# *Effects of Remifentanil and Morphine on Pharyngeal Swallowing: A Double Blind Randomized Cross-over Study in Healthy Volunteers*

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## Abstract

### Background

Exposure to remifentanil causes swallowing difficulties and increases the incidence of pulmonary aspiration in healthy volunteers. These effects may be explained by impairment of airway defence mechanisms and/or altered swallow function. Automated impedance manometry pressure-flow analysis (AIM analysis) is a technique that allows objective assessment of swallow function based on pressure-impedance patterns recorded during bolus swallowing. The aim of this study was to use AIM analysis to quantify the effect of remifentanil on pharyngeal swallowing in both young and old volunteers and to compare these effects with morphine.

### Methods

Eighteen healthy young and old volunteers participated in a double-blind, randomized, cross-over trial at the University Hospital in Örebro, Sweden. Subjects were studied on two occasions during which they received either target-controlled infusion of remifentanil (young: 3 ng/ml, older: 2 ng/ml) or a bolus injection of morphine (young: 0.1 mg/kg, older: 0.07 mg/kg). Pressure-impedance measurements were made with an indwelling catheter and ten liquid swallows were captured during each measuring condition. The pressure-flow variables defining swallow function were calculated and compared to determine drug effects.

### Results

Remifentanil influenced the variables towards the direction that is consistent with greater swallow dysfunction. Vigor of the pharyngeal contraction was weakened, pharyngeal bolus propulsion was diminished, and flow resistance was increased. The swallow risk index, a global index of swallowing dysfunction, increased overall. Similar effects were found with morphine but the impact of remifentanil was greater.

### Conclusions

Remifentanil over morphine induced dysfunction of pharyngeal swallowing; this may contribute to the elevated risk of aspiration.

## Introduction

Postoperative lung complications like pneumonia are common and result in both longer hospital stays and increased morbidity and mortality.[1,2] One important cause is thought to be silent, unwitnessed pulmonary aspiration that occurs perioperatively.[3] For instance, during the immediate postoperative period or during other circumstances when the patient is breathing spontaneously and the requirement of analgesics is high. Remifentanil is widely used in perioperative settings and in a previous study we showed that the incidence of pulmonary aspiration increases in healthy volunteers receiving remifentanil infusion[4]. The underlying mechanisms predisposing to aspiration in this experimental setting are unknown. One or more of the defence mechanisms against pulmonary aspiration could be affected. However disruption of the complex motor-sensory neural circuitry governing pharyngeal swallowing efficiency and/or airway protection appears the most likely cause of the increased aspiration risk.[5,6] Furthermore, advanced age is a known risk factor for postoperative lung complications.[1] One explanation for this age-related exacerbation of risk may be the decline in swallowing functional reserve that occurs as part of normal aging. Hence aspiration may be more likely to occur in association with sedation/anaesthesia, even though patients may present pre-operatively without any history of symptoms of dysphagia[5,7]

We hypothesized that remifentanil increases the risk of aspiration by interfering with pharyngeal swallowing leading to a reduction in swallowing functional reserve. Thus, the principal aim of this study was to quantify the effect of remifentanil on the pharyngeal swallowing mechanism. To assess pharyngeal function we performed high resolution impedance manometry (HRIM) and combined this with a recently developed analysis technique by Omari el al.[8] called automated impedance manometry pressure-flow analysis (AIM analysis). AIM analysis is a non-radiological method and derives individual *pressure-*

*flow metrics* which quantify bolus flow timing, flow resistance, and contractile strength during swallowing, thus providing objective numerical values for the different physiological processes governing pharyngeal swallowing. We also compared remifentanil with morphine, the golden standard analgesia. Age-related exacerbation was examined by enrolling both young and elderly volunteers. Finally, difficulty with swallowing was subjectively recorded during the experiment.

## Methods and Materials

### Subjects

Twenty healthy volunteers (12 young < 30 years, 8 male, mean age 23 ± 3, and 8 older > 65 years, 5 male, mean age 73 ± 4) were invited to participate in a double-blind, randomized, placebo-controlled, cross-over study. The trial was conducted at the Department of Anaesthesiology, University Hospital in Örebro, Sweden, and the study protocol was approved by the central Ethics Review Board (Uppsala, Sweden). Written informed consent was obtained from the volunteers, who were fully informed about the study details beforehand and who received financial compensation. The volunteers were non-smokers, had no history of dysphagia symptoms or upper gastrointestinal diseases, and were not taking any medication that could affect pharyngeal or esophageal function. The exclusion criteria included pregnancy, breastfeeding, and previous participation in a medical study. Volunteers were recruited by means of notices on university and hospital bulletin boards.

