Upper Airway Reflexes during a Combination of Propofol and Fentanyl Anesthesia

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Background: The effects of intravenous anesthetics on airway protective reflexes have not been fully explored. The purpose of the present study was to characterize respiratory and laryngeal responses to laryngeal irritation during increasing doses of fentanyl under propofol anesthesia.

Methods: Twenty-two female patients anesthetized with propofol and breathing through the laryngeal mask airway were randomly allocated to three groups: (1) eight patients who received cumulative total doses of 200 μg fentanyl given in the form of two doses of 50 μg and one dose of 100 μg spaced 6 min under mechanical controlled ventilation while end-tidal carbon dioxide tension (Paco2) was maintained at 38 mmHg (fentanyl-controlled ventilation group), (2) eight patients who received cumulative total doses of 200 μg fentanyl while breathing spontaneously while end-tidal Paco2 was allowed to increase spontaneously (fentanyl-spontaneous ventilation group), and (3) six spontaneously breathing patients who were anesthetized with propofol alone (propofol group). The laryngeal mucosa of each patient was stimulated by spraying the cord with distilled water, and the evoked responses were assessed by analyzing the respiratory variables and endoscopic images.

Results: Before administration of fentanyl, laryngeal stimulation caused vigorous reflex responses, such as expiration reflex spasmodic panting, cough reflex, and apnea with laryngospasm. Increasing doses of fentanyl reduced the incidences of all these responses, except for apnea with laryngospasm, in a dose-related manner in both the fentanyl-controlled ventilation and the fentanyl-spontaneous ventilation groups. Detailed analysis of endoscopic images revealed several characteristics of laryngeal behavior during the airway reflex responses.

Conclusion: Incremental doses of fentanyl depress airway reflex responses in a dose-related manner, except for apnea with laryngospasm. (Key words: Airway; fentanyl; intravenous anesthetics; opioids; propofol; reflex.)

PROTECTIVE airway reflexes such as coughing, the expiration reflex, and apnea are important in protecting the lower airway from aspiration.3 Although, in general, the airway protective reflexes can be obtunded by general anesthesia, the effects of intravenous anesthetics on these reflexes have not been fully explored. Infusion of propofol and an opioid has become a popular anesthetic technique. Considering that intravenous anesthetic agents including propofol may have depressant effects on the airway reflexes2-4 and that opioid agonists such as fentanyl are centrally acting antitussive agents,5 it is possible that the combination of propofol and fentanyl may modify the airway reflexes in a particular manner. However, there is little qualitative or quantitative information about the effect of the combination of propofol and fentanyl on the airway reflexes. The purpose of the present study was to characterize respiratory and laryngeal responses to laryngeal irritation during increasing doses of fentanyl under propofol anesthesia. Incremental doses of fentanyl cause a marked depression of ventilation, which in turn causes a progressive increase in the partial pressure of carbon dioxide (PaCO2). Previous studies have shown that an increase in the carbon dioxide ventilatory drive exerts inhibitory effects on the airway protective reflexes.6-8 Thus an additional question of interest is whether an increase in PaCO2 associated with incremental doses of
Table 1. Anthropometric Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl-controlled ventilation (n = 8)</td>
<td>31.6 ± 10.0</td>
<td>157.7 ± 3.3</td>
<td>53.2 ± 5.0</td>
</tr>
<tr>
<td>Fentanyl-spontaneous ventilation (n = 8)</td>
<td>39.1 ± 12.5</td>
<td>159.0 ± 4.5</td>
<td>49.3 ± 2.0</td>
</tr>
<tr>
<td>Propofol (n = 6)</td>
<td>43.3 ± 9.0</td>
<td>157.1 ± 2.1</td>
<td>52.8 ± 6.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD. No significant difference was detected among the groups.

fentanyl modifies the evoked responses to laryngeal stimulation.

Materials and Methods

Patients

Twenty-two female patients who were 21- to 52-yr-old were studied. Their average heights and weights were 158 ± 3.5 cm and 51.7 ± 4.8 kg, respectively (means ± SD). All were scheduled for elective surgery. None of them had clinical evidence of any respiratory, cardiovascular, or neuromuscular disorders. None of them was a habitual smoker. The patients were randomly assigned to three groups: a spontaneously breathing group (fentanyl-spontaneous ventilation group, n = 8); a mechanically ventilated group (fentanyl-controlled ventilation group, n = 8); and a control group (propofol group, n = 6). Table 1 shows their anthropometric data. The protocol of the present study was approved by the ethics committee of the hospital, and written informed consent was obtained from all the participants.

