Remifentanil alters sensory neuromodulation of swallowing in healthy volunteers: Quantification by a novel pressure-impedance analysis

American Journal of Physiology – Gastrointestinal and Liver Physiology

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Running title: Remifentanil and sensory neuromodulation of swallowing

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SHD (interpretation of data for the work; drafting the work and revising the work critically for important intellectual content);
TIO (interpretation of data for the work; drafting the work and revising the work critically for important intellectual content);
JS (conception of the work, design of the work, data collection, revising the work critically for important intellectual content)

All authors have read and approved the final submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All individuals designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Keywords: Remifentanil, swallowing, high resolution manometry, upper esophageal sphincter, μ–opioid receptor

Key points

- Exposure to remifentanil contributes to an increased risk of pulmonary aspiration
- We employed a novel high resolution pressure-flow analysis to quantify the swallowing-related biomechanical changes across the upper esophageal sphincter (UES) during remifentanil exposure in healthy volunteers.
- Remifentanil increased residual UES pressure, shortened the time period of UES opening and shortened the latencies between the different phases of the stereotypical UES relaxation sequence.
- Reduced duration of bolus flow during shortened UES opening in concert with increased hypopharyngeal distension pressures are mechanically consistent with increased flow resistance due to a more rapid bolus flow rate.
- These biomechanical changes are congruent with modification of the physiologic neuro-regulatory mechanism governing accommodation to bolus volume.

Abstract

Exposure to remifentanil contributes to an increased risk of pulmonary aspiration, likely through reduced pharyngeal contractile vigour and diminished bolus propulsion during swallowing. Here, we employed a novel high resolution pressure-flow analysis to quantify the biomechanical changes across the upper esophageal sphincter (UES). Eleven healthy young participants (mean age 23.3±3.1 years, 7 male) received remifentanil via intravenous target controlled infusion with an effect-site concentration of 3 ng/ml. Before and 30 min following commencement of remifentanil administration, participants performed ten 10 ml saline swallows while pharyngo-esophageal manometry and electrical impedance data were recorded using a 4.2 mm diameter catheter housing 36 circumferential pressure sensors. Remifentanil significantly shortened the time period of UES opening ($p<0.001$) and increased residual UES pressure ($p=0.003$). At the level of the hypopharynx, remifentanil significantly shortened the time latency from maximum bolus distension to peak contraction ($p=0.004$) and significantly increased intrabolus distension pressure ($p=0.024$). Novel mechanical states analysis revealed that the latencies between the different phases of the stereotypical UES relaxation sequence were shortened by remifentanil. Reduced duration of bolus flow during shortened UES opening in concert with increased hypopharyngeal distension pressures are mechanically consistent with increased flow resistance due to a more rapid bolus flow rate. These biomechanical changes are congruent with modification of the physiologic neuro-regulatory mechanism governing accommodation to bolus volume.

Abbrevations. CNS, Central nervous system; CP, cricopharyngeus; CPG, central pattern generator; DSG, Dorsal swallowing group; NTS, Nucleus tractus solitarius; UCI, Upper esophageal sphincter contractile integral; UES, Upper esophageal sphincter.

Introduction

Recent research into potential underlying causes of postoperative respiratory complications, such as pneumonia, suggests that exposure to remifentanil, a short-acting opioid analgesic drug, can induce swallowing difficulties (29) and an increased incidence of pulmonary aspiration (28). Remifentanil-induced swallowing difficulties are characterised by reduced pharyngeal contractile vigour and diminished bolus propulsion as reflected by an increase in the Swallowing Risk Index (27), a novel pressure- and electrical impedance-based composite score of swallowing function (20,21,22). At the level of the upper esophageal sphincter (UES), residual pressure and overall flow resistance also increase (27).

These findings suggest that changes in the neuro-biomechanical mechanisms driving and coordinating pharyngeal bolus propulsion, as well as UES relaxation and opening, may contribute to the swallowing difficulties reported following exposure to remifentanil. Remifentanil is an opioid analgesic drug which primarily acts as a μ–opioid receptor agonist. μ–opioid receptors are abundant in peripheral vagal afferents (4) and are the predominant opioid receptor in the nucleus tractus solitarius (NTS) (8, 34). Both of these systems play a critical role in integrating peripheral afferent feedback into an effective and safe swallowing response. Therefore, it is possible that remifentanial affects swallowing function via modification of peripheral or central synaptic mechanisms, or both.

Based on this premise and in the context of the biomechanical effects of remifentanil on pharyngo-esophageal swallowing that we described previously (27, 28, 29), we hypothesised that exposure to remifentanil results in quantifiable changes in pharyngeal bolus propulsion and UES relaxation and opening, producing knock-on effects such as increased flow resistance across the UES and overall aspiration risk. To test this hypothesis, we conducted an in-depth analysis of the effects of remifentanil on swallowing function using recently

nuanced analytical methods aimed specifically at quantifying critical event timing during the act of swallowing. Specifically, we evaluated the relationship between intraluminal pressure and luminal diameter, as assessed by concurrent pharyngo-esophageal high resolution intraluminal pressure and impedance recording, off and on remifentanil.

