

# Aspiration Induced by Remifentanyl

## A Double-blind, Randomized, Crossover Study in Healthy Volunteers

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### ABSTRACT

**Background:** Remifentanyl is widely used for monitored anesthesia care in spontaneously breathing patients. However, the authors' previous studies have shown that remifentanyl induces subjective swallowing difficulties, which may increase the risk of aspiration.

**Methods:** Twenty-five healthy volunteers participated in a double-blind, randomized, crossover trial at the University Hospital in Örebro, Örebro, Sweden. The volunteers were studied on two different occasions during which they received either remifentanyl with an effect-site target concentration of 3 ng/ml or saline over 1 h. A radionuclide tracer was infused simultaneously into the nasopharynx at a rate of 0.1 ml/min. Aspiration was determined by lung scans, and subjective swallowing difficulties and grip strength were evaluated. The primary outcome was the difference in occurrence of aspiration between remifentanyl and placebo treatments. The secondary outcomes were differences in swallowing difficulty and grip strength and the association between aspiration and swallowing difficulty.

**Results:** During remifentanyl and placebo infusion, 48 and 12% of the volunteers aspirated, respectively, difference: 36% (95% CI, 10 to 62%). A similar significant difference was found for swallowing difficulties but not for the association between aspiration and swallowing. No difference was found in grip strength between the two treatments.

**Conclusions:** Remifentanyl infusion at concentrations used in monitored anesthesia care increases the incidence of aspiration. However, the subjective swallowing difficulty induced by remifentanyl is not indicative of the aspiration risk. (**ANESTHESIOLOGY** 2014; 121:52-8)

REMIFENTANIL has gained wide acceptance in clinical settings and is used as an adjuvant not only in general anesthesia but also in monitored anesthesia care as a single infusion or in combination with hypnotics.<sup>1</sup> The adverse-effect profile of remifentanyl is similar to that of other opioids in the fentanyl group with respiratory depression and muscle rigidity.<sup>1</sup> Furthermore, volunteers in previous studies<sup>2,3</sup> have reported subjective swallowing difficulties when receiving remifentanyl, and this may be a poorly recognized side effect. In monitored anesthesia care settings, when the patient is spontaneously breathing, swallowing difficulty may increase the risk of aspiration by aggravating pharynx clearance. We hypothesized that remifentanyl increases the risk of aspiration by inducing swallowing difficulties. Thus, the principal aim of this study was to determine whether remifentanyl results in aspiration. We used a method previously described by Gleeson *et al.*<sup>4</sup> based on the detection of a radionuclide tracer in lung scan. We also studied subjective swallowing difficulties in volunteers during remifentanyl infusion and grip strength as a measure of muscle strength.

#### What We Already Know about This Topic

- Remifentanyl infusion is often used for monitored anesthesia care
- Respiratory depression and muscle rigidity are well documented, but we know little about influences of remifentanyl on airway-protective mechanisms

#### What This Article Tells Us That Is New

- Using randomized crossover study design, continuous slow infusion of radionuclide tracer into the pharynx in 26 healthy volunteers revealed incidence of pulmonary aspiration, directly determined by the tracer in the lung field, during remifentanyl (48%) than during placebo infusion (12%)
- Subjective symptoms such as swallowing difficulty and hand grip strength were not associated with the aspiration

### Materials and Methods

#### Subjects

A total of 26 healthy volunteers were invited to participate in a double-blind, randomized, placebo-controlled, crossover

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study. The trial was conducted at the Department of Anaesthesiology, University Hospital in Örebro, Örebro, Sweden, and the study protocol was approved by the Central Ethics Review Board, Uppsala, Sweden, and by the Radiation Protection Committee in Örebro County Council, Örebro, Sweden. Written informed consent was obtained from the volunteers, who were fully informed about the study details beforehand and received financial compensation. None of the volunteers had any significant medical condition. The exclusion criteria were pregnancy, breastfeeding, or previous participation in a medical study. The volunteers were recruited by notices on university and hospital bulletin boards.

