimulated by injection of distilled water,[19] indicating that adaptation, if any, to ongoing stimuli from the airway devices had negligible influences on the current results. Furthermore, the CVRs to airway stimulation could be larger in magnitude and longer in duration when the stimulation gets longer[2] and stronger. In the current study, because we stimulated the three parts of the airway in the same manner in the same duration, we can conclude that the differences in the intensity of the responses would be due to differing sensitivities of the airway portions stimulated and not to the differing features of the stimulation on each airway portion.

Because lidocaine topically applied to the airways was rapidly absorbed from the airways to increase serum concentration levels, we cannot exclude the possibility that a systemic action of lidocaine suppressed, at least partly, the responses to tactile simulation of the airways. The fact that intravenously applied lidocaine significantly, but not completely, suppressed the airway-CVRs (fig. 3) supports this possibility. Lidocaine given intravenously has an analgesic effect on the dorsal horn neurons,[20] and at a plasma concentrations exceeding 5 μg/ml has been reported to produce cardiovascular suppression *via* an effect on the central nervous system[21] and to suppress the cough reflex in humans.[22] However, it is apparent that topical application of lidocaine did have local effects, because CVRs to the stimulation of the larynx, which were the most intense in nature (fig. 2), were completely suppressed by lidocaine spraying that yielded lower serum concentrations at the time of airway

Table 3. Physiologic Variables at 5 Min after the Administration of Lidocaine within the Airways or Intravenously

Site of anesthesia		pH	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	HCO_3^- (mEq/l)	Na (mEq/l)	K (mEq/l)	BT (°C)
Larynx								
Airway	n = 15	7.44 ± 0.05	35.1 ± 4.5	143 ± 25	23.3 ± 1.9	135 ± 2.3	3.2 ± 0.3	36.7 ± 0.6
Intravenous	n = 5	7.46 ± 0.04	34.9 ± 4.3	142 ± 25	23.8 ± 2.3	135 ± 3.1	3.4 ± 0.3	36.8 ± 0.6
Trachea								
Airway	n = 15	7.44 ± 0.04	36.8 ± 3.5	141 ± 30	23.5 ± 2.2	135 ± 2.8	3.3 ± 0.3	36.4 ± 0.6
Intravenous	n = 5	7.44 ± 0.04	34.0 ± 5.1	145 ± 27	23.9 ± 2.1	134 ± 3.2	3.1 ± 0.3	36.6 ± 0.6
Bronchus								
Airway	n = 15	7.43 ± 0.05	36.9 ± 3.6	146 ± 29	24.4 ± 2.6	133 ± 3.4	3.2 ± 0.2	36.4 ± 0.5
Intravenous	n = 5	7.45 ± 0.04	35.2 ± 4.2	144 ± 29	24.1 ± 2.3	135 ± 2.9	3.2 ± 0.3	36.9 ± 0.7

Values are mean ± SD. Measurements of pH, carbon dioxide tension (Pa_{CO_2}), oxygen tension (Pa_{O_2}), bicarbonate concentration (HCO_3^-), plasma sodium (Na), and plasma potassium (K) were all taken from the arterial blood.

BT = body temperature.

stimulation, yet the intravenous lidocaine did not completely suppressed the CVRs (fig. 3) at serum concentrations similar to (5 and 10 min) those in the larynx group (fig. 4). The current results clearly demonstrate for the first time that the peak concentration of serum lidocaine and the time-course of its appearance can differ significantly depending on the part of the airway to which it is applied (fig. 4). A possible mechanism for these differences is the differing absorption rates of lidocaine among the airway portions, of which anatomic structures of the connective tissues and blood vessels vary. The bronchus are the richest in vascular supplies in comparison with the other two portions; the bronchial circulation receives approximately 1% of the cardiac output.[23] More importantly, adjacent to the bronchus are alveoli, which are extraordinary rich in the pulmonary capillary bed, and it is possible that a part of the lidocaine applied to the bronchus drained into the pulmonary vascular system.

The presence of a potent inhalational anesthetic in the airway could affect or modulate, as a chemical stimulator to the airways as well as an effector on the autonomic nervous activity, the reflex CVRs.[24-28] It has been reported that sympathoexcitatory effects such as tachycardia and hypertension are negligible with rapid inhalation of isoflurane compared with desflurane.[27] And the use of 0.5 minimum alveolar concentration isoflurane, as in the current study, has been reported to preserve baroreflex sensitivity in humans[29] and to maintain HR with only minimal changes.[30] Thus the effect of 0.5 minimum alveolar concentration isoflurane, if any, might be small or negligible.

The current study in anesthetized humans indicates that sympathetic afferent activity induced *via* stimulation of mechanoreceptors in the airways contributes to the CVRs elicited by application of tactile stimuli to the larynx, trachea and carina, and bronchi. The apparently sympathetically mediated responses to mechanical stimulation of the larynx, trachea and carina, and bronchi were completely blocked by topical application of lidocaine to the appropriate part of the airway and were partially blocked by intravenous lidocaine without significant cardiovagal reflex.