Methods and Materials

Subjects

We report data from 11 healthy young participants (mean age 23.3±3.1, 7 male) who were previously enrolled in a double-blind, randomised, placebo-controlled, cross-over study of opioid drugs (27). In this previous publication, we reported pharmacodynamic effects at two time points, 15 min and 30 min, following commencement of remifentanil infusion. As the steady state plasm concentration is rapidly achieved by target controlled infusion systems, and there were no differences between the time points, in this follow up physiological analysis we report the effects at 30 min compared to baseline only. Data were collected at the Department of Anaesthesiology, University Hospital in Örebro, Sweden, following informed consent being provided by each participant. This study was approved by the Central Ethics Review Board in Uppsala, Sweden. None of the participants reported any current or past symptoms of dysphagia or upper gastrointestinal diseases, smoked or took any medications that could affect pharyngeal or esophageal function. Potential participants were excluded if they were pregnant, breastfeeding, or had previously participated in a medical study.

Treatment

Remifentanil was administered via intravenous infusion with an effect-site target concentration of 3 ng/ml using target controlled infusion (Minto Model, Alaris PK syringe pump, Alaris Medical Nordic AB, Sollentuna, Sweden).

High resolution impedance manometry

Manometry and impedance data were recorded using a 4.2 mm diameter catheter housing 36 circumferential pressure sensors that were spaced 1 cm apart and 18 2-cm long impedance segments (Sierra Scientific Instruments, Inc., Los Angeles, CA). Following standard calibration in accordance with the manufacturer's specifications, catheter placement was performed transnasally with sensors straddling the entire pharyngo-esophageal segment. Following a 5 minute accommodation period, participants ingested 10 ml saline boluses on command that were administered orally via a syringe at > 20 s intervals. We analysed 10 swallows that were recorded at baseline and a further 10 swallows recorded 30 min following drug infusion for each participant.

Analysis of pressure and impedance recordings

Swallows were analysed consecutively using a purpose-designed software (based in MATLAB version 8.5.0.197613–R2015a; MathWorks Inc). Colour pressure isocontour plots of each swallow file were opened, the pressure and impedance data were automatically interpolated (Piecewise Cubic Hermite Interpolating Polynomial) to increase the dataset to a 1 mm spatial resolution.

Four space-time landmarks were determined on the plot. These are described below (see also Figure 1):

1. The time of onset of complete UES relaxation, indicating UES opening.
2. The time of offset of complete UES relaxation, indicating UES closure.
3. The apogee position of the UES high pressure zone, defined by visualisation of the upward movement of the UES high pressure zone to determine the highest

position of the proximal edge of the high pressure zone during the swallowing event.

4. The distal margin position of the UES high pressure zone, defined by the lowest position of the distal edge of the high pressure zone pre- and/or post-swallow.

Guided by definition of these landmarks, values for a range of swallow function variables were derived.

Swallow function variables

Swallow variables were separated into four sub-classes: 1) measures of flow/event timing, 2) measures distension pressure, 3) measures of luminal cross-sectional area and 4) measures of contractility. We provide specific details of all variables below (see also Figure 1).

During passage of a highly conductive bolus, the inverse of impedance or *admittance* (expressed in millisiemens, mS, the unit of electric conductance) increases when the lumen is increasing in diameter and decreases when the lumen is decreasing in diameter. The *maximum* admittance corresponds to the time and position where the lumen is most conductive. In normal circumstances this identifies the axial centre, or most distended part, of the intra-bolus bolus domain during transport (9, 16, 23). Hence, pressure measured at, or timing of, maximum admittance is an accurate measure of intrabolus distension pressure and timing of maximum distension respectively.

The UES can undergo up to 2cm or more elevation before complete UES relaxation. The manometry catheter itself may also elevate during swallowing, asynchronous to UES elevation. UES pressure and impedance data were therefore analysed within an area of interest corresponding to the region from the distal margin of the UES high pressure zone to the estimated apogee position of the UES during swallow. The maximum axial UES pressure

during the swallow was measured within the limits of UES area of interest over time. The location of maximum axial pressure was used to track the superior and inferior movement of the UES based on the method of Ghosh and colleagues (7), now routinely referred to at the *'e-sleeve'* method (Figure 1). Consecutive pressure and admittance values mapped to the corresponding position of the UES over time can be used to derive an optimal profile of pressure and admittance during the swallow.

The following flow timing measures were determined: 1) the UES opening period, based on the UES admittance curve (UES rapid admittance upstroke to the inflexion of the admittance downstroke); 2) time from opening to maximum hypopharyngeal distension (UES admittance upstroke to hypopharyngeal admittance peak); 3) time from maximum hypopharyngeal bolus distension to maximal contraction (admittance peak to contraction peak) and 4) hypopharyngeal bolus presence (hypopharyngeal admittance upstroke to inflexion on downstroke).

The following pharyngeal and UES distension pressures were determined: 1) three discrete hypopharyngeal intrabolus pressures (IBP1, 2 and 3), measured 1 cm proximal to the UES apogee position and temporally aligned to maximum admittance (maximum distension) at the hypopharynx (IBP1), maximum admittance at the UES apogee (IBP2) and maximum admittance 1 cm below the UES apogee (IBP3). Using the '*e-sleeve'* method based on maximum axial UES pressures (as described above): 2) the UES residual pressure and 3) the UES 0.25 sec integrated relaxation pressure. This is the median of all lowest UES pressures (contiguous or non-contiguous) recorded measured over a 0.25 sec period (32).