### Treatment

The volunteers were studied on two different occasions at an approximately 1-week interval. Treatment comprised intravenous remifentanyl infusion with an effect-site target concentration of 3 ng/ml *via* target-controlled infusion (Minto Model, Alaris PK syringe pump; Alaris Medical Nordic AB, Sollentuna, Sweden) on one occasion and an equal amount of saline on the other occasion. Using a random number generator, volunteers were randomly assigned in blocks to remifentanyl first or placebo in a 1:1 ratio. The volunteers as well as the nuclear physician who reviewed the lung images were blinded as to who received the study drug. Each infusion syringe was marked for both remifentanyl and saline and placed outside the field of view of the volunteers. For safety reasons, the study investigators who administered the infusion and assessed swallowing difficulty and grip strength were not blinded. The nuclear physician was not present during infusion and reviewed the images without knowledge of drug administration.

A pliable polyurethane tube (Compat Soft 10FR; Nestlé Sweden AB, Helsingborg, Sweden) was placed approximately 7 cm into the naris to attain access to the nasopharynx, and the tube was secured to the nose with adhesive tape. This 120-cm-long tube was attached to a 20-ml syringe containing 12 ml of 80 MBq <sup>99m</sup>Tc-labeled colloid albumin (Nanocoll; GE Healthcare, Milano, Italy). The tube housing a volume of 6 ml was prefilled. The radionuclide solution at room temperature was infused into the nose using a syringe pump (Alaris Asena Syringe Pump; CareFusion, Sollentuna, Sweden).

### Measurements

Lung scans were obtained using a dual-head gamma camera (e.cam; Siemens, Erlangen, Germany). Frontal and dorsal planar images were acquired in the supine position for 10 min using a low-energy high-resolution collimator and 256 × 256 matrix (LEHR Collimator; Siemens). All images were reviewed by the same nuclear medicine physician and scored as positive or negative for aspiration. Aspiration was diagnosed when activity was present in the lung fields on either side of the midline structures, such as the esophagus and trachea, according to the method described by Gleeson *et al.*<sup>4</sup>

Swallowing difficulties were assessed by asking the volunteers to perform a swallow and define any difficulty on a four-point scale (no difficulty, mild difficulty, moderate

difficulty, or severe difficulty). This test was performed three times during the study: before (T1), during (T2), and after (T3) the remifentanyl infusion. Otherwise, the volunteers were allowed to swallow as desired.

A portable Jamar hydraulic hand dynamometer (North Coast Medical, Gilroy, CA) was used to measure grip strength. This method is widely used to assess muscle strength.<sup>5</sup> The dynamometer, using the second handle position for all volunteers, was placed in the dominant hand with the volunteer in the supine position and the elbow flexed to 90°. The examiner held the device loosely around the readout dial to prevent dropping. Three maximum voluntary grip strength contractions were measured and the mean value used for analysis. Measurements were made three times during the study: before (T1), during (T2), and after (T3) the remifentanyl infusion.

### Protocol

Intravenous access was obtained before the study commenced. Throughout the procedure, the volunteers were monitored by electrocardiography, pulse oximetry, respiratory rate, and automatic noninvasive blood pressure measurement. After inserting the tube into the nose with the volunteers in the supine position, grip strength was measured with a dynamometer. The volunteers were also asked to swallow and assess any swallowing difficulty. Next, the intravenous remifentanyl or placebo infusion was started. After the target concentration was achieved, radionuclide solution was infused into the nose at a rate of 0.1 ml/min. Both infusions were continued for 60 min; every volunteer received 40 MBq <sup>99m</sup>Tc-labeled colloid albumin (6 ml of the solution). The volunteers were provided with supplement oxygen if their oxygen saturation decreased less than 92%, and they were instructed to breathe more frequently if their respiratory frequency decreased less than 6 breaths/min. Grip strength was measured 30 min after the infusions started. Just before the infusions ceased, the volunteers were asked to swallow and any swallowing difficulty was assessed. The remifentanyl or placebo infusion was then stopped and the catheter removed from the nose and isolated with the syringe. After a 15-min washout period, grip strength and any swallowing difficulty were reassessed. The volunteer was then given 100 ml of water to rinse the oral cavity and esophagus and he/she was moved to an adjoining room for imaging with the gamma camera.