### Treatment

Treatment comprised intravenous remifentanil infusion with an effect-site target concentration of 3 ng/ml for young volunteers and 2 ng/ml for elderly volunteers *via* target-controlled infusion (Minto Model, Alaris PK syringe pump; Alaris Medical Nordic AB, Sollentuna, Sweden) on one occasion and a morphine bolus injection of 0.1 mg/kg for young volunteers and 0.07 mg/kg for elderly volunteers on the other occasion. Using a random number generator, order of treatment was randomly assigned in blocks to remifentanil first or morphine in a 1:1 ratio stratified by age. The volunteers as well as the assessor of the manometric and impedance recordings were blinded as to who received which study drug. Remifentanil and morphine were administered with unmarked syringes by study personnel, who did not participate in data analysis.

**Measurement Technique**

A combined solid-state manometric and impedance catheter with 4.2 mm outer diameter incorporating 36 circumferential 1 cm-spaced pressure sensors and 18 2 cm long impedance segments was used to acquire pressure and impedance data (Sierra Scientific Instruments, Inc., Los Angeles, CA). After a short physical exam, the volunteers underwent transnasal placement of the catheter, which was positioned with sensors straddling the entire pharyngoesophageal segment. Before and immediately after the investigation, the catheter was calibrated outside the body using the calibration options provided by the software. Boluses of 10 ml saline (used instead of water to enhance bolus conductivity) were administrated orally via a syringe at > 20 s intervals and volunteers were asked to swallow on command. Swallows of saline were performed ten times before any treatment as baseline (T0), 15 min after treatment start (T1), and 30 min after treatment start (T2). In parallel with swallowing, volunteers were asked to assess any swallowing difficulty based on four-point scale (no difficulty, mild difficulty, moderate difficulty, or severe difficulty).

**Data Analysis**

Raw manometric and impedance data for each swallow were exported from the recording system in text format and analysed using AIM analysis, a purpose-designed MATLAB-based (MathWorks, Natick, MA) analysis program (AIMplot software copyright, Taher Omari, Adelaide, Australia). To operate AIM analysis, the assessor defined four space-time landmarks from a standard pressure iso-contour plot of the pharyngeal swallow (Figure 1A). These were the following: (1) the time of onset of pharyngeal swallow, defined by the onset of upper esophageal sphincter (UES) relaxation that is often but not always associated with a proximal excursion of the UES high pressure zone; (2) the position of the UES proximal margin immediately after pharyngeal swallow; (3) the position of the velopharynx, defined as

the pressure zone immediately above the propagated pharyngeal stripping wave; and (4) the position of the UES distal margin pre-swallow. Guided by definition of these landmarks, the AIM analysis software automatically derived and exported the pharyngeal pressure-flow variables, and two global indices for the level of swallow dysfunction on the basis of established method of Omari[8-11] which has been summarised in brief in Figure 1. UES relaxation variables were derived by the method of Ghosh.[12] A summary description of all variables calculated has been provided in Table 1.

**Pharyngeal pressure-Flow Variables**

Pressure flow-variables were (1) peak pressure (PeakP), (2) pressure at nadir impedance (PZn), (3) time from nadir impedance to peak pressure (TZn-PeakP), and (4) bolus flow interval (Flow interval). All four pharyngeal pressure-flow variables were then combined to derive a swallow risk index (SRI) that provides a global assessment of swallowing and defines a level of swallowing dysfunction that may predispose to aspiration risk.

**UES Relaxation Variables**

UES relaxation characteristics were measured using the established method of Ghosh et al[12] that objectively calculated UES relaxation interval (UES-RI), the UES nadir relaxation pressure (UES-NadP), the UES median intrabolus pressure (UES-IBP), and the UES resistance (calculated as UES-IBP/UES-RI).