The maximum luminal cross-sectional area during bolus flow was inferred based on maximum admittance at the hypopharynx, UES apogee and 1 cm below the UES apogee (23).

The following pharyngeal and UES contractility measures were determined: 1) hypopharyngeal peak pressure at 1 cm proximal to the UES apogee position; 2) the pharyngeal contractile integral based on pressures for the whole pharynx greater than 20 mm Hg from onset of complete UES relaxation to 0.5 sec after offset of relaxation. 3) Using the *e-sleeve* method based on maximum axial UES pressures, basal UES pressure was determined using the average pressure up to 0.25 sec prior to complete UES relaxation. 4) Post-relaxation peak pressure was determined by the maximum post-relaxation pressure up to 1 sec after relaxation offset. 5) The UES contractile integral (UCI) was determined based on post-relaxation pressures greater than 20 mmHg up to 1 sec after relaxation offset.

Mechanical states analysis

In the cricopharyngeus (CP) muscle segment, activation of inhibitory or excitatory neural inputs during swallowing changes the diameter of the CP lumen, consequently modifying intraluminal pressure and bolus flow across the sphincter. This real-time relationship between UES luminal opening and corresponding changes in intraluminal pressure recorded at the same location was recently used to describe a novel method of inferentially evaluating the mechanical states of the contributing musculature, in particular the CP fibres (23). Omari and colleagues (23, 24) demonstrated the feasibility and validity of this technique, identifying eight UES mechanical states ubiquitously present in unimpaired swallowing. For example, UES mechanical states analysis was able to detect differences in UES biomechanics between age-matched non-dysphagic volunteers and individuals with swallowing impairment secondary to motor neuron disease, and these corresponded to the known neural innervation patterns of the UES (23). Furthermore, in healthy volunteers mechanical states analysis has been shown to successfully predict the activity of the CP-muscle as measured by CP-electromyography. Mechanical states analysis was used in the present study to inferentially characterise the neurological modulations in UES innervation that may contribute to the

changes in swallowing function recently reported during exposure to remifentanil (27). Specifically, we used mechanical states analysis to deduce the duration of 'pause' of neural activation of the CP muscle (23, 24). As illustrated in Figure 2, the pause was defined by the period from auxotonic (lumen opening) relaxation (marking deactivation of CP neural inputs) to auxotonic (lumen closing) contraction (marking CP re-activation).

Statistical analysis

Variables measured before and after exposure to remifentanil were compared by paired t-test and presented as mean ± standard error (t statistic). A p-value <0.05 was considered statistically significant.

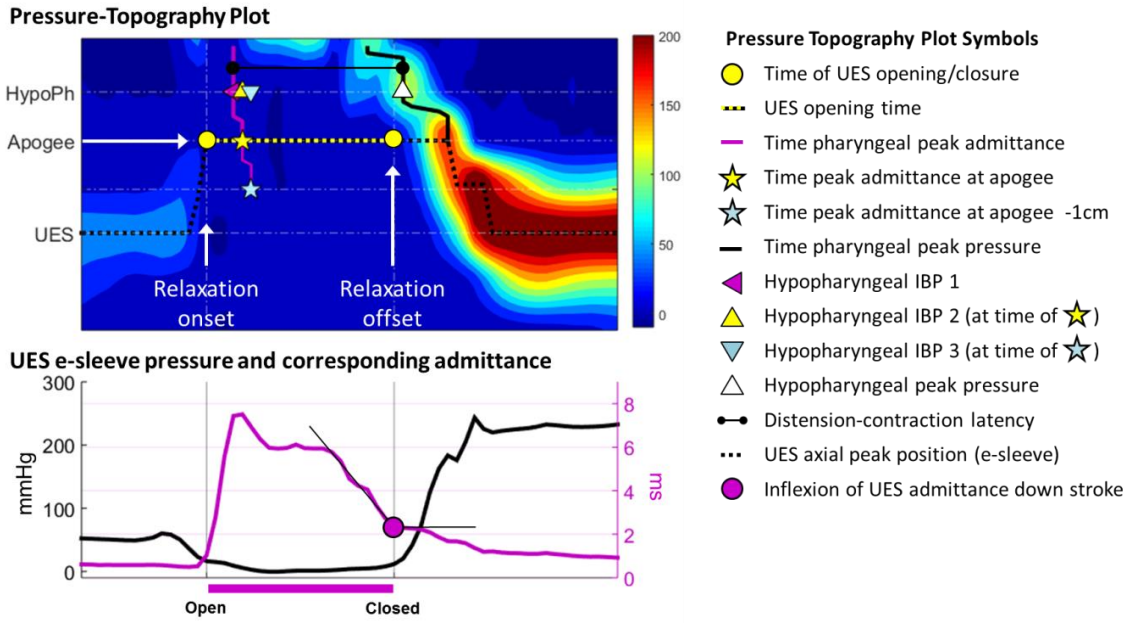

Figure 1. Analysis was performed using a semi-automated software routine. The first step in the analysis was to manually input the positions of the UES distal margin and UES apogee and the approximate time of UES opening and closure based on the relaxation onset and offset. The software then created a magnified pressure topography plot of the UES region that was automatically populated with relevant analysis landmarks defining where pressure, admittance and timing variables are measured (top panel). Axial movement of the UES high

pressure zone was determined by the position of maximum ‘e-sleeve’ pressure. Consecutive pressure and admittance values mapped to the corresponding position of the UES over time was used to derive an optimal profile of pressure and admittance during the swallow. The UES pressure-admittance curve (bottom panel) was used to adjust the onset of UES opening, based on the rapid admittance upstroke, and UES closure based on the inflexion of the admittance downstroke.