Preparation of the Patients

All patients were premedicated with 0.5 mg atropine given intramuscularly 45 min before anesthesia. Anesthesia was induced with a bolus injection of 2 mg/kg propofol and maintained with a continuous infusion of propofol commenced immediately after induction. The infusion rate was set to 167 µg·kg⁻¹·min⁻¹ for the first 10 min, followed by 135 µg·kg⁻¹·min⁻¹ for the next 10 min, and 100 µg·kg⁻¹·min⁻¹ thereafter, according to a modification of Roberts' protocol. When the depth of anesthesia was judged to be too light as evidenced by the presence of tachycardia, hypertension, and irregular patterns of breathing, an additional 10–30 mg propofol was administered.

After induction of anesthesia, succinylcholine (1 mg/kg) was given intravenously to facilitate the blinded insertion of a laryngeal mask airway (LMA). The distal end of the LMA was connected to an elbow connector and then to an experimental apparatus incorporated into a semiclosed anesthetic circuit through which 100% oxygen was delivered at a fresh gas flow rate of 6 l/min (fig. 1). A fiberoptic endoscope (FB-10X; Pentax, Tokyo, Japan) was passed through a self-sealing diaphragm of the elbow connector down to the end of the LMA and connected to a video camera (AP-C25; Pentax) to visualize the laryngeal aperture. Laryngeal images were recorded with a video recording system (ETV9X; Nisco, Saitama, Japan). Ventilatory air flow was measured using a Fleisch no. 2 pneumotachograph (Dynasciences, Blue Bell, PA) and a differential pressure transducer (TP-603T; Nihon Koden, Tokyo, Japan), and tidal volume was obtained by electrical integration of the inspired-flow signal. Airway pressure was measured continuously using a pressure transducer (23NB005G; ICsensors, Silicon Valley, CA). End-tidal carbon dioxide tension (PETCO2) was measured continuously using a sidestream capnometer (CAPNOX CX-1; Nippon Colin, Aichi, Japan). The ventilatory air flow, tidal volume, airway pressure, and PETCO2 were recorded on an eight-channel thermal array recorder (WS-682G; Nihon Koden) and stored simultaneously in a computer with a sampling frequency of 30 times per second. Each video frame (30 frames/s) was marked with a time code (time code generator 15010; Telcom Research, Ontario, Canada) so that each image could be correlated with concurrent values of respiratory parameters in the computer.

Laryngeal Stimulation

An epidural catheter was placed through a suction channel of the endoscope so that the tip of the catheter lay just above the glottis. To elicit airway reflexes, 0.2 ml distilled water was injected through the catheter onto the laryngeal mucosa around the vocal cords, and the respiratory responses were evaluated. The respiratory responses elicited by the laryngeal stimulation were classified into the following four categories: (1)
expiration reflex, defined as a forceful expiration without a preceding inspiration; (2) spasmodic panting, defined as a rapid, shallow breathing (respiratory frequency >60/min) lasting >10 s; (3) cough reflex, which is a forceful expiration with prior inspiration; and (4) apnea with laryngospasm, which is defined as a complete closure of the glottis lasting >10 s on the video images.

**Experimental Procedures**

The experiment was started at least 10 min after the insertion of LMA when all the respiratory variables were stable.

In both the fentanyl-spontaneous ventilation group and the fentanyl-controlled ventilation group, the larynx was stimulated four times: before receiving fentanyl, after receiving 50 μg fentanyl, after another 50 μg fentanyl, and after an additional 100 μg fentanyl. Each laryngeal stimulation was performed with an interval of 6 min, and at least 2 min after ensuring that all the respiratory variables were stable after each dose of fentanyl.

In the fentanyl-spontaneous ventilation group, the patients were allowed to breathe spontaneously, and laryngeal stimulation was performed at the end-expiration phase. In the fentanyl-controlled ventilation group, mechanical ventilation was set to maintain a P_{ETCO2} of 38 mmHg, and the ventilation was stopped just before the stimulation. Mechanical ventilation was not resumed until any reflex activity ceased.