**Postswallow Residue**

Postswallow residue was determined using the integrated ratio of nadir impedance to impedance (iZn/Z) that relates postswallow impedance to the impedance during bolus passage and is elevated with large clinically significant postswallow residues.[10]

**Protocol**

The volunteers were studied on two different occasions at an approximately 1-week interval. Intravenous access was obtained before the study commenced. Throughout the procedure, the

volunteers were monitored by electrocardiography, pulse oximetry, respiratory rate, automatic noninvasive blood pressure measurement, and end-tidal carbon dioxide. After correct positioning, the manometric catheter was taped to the nose and continuous manometric and impedance recordings were started, with the volunteers in the supine position with 30º elevation of the headboard. After a 5-min stabilization period, the volunteers performed a series of 10 swallows of 10 ml boluses of saline and thereafter, remifentanil infusion was started or morphine injection was given. Fifteen minutes after treatment start the volunteers swallowed saline ten times again and the procedure was repeated once more 30 min after treatment start. Then the catheter was removed and the study session was finished. During the study sessions, the volunteers were provided with supplemental oxygen if their oxygen saturation decreased to < 92%, and they were instructed to breathe more frequently if their respiratory frequency decreased to < 6 breaths/min.

The primary outcome was the pressure-flow and UES relaxation variables. The secondary outcome was the subjective swallowing difficulties.

**Statistical Analysis**

Statistical comparisons were performed using the averages calculated for the 10x10ml saline swallows recorded for each subject in each study condition. Pressure-flow variables are presented with boxplots indicating medians and IQR (Inter Quartile range). Normality assumptions were evaluated with Shapiro-Wilk test and due to non-normality all statistical evaluation were performed after logarithmic (log10) transformation. Non-parametric methods were used for sensitivity analysis in circumstances of non-normality after log transformation (Shapiro-Wilk test). These results are indicated in tables.

The remifentanil effect on variables was determined by a one-way ANOVA with time (T0, T1, T2) as within factor and mean ratios of treatment effect, post vs. pre treatment (mean T1, T2 vs. T0) with 95% confidence intervals (CI) and p-values are presented. A mean ratio is a relative mean difference and a mean ratio of 1 indicates no difference and a mean ratio of 1.4 indicates 40% higher mean level post compared to pre treatment. Secondly we tested, by a two-way ANOVA, if age (young < 30 years and old > 65 years) had different treatment effects, as well as presented treatment effects stratified by age. The same analysis strategy was used for evaluation of the morphine effect.

Remifentanil and morphine effects were compared by three-way ANOVA to evaluate if the marker responded differently to remifentanil and morphine and if this potential difference interacts with age. Response variable was the difference from baseline (T0) for each marker with two within subject factors: time (T1, T2) and agent (remifentanil, morphine) and age (old, young) as between subject factor and the interaction agent*age indicating if the age groups have heterogeneous effects. The mean ratio of response variable (mean T1 T2) between remifentanil and morphine effects with 95% CI and p-values are presented as well as stratified effects by age groups. A mean ratio of 1.4 interprets as 40% higher mean effect post vs. pre with remifentanil compared to morphine.

Vital parameters were evaluated with two-way repeated measure ANOVA. The response variable was the difference from baseline for each vital parameter and within factors were agent and time and their interaction.

The Wilcoxon paired signed-rank test was used to determine statistically significant differences in swallowing experiences by comparing for each agent at T0 to T1 and T2.

A two-tailed significance level of 5 % was used. All statistical analyses were performed using SPSS version 19 ((IBM Corp., Armonk, NY, USA).

**Power analysis**

Number of study subjects was estimated regarding pressure-flow variable PeakP with help from a study of Omari et al[8].Assuming a similar magnitude of effect in the present study a sample size of 11 would have 80% power to detect a mean difference of 39 mmHg with a standard deviation of 40 mmHg using paired t-test with 5% two-sided significance level. The present study was planned to include 12 young and 12 old study subjects to compensate for some potential dropouts.

## Results

Twenty volunteers provided informed consent to participate in the study. Recordings of one young volunteer were not evaluable due to a technical malfunction, and one elderly volunteer withdrew before the protocol was complete due to intolerance of the catheter placement. Therefore, data were available from 18 subjects: 11 young and 7 elderly, five women and 13 men, with a mean age of 23 years (range 18–28 years) for young volunteers and 73 years (range 65–79 years) for elderly volunteers. Mean body mass index was 22 ± 4 kg/m² for young volunteers and 27 ± 2 kg/m² for elderly volunteers. No unintended effects were associated with the study.