Results

Remifentanil exposure significantly altered the timing of several, but not all, sub-components of the swallowing mechanism. The main effects are demonstrated in Figure 2 with mean values shown in Table 1. At the level of the UES, remifentanil exposure for 30 min significantly shortened the time period of UES opening (Figure 2 A vs. E and C vs. G) and increased residual UES pressures (Table 1). At the level of the hypopharynx, remifentanil significantly shortened the time latency from maximum bolus distension (time of maximum admittance) to peak contraction (time of maximum pressure) (Figure 2 B vs. F) and significantly increased intrabolus distension pressures (Table 1). UES and pharyngeal maximum admittance (bolus distension area) was not significantly different overall (Table 1). In contrast to the timing and distension variables, the contractility of the pharynx and UES was unaffected by remifentanil in this group of participants.

Using mechanical states analysis, we could demonstrate changes in the mechanical state of the muscle consistent with activation and deactivation of the CP muscle by corticobulbar motor neurones. The CP muscle is tonically active at rest and undergoes neurally mediated deactivation immediately prior to UES opening (Lang, 2006). Following UES opening, inferred neural activity follows a pattern of re-activation, tonic activation and then deactivation, returning to a steady tonic activation state; i.e., basal conditions (Figure 2D). This stereotypical sequence of events was also observed after exposure to remifentanil

(Figure 2E). However, as with other temporal variables, the latencies between the different phases of the sequence were shortened, as indicated by the reduced period of predicted CP pause (Table 1).

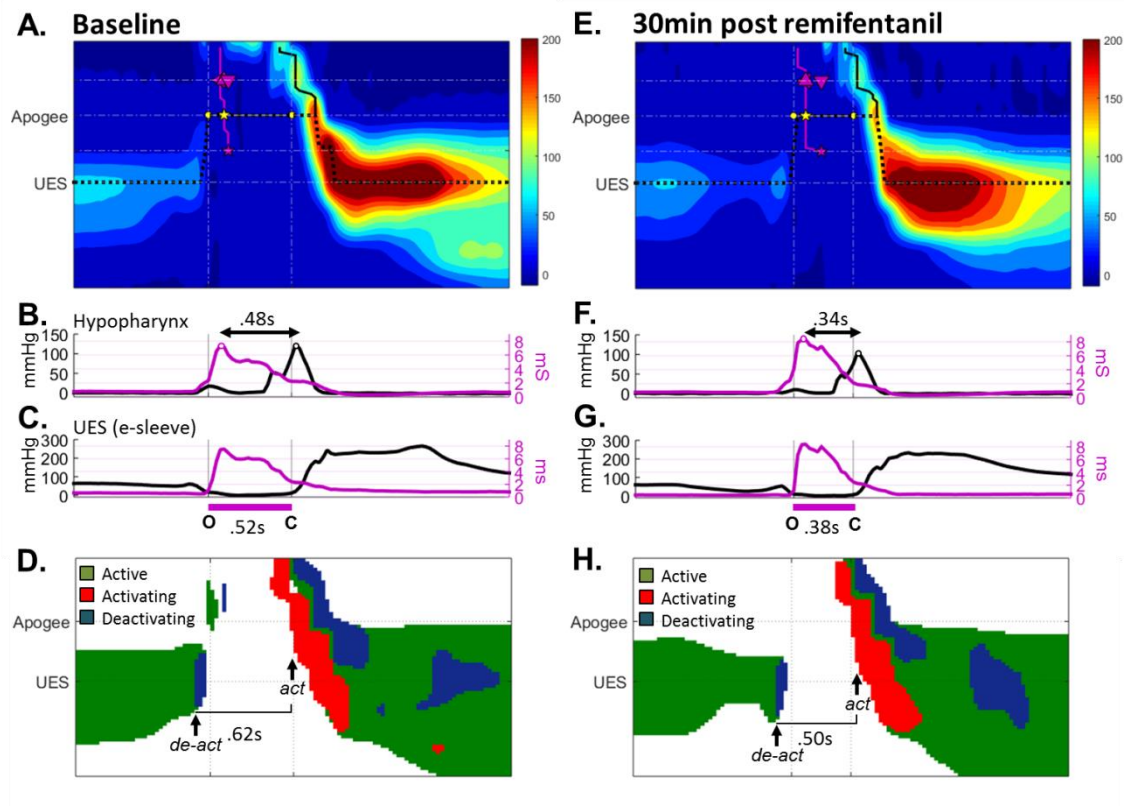

Figure 2. Effects of remifentanil on swallowing biomechanics based on example 10 ml swallows recorded in a subject before (A–D) and after (E–H) remifentanil exposure.
A, E: Pressure isocontour plots of the pharynx and UES region as per Figure 1. The black dotted line shows location of maximum axial UES pressure during the swallow and tracks the superior movement of the UES high pressure zone from its resting position to its apogee position and back to resting over the time-base.
Note that the maximum admittance line (purple) and peak pressure line (black) are closer together in E, indicating shorter distention-contraction latency;
B, F: Hypopharyngeal pressure (black line) and admittance (purple line) profiles recorded at 1cm proximal of the apogee position. Note that the hypopharyngeal admittance and pressure peaks are closer in time in F indicating a shorter distention-contraction latency.