The primary outcome was the difference in the occurrence of aspiration between remifentanyl and placebo treatment. The secondary outcomes were differences in swallowing difficulty and grip strength between remifentanyl and placebo and the association between the occurrence of aspiration and swallowing difficulties.

### Statistical Analysis

The occurrence of aspiration between remifentanyl and placebo treatment was compared by an exact test for paired proportions. The results are presented as proportion differences with normal approximated 95% CIs.

The Wilcoxon paired signed-rank test was used to compare swallowing difficulty between T1 and T2 within each treatment event and to compare placebo and remifentanyl treatments. The chi-square test was used to test the association between swallowing difficulties and aspiration.

Vital parameters were summarized using mean and SD and the differences from T1 analyzed using a two-way repeated-measure ANOVA with group, time, and their interaction as factors. A *post hoc* test between groups was planned for each time point if the interaction factor was significant. However, no interaction factor was significant; therefore, no *post hoc* test was performed.

Grip strength was expressed in kilogram force and summarized using mean and SD. Two-way repeated-measure ANOVA was used to evaluate grip strength in the same way as the vital parameters.

A two-tailed significance level of 5% was used. Statistical analyses were performed using SPSS version 19 (IBM Corp., Armonk, NY) or STATA release 11 (STATA Corp., College Station, TX).

### Power Analysis

To the best of our knowledge, no previous studies have investigated opioids and the occurrence of aspiration. We determined a 40% increase in the occurrence of aspiration due to remifentanyl compared with that due to placebo to be clinically relevant. A sample size of 25 pairs will have 82% power to detect a difference in proportions of 0.4, and the method of analysis is exact binomial test of paired proportions with a 5% two-sided significance level when the proportion of discordant pairs is expected to be 0.5. A total of 26 volunteers were included due to eventual drop outs. The sample size estimation was performed using NQuery Advisor (Statistical Solution, Cork, Ireland).

## Results

A total of 26 volunteers provided informed consent to participate in the study. One volunteer did not show up for the second treatment and was excluded from the study. Therefore, data were available for 25 subjects: 11 women and 14 men

(mean age, 29 yr, range, 18 to 45; mean body mass index,  $25 \pm 3$  kg/m<sup>2</sup>). No unintended effects were associated with the study. From the total amount of remifentanyl given during target-controlled infusion, the average infusion rate was calculated as  $0.14 \pm 0.016$   $\mu\text{g kg}^{-1} \text{min}^{-1}$ . The vital parameters are presented in table 1. A minor but significant decrease in respiratory rate occurred during remifentanyl treatment compared with that during placebo treatment, and some minor differences in the respiratory rate over time was present in both groups, but no clinically relevant differences were found in the vital parameters between placebo and remifentanyl treatment.

### Aspiration

The occurrence of aspiration during the study is presented in table 2. Ten of the 25 subjects had evident radionuclide tracer in the lung fields, indicating aspiration, after remifentanyl treatment but not after placebo. Twelve subjects did not have apparent radionuclide tracer in the lungs after either treatment, two subjects had positive lung scans after both treatments, and one subject had radionuclide in the lungs only after placebo treatment. The difference between remifentanyl and placebo treatment was significant with 48 and 12% of the volunteers aspirating after remifentanyl and placebo, respectively, difference: 36% (95% CI, 10 to 62%). The lung scans obtained in one of the volunteers who aspirated during remifentanyl treatment are shown in figure 1. The location of the tracer in the lung fields is given in table 3, showing that majority of volunteers aspirated into the right lung field.

### Swallowing

During remifentanyl treatment, seven volunteers experienced moderate swallowing difficulties and five volunteers experienced severe swallowing difficulties. None of these 12 volunteers had swallowing difficulties before the infusion and all returned to normal swallowing after the infusion. The remaining 13 volunteers experienced no difficulty swallowing before, during, or after the infusion. The difference in swallowing difficulty before infusion (0%) and during infusion (48%) was significant ( $P = 0.002$ ).