Vital parameters are presented in Table 2. Heart rate decreased significantly over time in both groups but no significant differences were found in the vital parameters between remifentanil and morphine treatment.

The effects of each treatment on the different swallow function variables calculated are presented as effect ratio´s (Table 3) and visualized as box plots in Figure 2. Comparisons of the two treatments are presented in Table 4 and Figure 2. Six of the ten variables (PZn, SRI, UES-RI, UES-Nad-P, UES-IBP, and UES-Resistance) showed a significant general age effect with the old volunteers having higher values.

### Pharyngeal Pressure-Flow Variables

The PeakP decreased statistically significantly with remifentanil with the mean level being 12 % lower compared to baseline, mean ratio 0.88 (95 % CI 0.78 – 0.99), P = 0.034, (Figure 2A and Table 2). Similar results were found with morphine (P = 0.013).

The PZn (Figure 2B) increased significantly with remifentanil (P = 0.024), and with morphine (P = 0.046). However, with non-parametric methods the increase was not significant with remifentanil (P = 0.066).

The TZn-PeakP (Figure 2C) shortened significantly with remifentanil (P = 0.003) while with morphine the difference from baseline was not statistically significant.

No significant effects were found in relation to flow interval (Figure 2D).

The swallow risk index (SRI), a global measure of swallow dysfunction, increased significantly both with remifentanil (P = 0.002) and with morphine (P = 0.022) consistent with drug induced impairment of swallowing function (Figure 2E).

The Nadir Impedance to Post-Swallow Impedance-ratio (iZn/Z) was found to be low in these healthy subjects, and decreased following exposure to remifentanil (P < 0.001) and with morphine (P = 0.007) (Figure 2F), hence post-swallow residues did not increase even though overall swallowing function was impaired.

**UES Relaxation Variables**

No significant effects were found on UES relaxation interval (Figure 2G), however measures of flow resistance were increased following the drug treatments. The UES-Nad-P (Figure 2H), UES-IBP (Figure 2I), and UES resistance (Figure 2J) increased significantly with remifentanil and with morphine. Furthermore, with remifentanil both UES-Nad-P and UES-IBP showed significant interaction with age; stratified by age, young volunteers showed significant increase in UES-Nad-P and UES-IBP while no significant effect was seen with the old volunteers.

**Remifentanil versus Morphine**

The remifentanil effects were compared with morphine effects (Table 3) to determine if the treatments effects were heterogeneous, and also to evaluate if age interacted with these effects.

In all volunteers, statistically significant differences between treatment effects were found with two variables, TZn-PeakP and UES resistance. TZn-PeakP decreased significantly with remifentanil, while no significant differences were found with morphine, difference in mean effects 12 % (P = 0.018). UES resistance increased significantly with both treatments but the increase was 30 % greater with remifentanil (P = 0.044).

Three of the variables showed a significant interaction effect (agent × age). In older volunteers, PeakP decreased by a significantly greater degree with remifentanil when compared to morphine, while no such differences were found with the young volunteers. In contrast UES-Nad-P and UES-IBP, increased by a significantly greater degree in the young volunteers with remifentanil compared to morphine, while no differences between remifentanil and morphine were found with the older volunteers.

**Subjective Swallowing Difficulties**

At baseline one subject reported swallowing difficulties with both treatments (remifentanil: male aged 26 years, morphine: male aged 27 years). No subjects reported swallowing difficulties during morphine exposure, whilst two subjects (two males, aged 22 and 65 years) reported swallowing difficulties during remifentanil exposure. This increase in proportion was not statistically significant (p=0.41).

## Discussion

In this study, we evaluated the effects of remifentanil on pharyngeal swallowing using HRIM combined with AIM pressure-flow analysis. Remifentanil in particular influenced most pressure flow variables towards the direction that suggests greater swallow dysfunction i.e. vigor of the pharyngeal contraction was weakened, pharyngeal bolus propulsion was diminished, and UES flow resistance increased. Whilst the net effect of these changes to pressure-flow metrics led to a deterioration of swallowing function, the global SRI and iZn/Z still remained within the sub-clinical normal ranges (SRI <15, iZn/Z<250).[13] These findings are consistent with the fact that, despite interfering with some aspects of swallowing function, the exposure to the drugs did not cause subjects to experience significant symptoms overall. However, it is important to note that previous validation studies of AIM analysis with simultaneous videofluoroscopy[8,14] were based on a different acquisition system and catheter and therefore the extent to which the normative ranges determined in past studies can be directly translated to the current study remains unknown.