C, G: UES pressure (black line) and admittance (purple line) profiles defined at maximum axial UES pressure (shown A and B). Note that the UES opening period defined by the admittance inflexion points is shorter in G;

D, H: UES mechanical states analysis defining when the muscle state is tonically active, activating (contracting) or de-activating (relaxing) due to neural inputs. Note that the *CP pause*, defined by the period from *de-act* (marking onset of inferred neural deactivation) to *act* (marking offset of inferred deactivation), is shorter in H. However, the sequence order of CP muscle activation (i.e., tonic activation–deactivation–re-activation–tonic activation–deactivation–tonic activation) remains unchanged by remifentanil.

Swallow Function Variables	Drug Effect (mean±SEM)			
	Baseline	*Remifentanil*	*t*	*p*
Timing (sec)				
CP Pause (muscle deactivation to re-activation)	0.62 ± 0.03	0.54 ± 0.04	2.509	**.033**
UES open period	0.52 ± 0.03	0.40 ± 0.02	6.246	**.000**
UES open to maximum hypo-pharyngeal distension	0.12 ± 0.01	0.09 ± 0.01	1.682	.127
Maximum hypo-pharyngeal distension to UES closure	0.38 ± 0.03	0.29 ± 0.02	4.363	**.002**
Maximum hypo-pharyngeal distension to contractile peak	0.40 ± 0.03	0.34 ± 0.02	3.807	**.004**
Hypo-pharyngeal bolus presence	0.49 ± 0.03	0.40 ±0.04	2.833	**.020**
Hypo-pharyngeal bolus presence prior to UES opening	0.04 ± 0.01	0.08 ± 0.03	1.453	.180
Distension Pressure (mmHg)				
Hypo-pharyngeal IBP1	3.6 ± 1.8	8.0 ± 1.6	-2.702	**.024**
Hypo-pharyngeal IBP2	4.0 ± 1.8	8.0 ± 1.7	-2.044	.071
Hypo-pharyngeal IBP3	2.9 ±2.0	7.3 ± 1.8	-2.542	**.032**
UES residual pressure	-1.8 ± 1.7	4.2 ± 1.8	-4.024	**.003**
UES 0.25sec integrated residual pressure	0.3 ± 1.8	6.3 ± 2.1	-3.664	**.005**
Cross-Sectional Area (maximum admittance, mS)				
Hypo-pharyngeal admittance	5.5 ± 0.2	5.4 ± 0.3	.146	.887
Admittance at UES apogee	5.7 ± 0.2	5.8 ± 0.2	-.712	.494
Admittance at 1cm below UES apogee	5.7 ± 0.2	5.8 ± 0.2	-.426	.680
Contractile Pressure (mmHg, intergral mmHg.cm.sec)				
Hypo-pharyngeal contractile peak pressure	147 ± 25	121 ± 12	1.102	.299
Pharyngeal contractile integral	54 ± 16	43 ± 7	.749	.473
UES pre-swallow basal pressure	103 ±11	104 ± 20	-.079	.938
UES post swallow contractile peak pressure	337 ± 37	278 ± 20	1.994	.077
UES post swallow contractile pressure integral	384 ± 25	384 ± 32	-.007	.994

Table 1. Effects of 30 min exposure of remifentanil on measures of swallowing function. Mean ± standard error (SEM) of all swallows from all participants are presented at each time point. The t statistic and p-value of the pairwise comparison are also shown.

Discussion

In young healthy subjects, exposure to remifentanil caused a delay in the timing of the onset of UES relaxation and opening during the swallow sequence that reduced the duration of flow during UES relaxation and opening. Pharyngeal contractile forces driving propulsion of the bolus through the open UES, as well as extrinsic contractile forces responsible for UES distraction and the extent of UES opening, appeared to be least affected by remifentanil exposure. Finally, hypopharyngeal distension pressures increased in circumstances where propulsive forces and UES aperture were unaffected, an observation mechanically consistent with increased flow resistance due to more rapid bolus flow rate in conjunction with a shorter flow permissive time. These biomechanical changes are analogous to differences previously observed between larger and smaller bolus volumes (5, 13) We propose that together, these findings suggest that remifentanil exposure experimentally induces a specific sensory deficit and that the resulting biomechanical changes are congruent with modification of the neuroregulatory mechanisms governing the accommodation to bolus volume; specifically, during exposure to remifentanil, a motor response appropriate for a smaller bolus is generated even in the presence of a much larger bolus.