**Table 1.** Vital Parameters

	ANOVA										
	T1		T2-30		T2-60		T3		Group	Time	Group $\times$ Time
	Rem	Placebo	Rem	Placebo	Rem	Placebo	Rem	Placebo	P Value	P Value	P Value
MAP, mmHg	93 $\pm$ 9	90 $\pm$ 6	88 $\pm$ 8	85 $\pm$ 6	84 $\pm$ 8	85 $\pm$ 7	87 $\pm$ 8	85 $\pm$ 6	0.65	0.12	0.65
HR, beats/min	70 $\pm$ 11	70 $\pm$ 11	65 $\pm$ 10	64 $\pm$ 9	66 $\pm$ 9	62 $\pm$ 9	68 $\pm$ 10	63 $\pm$ 9	0.054	0.24	0.14
RR, breaths/min	14 $\pm$ 3	13 $\pm$ 2	13 $\pm$ 2	13 $\pm$ 2	13 $\pm$ 2	14 $\pm$ 2	12 $\pm$ 2	13 $\pm$ 2	0.04	0.047	0.62
Saturation, %	98 $\pm$ 1	98 $\pm$ 1	97 $\pm$ 1	97 $\pm$ 1	98 $\pm$ 1	98 $\pm$ 1	98 $\pm$ 1	98 $\pm$ 1	0.88	0.054	0.29

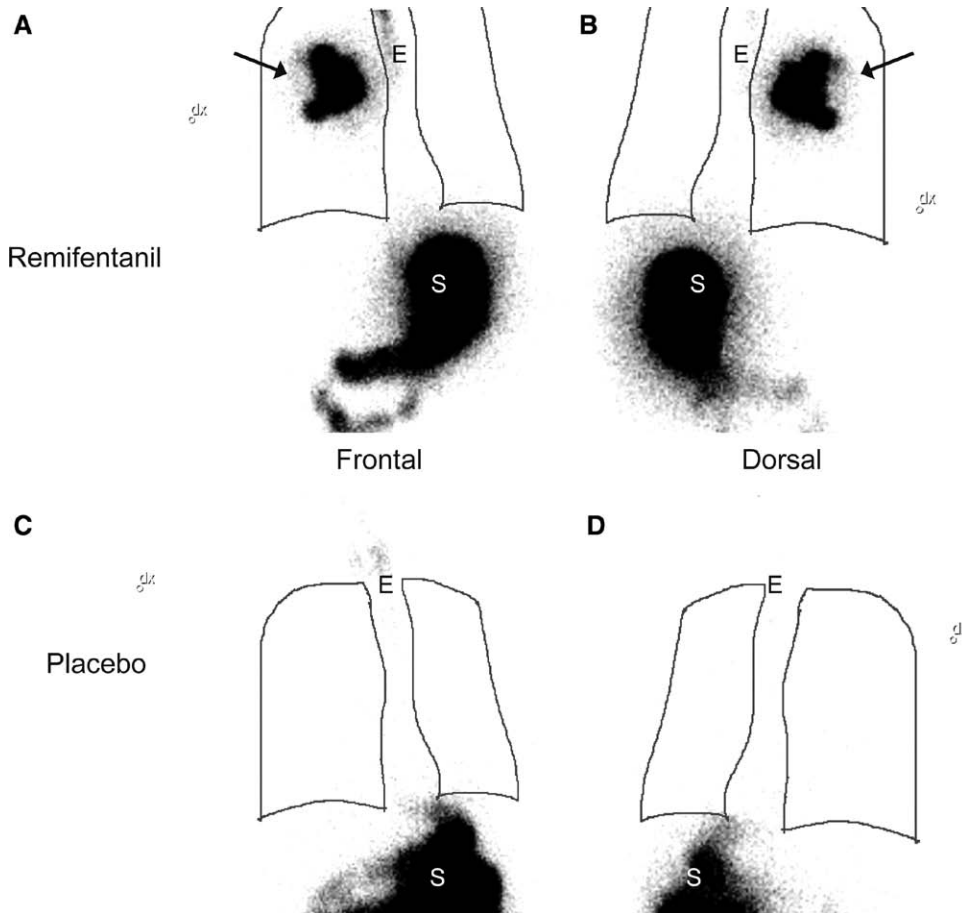
Data are mean  $\pm$  SD. The statistical analysis of group, time, and group  $\times$  time was repeated-measures two-way ANOVA between remifentanyl and placebo. The absolute differences from T1 were used as the outcome variables for each vital parameter.