In the propofol group, without administration of fentanyl, a series of laryngeal stimulation was performed simulating the same time course of the fentanyl-spontaneous ventilation group and the fentanyl-controlled ventilation group while the patient was breathing spontaneously.

**Statistical Analysis**

Anthropometric data were tested by one-way analysis of variance. The P_{ETCO2} values of each group were compared using analysis of variance for repeated measurements, and post hoc data were analyzed using paired Student’s t tests with Bonferroni corrections. Between-group comparisons of the P_{ETCO2} values were performed using unpaired t tests. To determine whether fentanyl has a dose-dependent effect on the incidences of each reflex response, we used an extension of the Mantel-Haenszel procedure. Fisher’s exact probability test evaluated differences of the incidences of reflexes between the fentanyl-spontaneous ventilation group and the fentanyl-controlled ventilation group at each dose of fentanyl. In all analyses, \( P < 0.05 \) was considered significant.

**Results**

**P_{ETCO2} Status**

Table 2 summarizes the P_{ETCO2} values just before laryngeal stimulation in the three groups. In the fentanyl-spontaneous
Table 2. PTrCO₂ Status (mmHg)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Stimulation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Fentanyl-controlled ventilation</td>
<td>38.4 ± 2.2</td>
</tr>
<tr>
<td>Fentanyl-spontaneous ventilation</td>
<td>43.8 ± 3.4*</td>
</tr>
<tr>
<td>Propofol</td>
<td>44.3 ± 5.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
No significant difference was detected among the values of fentanyl-controlled ventilation group.

* P < 0.01.
† P < 0.001 vs. corresponding values of fentanyl-controlled ventilation group.
‡ P < 0.05 vs. preceding value.
No significant difference was detected among the values of propofol group and the values of fentanyl-spontaneous ventilation group at the first stimulation.

ventilation group, the PTrCO₂ values progressively increased with increasing doses of fentanyl. These increases in PTrCO₂ values were caused by progressive decreases in minute ventilation, resulting mainly from reductions of respiratory frequency. The PTrCO₂ values of the propofol group were maintained at a fairly constant level during repeated procedures of laryngeal stimulation.

Effects of Increasing Doses of Fentanyl on Airway Reflexes

Figure 2 illustrates typical responses to laryngeal stimulation observed in a single patient in the fentanyl-controlled ventilation group. Before administration of fentanyl, injection of distilled water immediately elicited vigorous responses commencing with one expiration reflex, which was followed promptly by spasmodic panting mingled with cough reflexes. After administration of 50 µg fentanyl, spasmodic panting and the cough reflex were reduced considerably, and laryngospasm replaced these reflex responses. As the cumulative doses of fentanyl increased, the duration of laryngospasm became shorter, and only a slight adduction of the vocal cords was observed after cumulative total doses of 200 µg fentanyl. In the fentanyl-spontaneous ventilation group, the components of reflex responses and the modification of reflex responses were essentially similar to those of the fentanyl-controlled ventilation group, despite the higher PTrCO₂ and the presence of spontaneous respiratory activity before laryngeal stimulation.

Figure 3 summarizes the types and the incidences

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Fig. 3. The incidences of various types of airway reflexes to laryngeal stimulation in the fentanyl-controlled ventilation group, the fentanyl-spontaneous ventilation group, and in the propofol group. A dose-dependent effect of fentanyl was detected for all types of reflexes in both the fentanyl-controlled ventilation and the fentanyl-spontaneous ventilation groups, except for apnea with laryngospasm. *P < 0.05, between the fentanyl-controlled ventilation and the fentanyl-spontaneous ventilation groups. No significant difference in the incidence of any types of reflexes was observed with repeated procedures of laryngeal stimulation in the propofol group.

of various reflex responses observed in three different groups. In the fentanyl-controlled ventilation group, before administration of fentanyl, the expiration reflex and spasmodic panting occurred in all patients, whereas the cough reflex and apnea with laryngospasm were observed in approximately one half of the patients. In the fentanyl-controlled ventilation and the fentanyl-spontaneous ventilation groups, incremental doses of fentanyl progressively reduced the incidence of all these reflex responses, except for apnea with laryngospasm, and there were significant dose-dependent relations between the incidence of reflex responses and the dose of fentanyl (expiration reflex, *P < 0.01; spasmodic panting, *P < 0.01; cough reflex, *P < 0.01).