There is biomechanical as well as neurophysiological evidence to support this hypothesis. Biomechanically, it is likely that the shortened UES opening duration was the main driver underlying the increased UES residual pressures, shortened time latency from maximum bolus distension to peak contraction and increased maximum bolus distension pressures. These knock-on effects are in line with biomechanical patterns that could be expected to occur when a larger bolus is swallowed using a swallowing pattern designed for a smaller bolus volume. Specifically, in the unimpaired system, swallowing larger bolus volumes leads to earlier and larger increases in UES diameter compared to when smaller bolus volumes are swallowed (5, 13). This accommodation of UES compliance is physiologically driven by

vagal afferent feedback regarding bolus volume, which enables pharyngo-esophageal segment compliance to be modified so that it accommodates a faster rate of bolus flow while maintaining low flow resistance. In line with this, using mechanical states analysis, we recently demonstrated that larger bolus volumes were accompanied by greater UES admittance (i.e., greater bolus distension area), and longer and faster UES opening, while pharyngeal and UES contractile patterns were less affected by bolus volume (23). In contrast, remifentanil exposure in the present study significantly shortened UES opening duration compared to control swallows, a finding consistent with shorter neural inhibition of the CP segment. This was evidenced in particular by the shortened CP pause duration, indicating a shorter period of neural CP deactivation on remifentanil. This resulted in impaired bolus flow across the sphincter region, consequently increasing UES residual pressures, shortening the latency between maximum bolus distension to peak contraction and increasing hypopharyngeal intrabolus distension pressures. Reduced sensory feedback during remifentanil exposure, misinterpreted as the presence of a smaller bolus, would likely induce this effect. The exact neurophysiological mechanisms underlying remifentanil-induced modulation of sensory feedback during swallowing are not yet known; however, as a μ–opioid receptor agonist, remifentanil would likely have modified swallowing-related activity in vagal afferent pathways as well as neural circuits in the NTS as μ–opioid receptors are abundant in both of these circuits (4, 8, 34). The scope of the current study did not allow to determine whether remifentanil exerts its effects on swallowing function via modification of μ–opioid receptors peripherally, centrally, or both. However, previous literature supports the notion that either site of modification may have contributed to the biomechanical effects reported here.

Action on peripheral vagal afferents

The region of the UES is primarily composed of the inferior pharyngeal constrictor and the CP muscle and is innervated by vagal afferents, in particular via the pharyngeal plexus proximally and the recurrent laryngeal nerve distally (18) and both vagal afferent pathways contain a significant number of μ–opioid receptors (4). In the context of cough it has been demonstrated that exposure to the μ–opioid receptor agonist H-Tyr-D-Arg-Gly-Phe-(4-NO_2)-Pro-NH_2 (BW443C) results in effective inhibition of an experimentally induced cough reflex in guinea pigs (3) and anaesthetised cats (1). Likewise, BW443C reduced capsaicin-evoked discharges in pulmonary and bronchial vagal C-fibre receptors in anaesthetised cats (2). The antitussive effects of morphine and codeine, themselves μ–opioid receptor agonists, can be countered by the peripherally-acting opioid antagonist N-methyl nalorphine (3) and levallorphan, which, like BW443C, have limited ability to cross into the central nervous system (CNS) (14). Taken together, these animal studies provide some evidence that μ–opioid receptor agonists have the ability to interfere with sensory vagal afferents at a peripheral level. Given the importance of peripheral vagal feedback during swallowing, it is possible that, through activation of μ–opioid receptors, remifentanil reduced the peripheral afferent input conveying information about bolus properties directly to the NTS. The NTS is the main sensory hub related to swallowing in the brainstem and a critical part of the swallowing central pattern generator (CPG) (11). Interestingly, the NTS also houses a significant number of μ–opioid receptors (8, 34). It is therefore also possible that the effects of remifentanil on swallowing originate, at least in part, at a central level.

Action at a central level

The NTS is located in the dorsomedial medulla and forms an integral part of the dorsal swallowing group (DSG), a network of premotor neurons thought to generate the sequential firing pattern required for the rhythmic oropharyngeal and esophageal muscle contractions required during swallowing (12). The NTS is the main sensory hub for vagal afferent input from the oropharynx, and almost all oropharyngeal NTS neurons receive input from vagal afferents (12). Animal experiments have shown that stimulation of SLN afferents evokes a short latency response in both oropharyngeal and proximal esophageal DSG neurons, providing evidence that vagal sensory afferents monosynaptically innervate this part of the swallowing CPG (15, 25). Importantly in the context of the present findings, several previous studies have reported that sensory feedback is a powerful modulator of neuronal activation in the swallowing CPG (10, 6) that can adjust motor outputs depending on the bolus swallowed (6). Given the high level of μ–opioid receptors in the NTS, it is therefore likely that any centrally acting μ–opioid receptor agonist can modulate the activity of the swallowing CPG, in particular of the DSG located in the NTS. In vitro studies of the rat NTS support this notion. For example, the μ–opioid receptor agonist D-Ala^2, N-MePhe^4, Gly-ol^5-enkephalin (DAMGO) is able to block excitatory glutamate-mediated postsynaptic potentials and in a subgroup of cells also blocked cellular activity via presynaptic mechanisms (26). In addition, studies in rats demonstrated that opioid agonists reduce activity of Ca^{2+} channels in sensory neurons (30) including the nodose ganglia (19), which contribute significant vagal afferent input to the NTS. Inhibition of Ca^{2+} currents in the terminals of presynaptic neurons would result in decreased neurotransmitter release, a common strategy associated with opioid receptors throughout the CNS (19). In the present study, modification of the NTS-driven swallowing motor sequence by altered vagal afferent input on remifentanil was reflected in the shorter period of UES deactivation. It is worth noting that modulation of sensory afferent

feedback by remifentanil as outlined here is not specific to this drug, but may equally apply to other μ–opioid agonists.