Exposure to morphine and remifentanil altered swallowing function. Oropharyngeal swallowing is a complex, stereotyped sequence of inhibition and activation of several pairs of muscles driven by several motor neuron pools located in various cranial motor nuclei in the brainstem and upper part of the cervical spinal cord[15] which in turn are triggered by both central and peripheral inputs. Consequently, several sites of action of opioid drugs, altering peripheral and central neural circuitry, or muscle tone/rigidity[16] would explain these findings. Overall, the effects with remifentanil were greater given the level statistical confidence and the numbers of individual measures that were affected. This finding, based on objective functional measures, is consistent with our clinical experience, of patients undergoing

anaesthesia, and our previously published study in controls, showing that remifentanil induces significant swallowing difficulties[17]

An important associated observation emerging from our study was that we detected significant differences between the treatments in relation to one metric in particular, that is, TZn-PeakP. TZn-PeakP measures the latency from maximum bolus distension of the pharynx to the time when pharyngeal contraction peaks. TZn-PeakP was selectively shortened during remifentanil exposure. During healthy liquid swallows, maximum bolus distension is driven by oro-lingual propulsion mechanisms, initiated with the onset of the reflexive pharyngeal swallow. Many dysphagia patients demonstrate weak lingual bolus propulsion, poor oral bolus containment and/or delayed pharyngeal trigger and it has been shown that TZn-PeakP is shorter in relation to these particular modes of swallow defect[18] As a corollary to these objective findings, our previous study[17] showed that subjects who reported swallowing problems following remifentanil exposure reported difficulty with initiation of a swallow. Hence we conclude that the remifentanil may have a greater effect on lingual bolus propulsion and/or pharyngeal swallow trigger, than morphine.

Generally the older volunteers showed differences in pressure flow variables that suggest greater swallow dysfunction when compared to young volunteers and these findings are consistent with a previous report evaluating older adults with AIM analysis[13]. Furthermore, stratified by age, pressures during UES relaxation (UES nadir pressure and UES intrabolus pressure) showed a heterogeneous treatment effect and even UES resistance showed a similar trend: young volunteers increased with remifentanil in particular while the old volunteers started from almost twofold higher baseline values and were influenced less by the treatments. One explanation may be that old volunteers already exhibit values near upper limit for a specific variable with no capacity to increase more. Another explanation may be that the

lower dosages of treatments given to older subjects were insufficient to induce an effect in these variables. Other variables in this study did not show differing effects by treatments when stratified by age, although this can be a power issue: twelve old volunteers were planned to participate according to power analysis but we only managed to include seven.

**Clinical Implications**

We have shown in a previous study an increased incidence of aspiration in healthy young volunteers receiving remifentanil[20] and this study suggests that remifentanil impairs pharyngeal swallowing. Changes in objective measures were consistent with impaired lingual bolus propulsion and/or pharyngeal swallow trigger and this may be a possible underlying mechanism exacerbating aspiration risk. In this study both young and old volunteers were included, and the pharyngeal swallowing was shown to be affected even in the younger age group. Impairment of pharyngeal swallowing is a clinically relevant concern specially in non-fasting patients like women in labour among which remifentanil has become more commonly used for pain relief.[21,22] Furthermore, the present study showed that even morphine affects pharyngeal swallowing towards greater dysfunction, although not to the same extent as remifentanil, and this may impair patients airway protection during postoperative period when morphine is commonly used.

**Limitations**

Dosage of remifentanil and morphine aimed to represent clinically relevant dosages and were adjusted according to age groups based on safety issues. No blood concentrations were measured or actual equipotency searched. Had we done so it would have been possible to correlate the level of pharmacological exposure to the physiological effects. However, the concentration of remifentanil used in young volunteers was same as in our previous study which showed aspiration induced by remifentanil[4] and dosage of morphine was chosen to be

clinically relevant to be given as a single injection and recording occasions during treatments were chosen according to the known peak effect interval of morphine after intravenous injection (15 to 30 min).[23]

## Conclusions

Remifentanil over morphine influences pharyngeal swallowing towards greater dysfunction, and this may contribute to elevated risk for aspiration.

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## Competing Interests

T Omari, Inventorship of patents detailing pressure-flow analysis methods. All other authors declare no competing interests.

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