HR = heart rate; MAP = mean arterial pressure; Rem = remifentanyl; RR = respiratory rate; T1 = before the infusion; T2-30 = first 30 min during the infusion; T2-60 = second 30 min during the infusion; T3 = after the infusion.

**Table 2.** Aspiration in Remifentanil and Placebo Groups

		PLACEBO, n = 25		Total
		Aspiration	No Aspiration	
Remifentanil, n = 25	Aspiration	8 % (2)	40 % (10)	48 % (12)
	No Aspiration	4 % (1)	48 % (12)	
Total		12 % (3)		

Proportions are presented as percentages with actual frequency counts in parentheses.



**Fig. 1.** Frontal and dorsal lung images obtained after remifentanil (A and B) and placebo (C and D) infusion for one volunteer who aspirated into the right lung field during remifentanil infusion. The lung field boundaries are defined by filled lines, and regions of tracer aspiration are indicated with arrows. E = tracer activity in the esophagus; S = tracer accumulation in the stomach.

None of the volunteers had difficulty swallowing before, during, or after placebo treatment. The difference in swallowing difficulty between placebo (0%) and remifentanil treatment (48%) was significant ( $P = 0.002$ ).

**Swallowing Difficulty versus Aspiration**

Swallowing difficulties were reported by 7 of the 12 volunteers (54%) who aspirated during remifentanil treatment compared with 5 of the 13 (38%) who did not aspirate during remifentanil treatment. The association between aspiration and swallowing difficulties was not significant ( $P = 0.32$ ). None of the three volunteers who aspirated during placebo treatment had swallowing difficulties.

**Grip Strength**

Grip strength was  $37.3 \pm 13.2$  kg and  $38.7 \pm 13.0$  kg for placebo and remifentanil, respectively, at T1. At T2, the grip strength was  $34.4 \pm 15.9$  kg and  $35.9 \pm 13.5$  kg for placebo and remifentanil, respectively, and at T3, it was  $34 \pm 13.9$  kg and  $35.7 \pm 13.7$  kg for placebo and remifentanil, respectively. The difference between placebo and remifentanil treatment was not significant.

**Discussion**

In the current study, remifentanil infusion with a target-site concentration of 3 ng/ml for 1 h resulted in aspiration in

**Table 3.** Location of Tracer in Each Subject

Subject No.	Remifentanyl	Placebo
1	Right lung	—
2	Right lung	—
3	—	Right lung
4	Right and left lung	—
5	Right lung	—
6	Right lung	—
7	Right and left lung	Left lung
8	Right lung	—
9	Right and left lung	—
10	Right and left lung	Right and left lung
11	Left lung	—
12	Right lung	—
13	Right lung	—

“—” indicates no aspiration.

healthy volunteers. Brock-Utne *et al.*<sup>6</sup> previously confirmed aspiration after anesthesia when using neuroleptanalgesia, a method inducing deep sedation which is not presently used. Other investigations have found impaired pharyngeal function as an indicator of increased aspiration risk, induced by light sedation or under recovery from general anesthesia with different anesthetic agents.<sup>7–10</sup> However, these studies did not confirm aspiration by showing aspirated material in lung parenchyma or below the level of the vocal cords. In our study, the aspiration of pharyngeal content induced by remifentanyl was directly demonstrated in the lung images. This finding is clinically important because remifentanyl in the dose administered in the current study is commonly used as sedation and analgesia in monitored anesthesia care settings for spontaneously breathing patients.<sup>1</sup> Even though the patients are fasting under these circumstances, they can still be silently regurgitating acidic stomach content into the pharynx. Furthermore, some studies have indicated that the competence of the esophagogastric junction is impaired by opioids,<sup>11–13</sup> increasing the risk of regurgitation.