Interestingly, remifentanil has previously been demonstrated to induce muscle rigidity, a common side effect of anilidopiperidine-opioids, in particular remifentanil (33, 31). Therefore, it may alternatively be possible that the biomechanical symptoms observed in this study, in particular the shortened UES opening duration, are due to remifentanil-induced rigidity of the UES musculature. Our mechanical states data argue against this possibility, as neither the rate nor the overall extent of UES opening were affected by remifentanil (Figure 2C, 2G). If rigidity was a major contributor to the findings reported here, then either (or both) measures would be expected to be reduced due to decreased UES compliance. In addition, muscle rigidity may occur when remifentanil is delivered as a high dose bolus (33), but it is unlikely that this occurred over the 30 minute period of target controlled infusion of remifentanil in this study. We acknowledge the limitation of not having included a placebo control group in this study or not having tested different bolus volumes. The latter in particular may have provided further support for the hypothesis that modulation of sensory feedback occurred if there had been a shift to the right of the volume opening curve. However, we draw attention to the striking effects observed during exposure to remifentanil, which were not observed during baseline swallows in this study. Similarly, a previous study of the effects of remifentanil on swallowing did not demonstrate any changes in swallowing function in the placebo control condition (28).

Taken together, there is compelling evidence to suggest that exposure to remifentanil reduced the sensory input of the swallowed 10 ml bolus, either via peripheral or central inhibitory mechanisms, or both, which was misinterpreted by the DSG as the presence of a much smaller bolus. Accordingly, the resulting swallowing motor plan, primarily characterised by a

shortened UES deactivation and opening period compared to the 10 ml control swallows, was unable to accommodate the larger swallowed bolus. The knock-on effects of increased UES residual pressure, increased intrabolus distension pressure and shortened latency between maximum bolus distension and the peak contraction support this notion as they are all indicative of a larger bolus travelling more rapidly through a UES lumen that is open for a shorter period. The effects reported here contribute to the previous literature in this field documenting increased occurrence of aspiration (28) and pharyngeal swallowing impairment (27) during exposure to remifentanil, highlighting the clinical relevance of this area of research.

Additional information

Grants

This research was supported by the Research Fund of the Örebro County Council, Sweden (OLL-367441).

TIO is the recipient of a National Health & Medical Research Council Senior Research Fellowship (APP1079715).

Disclosures

TIO holds inventorship of Australian Patent 2011301768 which covers the analytical methods described.

All other authors have no conflicts of interest to disclose.

References

1. Adcock JJ, Richardson PJ, Schneider C, Smith TW. Peripheral mechanism of antitussive activity of Tyr.o.Arg.Gly.Phe(4NOz).Pro.NH~(443C). Clin Respir Physiol 23: 297S. 1987a. Abstract.

2. Adcock JJ, Smith TW. Inhibitory effects of the opioid peptide BW443C on smaller diameter sensory nerve activity in the vagus. Br J Pharmaco1 96: 596P. 1987b. Abstract.

3. Adcock JJ, Schneider C, Smith TW. Effects of codeine, morphine and a novel opioid pentapeptide BW443C on cough, nociception and ventilation in the unanaesthetised guinea-pig. Br J Pharmacol 93: 93-100, 1988.

4. Adcock JJ. Peripheral opioid receptors and the cough reflex. Respir Med 85 (Supplement A): 43-46, 1991.

5. Cook IJ, Dodd WJ, Dantas RO, Massey B Kern MK, Lang IM, Brasseur JG, Hogan WJ. Opening mechanisms of the human upper esophageal sphincter. Am JPhysiol – Gastrointest Liver Physiol 257(5): G748-G759, 1989.

6. Falempin M, Madhloum A, Rousseau JP. Effects of vagal deafferentation on oesophageal motility and transit in the sheep. J Physiol 372: 425-436, 1986.

7. Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Kahrilas PJ. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. Am J Physiol Gastrointest Liver Physiol 291: G525–G531, 2006.

8. Hassen AH, Feuerstein G, Faden AI. Receptors and opioid cardiovascular effects in the NTS of rat. Peptides 3: 1031-1037, 1982.

9. Imam H, Marrero F, Shay S. Impedance nadir values correlate with barium bolus amount. Dis Esophagus 25(7): 600-607, 2012.

10. Jean A. Control of the central swallowing program by inputs from the peripheral receptors. A review. J Auton Nerv Syst 10: 225-233, 1984.

11. Jean A. Brain stem control of swallowing: Neuronal network and cellular mechanisms. Physiol Rev 81: 929-969, 2001.

12. Jean A, Dallaporta M. Electrophysiological characterisation of the swallowing pattern generator in the brainstem. GI Motility Online; DOI: 10.1038/gimo9.html. 2006.