In the fentanyl-controlled ventilation group, although the incidence of laryngospasm peaked at 50 μg fentanyl, a further increase in doses of fentanyl progressively decreased the incidence of laryngospasm. Comparison of the fentanyl-spontaneous ventilation and the fentanyl-controlled ventilation groups revealed a significant difference in the incidence of laryngospasm only at a dose of 50 μg fentanyl (*P < 0.05).

The responses to laryngeal stimulation by distilled water in the propofol group were essentially unchanged with repeated procedures of laryngeal stimulation, and the types of reflex responses were similar to those observed before fentanyl administration in both the fentanyl-controlled ventilation and the fentanyl-spontaneous ventilation groups (fig. 3).

Characteristics of Laryngeal Behavior

Figure 4 shows typical laryngeal images during a cough reflex. In accordance with the general sequences included in the cough mechanism, the cough reflex started with a brief inspiration. During this initial phase, the glottis opened, but the opening was usually small (fig. 4B). After the initial inspiration, there was a sudden complete closure of the glottis involving the closure of the false cords (fig. 4C). The glottic closure was then followed by a sudden opening of the glottis, during which time an explosive expiratory flow occurred (fig. 4D). The opening of the glottis during this phase was apparently wider than the opening observed during the initial inspiratory phase.

Endoscopic images obtained during elicitation of the expiration reflex and spasmodic panting are shown in figure 5. Before the expiration reflex, a strong laryngeal constriction was always present (fig. 5A). This strong laryngeal constriction was produced by closure of the false cords and was followed by a sudden opening of the laryngeal airway (fig. 5B). The laryngeal behavior during spasmodic panting was quite similar to that observed during the expiration reflex, although the rapid openings and closings of the glottis were repeated in perfect synchrony with the rapid breathing pattern (figs. 5C–E).

During prolonged laryngospasm, the laryngeal closure initially involved the closure of the false cords (fig. 6A), but the constriction of the false cords loosened quickly (fig. 6B), whereas the constriction of the true vocal cords lasted longer (fig. 6C).

Discussion

In this study, we showed that stimulation of the larynx during propofol anesthesia caused various types of reflex responses, including the expiration reflex, spas-
Fig. 4. Airflow (V) (up, inspiration; down, expiration) and corresponding endoscopic images during a cough reflex (A–E). The horizontal bars indicate the duration of laryngeal closure on the video images.

Fig. 5. Airflow (V) (up, inspiration; down, expiration) and corresponding endoscopic images during an expiration reflex (A,B) and spasmodic panting (C–E). The horizontal bars indicate the duration of laryngeal closure on the video images.

Fig. 6. Samples of endoscopic images during laryngospasm (A) immediately after stimulation of the larynx, (B) 10 s after the laryngeal stimulation, and (C) 20 s after the laryngeal stimulation. See the text for a more detailed explanation.

Modic panting, the cough reflex, and apnea with laryngospasm. Most of these reflex responses have also been observed in humans anesthetized lightly with inhalational anesthetics, suggesting that the effects of laryngeal stimulation with distilled water are essentially similar whether the background anesthetic is an intravenous agent or inhalational agent, as long as the depth of anesthesia is light enough to elicit the airway reflexes. The fact that vigorous airway reflexes were elicited under baseline propofol anesthesia also suggests that the
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infusion regimen of propofol administration proposed by Roberts et al.\(^9\) may not be effective in suppressing airway reflexes arising from the larynx.

The major finding in this study was that increasing doses of fentanyl under propofol anesthesia considerably modified the airway reflex responses, depending on whether the \(P_{\text{CO}_2}\) was maintained constant or allowed to increase spontaneously with incremental doses of fentanyl. The modification of airway reflex responses with increasing doses of fentanyl cannot be ascribed to adaptation to repeated stimulation or changes in anesthetic depth of baseline propofol anesthesia because the time control study showed that the responses to repeated injections of water were almost identical, indicating that the responses were reproducible.