The current study does not determine the mechanisms underlying aspiration induced by remifentanyl. Several levels are present in the line of defenses against pulmonary aspiration that can be influenced. The competence of the esophageal sphincters prevents retrograde regurgitation of already swallowed material, whereas the direct entrance into the airway is protected by several pharyngeal and laryngeal reflexes, with or without coincident swallowing.<sup>14–18</sup>

No association between subjective swallowing difficulty and aspiration was verified although the trial confirmed our previous findings that remifentanyl induces subjective swallowing difficulties.<sup>2,3</sup> The method we used to assess swallowing difficulty was based on the volunteers' subjective experiences concerning voluntary swallowing; thus, the components of the swallowing process may still be affected by remifentanyl, causing aspiration even though it was not uttered in the subjective swallowing experience. Vocal cord closure, aryepiglottic adduction, and epiglottal descent are

actions of the intrinsic laryngeal muscles and provide a sealed barrier against laryngeal penetration of the bolus during swallowing.<sup>14</sup> Impairment of this deglutitive glottic closure by remifentanyl is a possible cause of aspiration. Furthermore, different muscle groups are activated during swallowing to elevate the larynx away from the bolus path, to widen and shorten the pharynx, to create a contractile wave to transfer the bolus into the esophagus, and to open the upper esophageal sphincter (UES).<sup>15</sup> Discoordination of these muscle actions with the glottic closure induced by remifentanyl is another possible mechanism behind aspiration.

In addition, the airway is protected against aspiration by several reflexes in the larynx and pharynx.<sup>16,17</sup> The pharyngoglottal closure reflex, pharyngo-UES contractile reflex, and reflexive pharyngeal swallow are triggered by pharyngeal water stimulation and thought to protect the airway during both anterograde and retrograde flow of fluids through the pharynx.<sup>16–18</sup> In the current study, the tracer slowly poured from the nasopharynx and is probably insufficient to directly trigger these reflexes. However, as the tracer accumulated in the pharynx, the reflexive pharyngeal swallow should have eventually been activated. Impairment of this reflex by remifentanyl could be another reason for aspiration. Dysfunction of some of the aeroprotective reflexes was previously shown for propofol and inhalation anesthesia.<sup>7</sup> Furthermore, these reflexes are known to be impaired in the elderly,<sup>19,20</sup> suggesting that elderly patients may be even more susceptible to the risk of aspiration when receiving remifentanyl.

Muscle rigidity, a well-known side effect of the fentanyl group, in the pharyngeal and laryngeal muscles may be one explanation for dysfunction of the aeroprotective reflexes. Sufentanyl-induced rigidity in the laryngeal muscles results in closure of the vocal cords, leading to difficult ventilation,<sup>21</sup> and a possible mechanism underlying opioid-induced muscle rigidity is the activation of central  $\mu$ -receptors.<sup>22</sup> Muscle rigidity was not studied specifically in the current study; however, there was no difference in grip strength between remifentanyl and placebo treatments, indicating that remifentanyl does not reduce voluntary muscle strength.

As mentioned above, the barrier function of the esophagogastric junction can be impaired by opioids, but whether the UES is influenced by opioids is not as well studied. Two studies have investigated remifentanyl effects on resting UES pressure; one of the studies found a significant decrease in UES pressure in volunteers from 48 to 33 (mean  $\Delta P$ , 15.4; 95% CI, -7.5 to 23.5), whereas the other found no effect of remifentanyl on UES pressure in premedicated patients.<sup>23,24</sup> If the competence of UES is impaired by remifentanyl, esophagopharyngeal regurgitation of already swallowed tracer could have been a contributory cause of aspiration in the current study. However, we should emphasize that, in order for regurgitated material to enter the airway, the aeroprotective reflexes above the level of the UES should also be impaired.