13. Kahrilas PJ, Dodds WJ, Dent J, Logemann JA, Shaker R. Upper esophageal sphincter function during deglutition. Gastroenterology 95(1): 52-62, 1988.

14. Karlsson JA, Lanner AS, Forsberg K, Fuller RW, Persson CGA. Inhibition of cough and bronchoconstriction in the guinea pig by opiates: Evidence for a peripheral action. Br J Pharmaco1 93: 233P, 1988. Abstract.

15. Kessler JP, Jean A. Identification of the medullary swallowing regions in the rat. Exp Brain Res 57: 256-263, 1985.

16. Kim HJ, Mittal RK, Patel N, Ledgerwood M, Bhargava V. Esophageal distension during bolus transport: can it be detected by intraluminal impedance recordings? Neurogastroenterol Motil 26(8):1122-30, 2014.

17. Lang IM. Upper oesophageal sphincter. GI Motility Online; DOI: 10.1038/gimo12. 2006.

18. Mu L, Sanders I. The innervation of the human upper oesophageal sphincter. Dysphagia 11: 234-238, 1996.

19. North RA. Opioid actions on membrane ion channels. In: Handbook of Experimental Pharmacology, edited by Herz A, Akil H, Simon, EJ, Springer, Berlin. 1993.

20. Omari TI, Dejaeger E, Van Beckevoort D, Goeleven A, Davidson GP, Dent J, Tack J, Rommel N. A method to objectively assess swallow function in adults with suspected aspiration. Gastroenterology 140: 1454-1463, 2011a.

21. Omari TI, Papathanasopoulos A, Dejaeger E, Wauters L, Scarpellini E, Vos R, Slootmaekers S, Seghers V, Cornelissen L, Goevelen A, Tack J, Rommel N. Reproducibility and agreement of pharyngeal automated impedance manometry with videofluoroscopy. Clin Gastroenterol Hepat 9: 862-867, 2011b.

22. Omari TI, Dejaeger E, Van Beckevoort D, Goeleven A, De Cock P, Hoffman I, Smet MH, Davidson GP, Tack J, Rommel N. A novel method for the non-radiological assessment of ineffective swallowing. Am J Gastroenterol 106: 1796-1802, 2011c.

23. Omari TI, Wiklendt L, Dinning P, Costa M, Rommel N, Cock C. Upper oesophageal sphincter mechanical states analysis: A novel methodology to describe UES relaxation and opening. Front Syst Neurosci 8, 241; DOI: 10.3389/fnsys.2014.00241. 2015.

24. Omari TI, Jones CA, Hammer MJ, Cock C, Dinning PG, Wiklendt L, Costa MC, McCulloch TM. Predicting the Activation States of the Muscles Governing Upper Esophageal Sphincter Relaxation and Opening. Am J Physiol Gastrointest Liver Physiol. doi: 10.1152/ajpgi.00388.2015. [Epub ahead of print] 2016.

25. Ootani S, Umezaki T, Shin T, Murata Y. Convergence of afferents from the SLN and GPN in cat medullary swallowing neurons. Brain Res Bull 37: 397-404, 1995.

26. Rhim H, Glaum SR, Miller R. Selective opioid agonists modulate afferent transmission in the rat nucleus tractus solitaries. J Pharmacol Exp Ther 264: 795-800, 1993.

27. Savilampi J, Omari T, Magnuson A, Ahlstrand R. Effects of Remifentanil and Morphine on pharyngeal swallowing: A double blind randomised cross-over study in healthy volunteers. Eur J Anaesthesiol. In print. 2016.

28. Savilampi J, Ahlstrand R, Magnuson A, Geijer H, Wattwil M. Aspiration induced by remifentanil: A double-blind, randomized, crossover study in healthy volunteers. Anesthesiology 121: 52–58, 2014.

29. Savilampi J, Ahlstrand R, Magnuson A, Wattwil M. Effects of remifentanil on the esophagogastric junction and swallowing. Acta Anaesthesiol Scand 57: 1002–1009, 2013.

30. Schroeder JE, Fischbach P, Zheng D, McCleskey EW. Activation of z-opioid receptors inhibits transient high- and low-threshold Ca^{2+} currents, but spares a sustained current. Neuron 6: 13–20, 1991.

31. Schuettler J, Albrecht S, Breivik H, Osnes S, Prys-Roberts C, Holder K, Chauvin M, Viby-Mogensen J, Mogensen T, Gustafson I, Lof L, Noronha D, Kirkham AJT. A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. Anaesthesia, 52: 307–317, 1997.

32. Weijenborg PW, Kessing BF, Smout JPM, Bredenoord AJ. Normal values for solid-state esophageal high-resolution manometry in a European population; an overview of

all current metrics. Neurogastroenterol Motil 26, 654–659, 2014. doi:10.1111/nmo.12314.

33. Wilhelm W, Kreuer S. The place for short-acting opioids: Special emphasis on remifentanil. Crit Care 11: S5, 2008.

34. Xia Y, Haddad GG. Ontogeny and distribution of opioid receptors in the rat brainstem. Brain Res 549: 181–193, 1991.