In both the fentanyl-controlled ventilation group and the fentanyl-spontaneous ventilation group, all reflex responses except for apnea with laryngospasm were progressively depressed with increasing doses of fentanyl. Among these reflex responses, the cough reflex appeared to be most vulnerable to the depressant effect of fentanyl, whereas apnea with laryngospasm appeared to be least vulnerable. The marked vulnerability of the cough reflex in response to increasing doses of fentanyl corresponds with the generally accepted idea that opioid agonists such as fentanyl are centrally acting antitussive agents.\(^5\) The central mechanisms responsible for the depression of the cough reflex after administration of fentanyl are unclear. The idea that the depression results from a general decrease in excitation of the central nervous system may be an oversimplification. Recent studies showed that the antitussive effects of opioids are mediated predominantly by \(\mu\) and \(\kappa\)-opioid receptors in the central nervous system.\(^13,14\) Because there is no doubt that the medullary respiratory network is involved in producing the cough and other reflex responses,\(^15\) it is possible that activation of the opiate system after fentanyl administration may modify the central respiratory network and thereby cause the dose-related depression of the airway reflexes.

Based on the results of previous studies\(^6,7,8\) that showed that an increase in carbon dioxide ventilatory drive exerts inhibitory effects on airway protective reflexes, we predicted that the depression of airway reflexes would be more remarkable in the fentanyl-spontaneous ventilation group than in the fentanyl-controlled ventilation group. However, comparison of the incidence of various reflex responses in the two groups revealed that there was no difference in the incidence of the expiration reflex, spasmodic panting, and the cough reflex between the two groups, showing that there is no additive inhibitory effect of carbon dioxide on these types of airway reflex responses. In contrast, the incidence of laryngospasm was significantly higher in the fentanyl-controlled ventilation than in the fentanyl-spontaneous ventilation group when a dose of 50 \(\mu\)g fentanyl was given. Considering that apnea with laryngospasm is least vulnerable to the depressant effect of fentanyl, the response of apnea with laryngospasm may be unmasked when other types of reflex responses are depressed by a small dose of fentanyl, and that the inhibitory effect of carbon dioxide can be observed only in this situation.

The present study appears to be the first to simultaneously record changes in respiratory variables and endoscopic images of the larynx during various airway reflex responses to laryngeal stimulation. Detailed analysis of laryngeal behavior revealed several characteristics of laryngeal behavior during the airway reflex responses. First, although the glottis opened during inspiration and during the succeeding forcible expiration of the cough reflex, the opening of the glottis during the expiration was much wider than the opening during the inspiration. Second, although the rapid openings and closings of the glottis were repeated during spasmodic panting, there was always a rapid closure of the glottis before the expiration, and the expiration was immediately followed by a short duration of the laryngeal opening. These responses were quite similar to those observed during elicitation of the expiration reflex, except for the constant presence of a short inspiration during the laryngeal opening. It is possible that the short inspiration observed immediately after the expiration might occur passively due to an elastic recoil of the chest wall after the preceding strong expiration. Thus the expiration reflex and spasmodic panting might not be two separate reflexes, but rather spasmodic panting might be a form of the repeated expiration reflex responses. Third, prolonged laryngospasm consisted of two phases. The initial phase usually lasted for a short period and involved the closure of the false cords, indicating the involvement of activation of extrinsic laryngeal muscles. The succeeding phase involved the true vocal cords alone and lasted for a longer period. Finally, the laryngeal closure response characterized by closure of the true vocal cords was clearly observed even after administration of relatively large doses of fentanyl, indicating that this response is remarkably resistant to increasing doses of fentanyl. Apparently endoscopic im-

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ages provide us with a more complete assessment of the components of various airway reflexes.

The combination of propofol and an opioid is now a popular anesthetic technique used as an alternative to traditional techniques to maintain general anesthesia. The clinical implications of this study are that anesthesia with propofol alone does not greatly suppress the airway reflexes, and that, although in general incremental doses of fentanyl depress the airway reflex responses in a dose-related manner, the occurrence of laryngospasm is not reduced by administration of a small dose of fentanyl, particularly when normocapnia is maintained by controlled ventilation.

Thus it is possible that mechanical ventilation via an LMA in patients anesthetized with propofol alone, or with a small dose of fentanyl without the use of muscle relaxants, may increase the chance of compromising the security of the airway. Although some investigators suggest that the LMA can be inserted after propofol administration alone,16,17 this does not necessarily mean that the protective airway reflexes are greatly depressed during propofol anesthesia.

In conclusion, our study showed that vigorous airway reflexes are elicited by laryngeal stimulation in patients anesthetized with propofol alone. Although in general incremental doses of fentanyl depress the airway reflex responses in a dose-related manner, a small dose of fentanyl does not effectively prevent laryngospasm when normocapnia is maintained by controlled ventilation.

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References