References

1. Oczenski W, Krenn H, Dahaba AA, Binder M, El-Schahawi-Kienzl I, Jellinek H, Schwarz S, Fitzgerald RD: Hemodynamic and catecholamine stress responses to insertion of the Combitube, laryngeal mask airway or tracheal intubation. Anesth Analg 1999; 88:1389-94

2. Stoelting RK: Circulatory changes during direct laryngoscopy and tracheal intubation: Influence of duration of laryngoscopy with or without prior lidocaine. ANESTHESIOLOGY 1977; 47:381-4

3. Dohi S, Gold MI: Pulmonary mechanics during general anesthesia. The influence of mechanical irritation on the airway. Br J Anaesth 1979; 51:205-14

4. Dohi S, Nishikawa T, Ujike Y, Masumi T: Circulatory responses to airway stimulation and cervical epidural blockade. ANESTHESIOLOGY 1982; 57:359-63

5. Widdicombe JG: Pulmonary and respiratory tract receptors. J Exp Biol 1982; 100:41-57

6. Sant'Ambrogio G: Nervous receptors of the tracheobronchial tree. Annu Rev Physiol 1987; 49:611-27

7. Karlsson JA, Hansson L, Wollmer P, Dahlback M: Regional sensitivity of the respiratory tract to stimuli causing cough and reflex bronchoconstriction. Respir Med 1991; 85(suppl A):47-50

8. Chen Y, Potter JM: Fluorescence polarization immunoassay and HPLC assays compared for measuring monoethylglycinexylidide in liver-transplant patients. Clin Chem 1992; 38:2426-30

9. Bertol E, Mari F, Torracca F: Comparison of lidocaine by fluorescence polarization immunoassay, enzyme immunoassay, and high resolution gas chromatography. J Analyt Toxic 1987; 11:122-4

10. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal halothane concentration for endotracheal intubation. ANESTHESIOLOGY 1977; 47:386-8

11. Tam S, Chung F, Campbell M: Intravenous lidocaine: Optimal time of injection before tracheal intubation. Anesth Analg 1987; 66:1036-8

12. Martin DE, Rosenberg H, Aukburg SJ, Bartkowski RR, Edwards MW Jr, Greenhow DE, Klineberg PL: Low-dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 1982; 61:680-4

13. Orko R, Pouttu J, Ghignone M, Rosenberg PH: Effect of clonidine on haemodynamic responses to endotracheal intubation and on gastric acidity. Acta Anaesthesiol Scand 1987; 31:325-9

14. Gold MI, Brown M, Coverman S, Herrington C: Heart rate and blood pressure effects of esmolol after ketamine induction and intubation. ANESTHESIOLOGY 1986; 64:718-23

15. Stoelting RK: Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 1979; 58:116-9

16. Coleridge JCG, Coleridge HM: Lower respiratory tract afferents stimulated by inhaled irritants. Am Rev Respir Dis 1985; 131(suppl):S51-4

17. Barnes PJ: Neural control of human airways in health and disease. Am Rev Respir Dis 1986; 134:1289-1314

18. Widdicombe JG: Receptors in the trachea and bronchi of the cat. J Physiol (Lond) 1954; 123:71-104

19. Nishino T, Kochi T, Ishii M: Differences in respiratory reflex responses form the larynx, trachea, and bronchi in anesthetized female subjects. ANESTHESIOLOGY 1996; 84:70-4

20. Dohi S, Kitahata L, Toyooka H, Ohtani M, Namiki A, Taub A: An analgesic action of intravenously administered lidocaine on dorsal-horn neurons responding to noxious thermal stimulation. ANESTHESIOLOGY 1979; 51:123-6

21. Blair MR: Cardiovascular pharmacology of local anaesthetics. Br J Anaesth 1975; 47:247-52

22. Yukioka H, Yoshimoto N, Nishimura K, Fujimori M: Intravenous lidocaine as a suppressant of coughing during tracheal intubation. Anesth Analg 1985; 64:1189-92

23. Benumof JL: Anesthesia for Thoracic Surgery, 2nd Edition. Philadelphia, W.B. Sauders Company, 1995

24. Weiskopf RB, Moore MA, Eger EI II, Noorani M, McKay L,

Chorkoff B, Hart PS, Damask M: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. ANESTHESIOLOGY 1994; 80:1035-45

25. Moore MA, Weiskopf RB, Eger EI II, Noorani M, McKay L, Damask M: Rapid 1% increases of end-tidal desflurane concentration to greater than 5% transiently increase heart rate and blood pressure in humans. ANESTHESIOLOGY 1994; 81:94-8

26. Yli-Hankala A, Randell T, Seppälä T, Lindgren L: Increases in hemodynamic variables and catecholamine levels after rapid increase in isoflurane concentration. ANESTHESIOLOGY 1993; 78:266-71

27. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. ANESTHESIOLOGY 1993; 79:444-53

28. Muzi M, Ebert TJ, Hope WG, Robinson BJ, Bell LB: Site(s) mediating sympathetic activation with desflurane. ANESTHESIOLOGY 1996; 85:737-47

29. Muzi M, Ebert TJ: A comparison of baroreflex sensitivity during isoflurane and desflurane anesthesia in humans. ANESTHESIOLOGY 1995; 82:919-25

30. Muzi M, Lopatka CW, Ebert TJ: Desflurane-avemediated neurocirculatory activation in humans. ANESTHESIOLOGY 1996; 84:1035-42