The method of infusing radionuclide solution into the nose with subsequent lung scans is a suitable way to demonstrate aspiration of pharyngeal content into the airway.<sup>4</sup> The radionuclide tracer suspension used in the study, 80 MBq <sup>99m</sup>Tc-labeled colloid albumin, is insoluble in water and resists absorption through mucous membranes or the gastrointestinal tract, which assures that any radionuclide found in the lung parenchyma had to have been aspirated. There is no real possibility that the technetium suspension was absorbed into the systemic circulation and then transported to and somehow lodged in the pulmonary tissue. Furthermore, the second treatment was performed at least 6 days after the first, and the 6-h half-life of <sup>99m</sup>Tc ensured the absence of persistent pulmonary parenchymal radioactivity that would confound our results.<sup>4</sup> The infusion itself likely did not influence pharyngeal function because the tip of the tube was placed in the nasopharynx and the infusion rate was only a fraction of normal saliva production,<sup>25</sup> making it insufficient to trigger any protective reflexes by direct pharyngeal stimulation. Instead, the study situation mimicked a slow accumulation of secretion in the pharynx. The three subjects who aspirated during placebo treatment probably represent the normal variation in the population; for example, Sundman *et al.*<sup>7</sup> showed a 4 to 8% incidence of pharyngeal dysfunction in healthy volunteers before any intervention.

### Limitations

The current study has some limitations. First, the level of sedation was not monitored and whether eventual sedation induced by remifentanyl contributed to the increased incidence of aspiration cannot be addressed. Earlier studies reported that 45 to 50% of healthy subjects aspirate during deep night sleep<sup>4,26</sup>; however, a previous study using the modified observer's assessment of alertness–sedation scale showed that remifentanyl infusion with a target concentration of 3 ng/ml in combination with spinal anesthesia does not induce deep sedation.<sup>27</sup> Furthermore, remifentanyl alone in concentrations in the clinical range is insufficient to induce loss of consciousness.<sup>28,29</sup> During the current study, all volunteers responded promptly to the instructions to breathe more frequently and when swallowing difficulties and grip strength were assessed. Together with the fact that no difference in grip strength was found between remifentanyl and placebo treatment, the results indicate that the volunteers were not deeply sedated.

Second, spontaneous swallowing frequency was not recorded in the current study and whether an association exists between swallowing frequency and the aspiration risk cannot be determined. If remifentanyl depresses swallowing frequency, more tracer would have accumulated in the pharynx before every swallow, possibly increasing the aspiration risk. However, if remifentanyl increases swallowing frequency and swallowing dysfunction, more frequent misdirected swallowing would have increased the

aspiration risk. However, the infusion rate of the tracer was very slow and circumstances did not differ from normal physiology, indicating that remifentanyl induced pulmonary aspiration in the current study regardless of the mechanism.

Third, the blood concentration of remifentanyl was not measured. These data would have strengthened the study, as considerable individual variability exists in the actual blood concentrations reached with target-controlled infusion methodology. However, the volunteers in the current study were relatively young and of normal weight, minimizing this variability.

In addition, the volunteers drank 100 ml of water 15 min after the remifentanyl infusion ceased, and one could consider whether this procedure affected the results. The procedure was performed according to Gleeson *et al.*<sup>4</sup> to facilitate the interpretation of the lung images. The context-sensitive half-time of remifentanyl is 3 min after a 3-h infusion, and the pharmacodynamics offset time of remifentanyl after a 3-h infusion is 5.4 min.<sup>1</sup> Therefore, we considered the clinical effect of remifentanyl as nonexistent by the time the volunteers drank the water. Furthermore, none of the volunteers experienced swallowing difficulties at this time point, and they were sitting when drinking the water.

Finally, the investigators who administered the study medication and assessed swallowing difficulty and grip strength were not blinded to the order of treatments given to the volunteers. The lack of blinding was due to safety issues.

### Conclusion

Remifentanyl infusion at concentrations used in monitored anesthesia care increases the incidence of aspiration. However, the subjective swallowing difficulty induced by remifentanyl is not indicative of the increased risk for aspiration.

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### Competing Interests

The authors declare no competing interests.

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