Effects of Remifentanil on Esophageal and Esophagogastric Junction (EGJ) Bolus Transit in Healthy Volunteers Using Novel Pressure Flow Analysis

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Running Head: Esophageal effects of Mu-opioid Agonism

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ABBREVIATIONS:

LES  lower esophageal sphincter
MOR  Mu-opioid receptor
EGJ  esophagogastric junction
IRP4 4 second integrated relaxation pressure
DCI  distal contractile integral
DCL  distention contraction latency
Abstract

Background:

Remifentanil is associated with subjective dysphagia and an objective increase in aspiration risk.

Studies of opioid effects have shown decreased lower esophageal sphincter relaxation. We assessed bolus transit through the esophagus and esophagogastric junction (EGJ) during remifentanil administration using objective pressure flow analysis.

Methods:

Data from eleven healthy young participants (23±3 yrs., 7M) were assessed for bolus flow through the esophagus and EGJ using high-resolution impedance manometry (Manoscan™, Sierra Scientific Instruments, Inc., LES Angeles, CA) with 36 pressure and 18 impedance segments. Data was analyzed for esophageal pressure topography and pressure flow analysis using custom Matlab analyses (Mathworks, Natick, US). Paired t-tests were performed with a P-value of < 0.05 regarded as significant.

Key Results:

Duration of bolus flow through (remifentanil/R 3.0±0.3 vs baseline/B 5.0±0.4 sec; P < 0.001) and presence at the EGJ (R 5.1±0.5 vs. B 7.1±0.5 sec; P = 0.001) both decreased during remifentanil administration. Distal latency (R 5.2±0.4 vs B 7.5±0.2 sec; P < 0.001) and distal esophageal distention-contraction latency (R 3.5±0.1 vs. B 4.7±0.2 sec; P < 0.001) were both reduced. Intrabolus pressures were increased in both the proximal (R 5.3±0.9 vs. B 2.6±1.3mmHg; P = 0.01) and distal esophagus (R 8.6±1.7 vs B 3.1±0.8mmHg; P = 0.001). There was no evidence of increased esophageal bolus residue.

Conclusions & Inferences:
Remifentanil-induced effects which were different for proximal and distal esophagus, with a reduced time for trans-sphincteric bolus flow at the EGJ, suggestive of central and peripheral μ-opioid agonism. There were no functional consequences in healthy subjects.
Keywords:

- Dysphagia
- Esophagus
- Motility
- Opioids
Key points:

- Mu-opioid receptor agonism induces the symptom dysphagia, as well as changes in esophageal motility and lower esophageal sphincter relaxation. We assessed the functional effects of such changes.

- MOR agonism has differential effects in the proximal and distal esophagus, however trans-sphincteric bolus flow is maintained through increased intrabolus pressure.

- Remifentanil leads to reduced proximal skeletal muscle contractility and a loss of inhibition in the distal (smooth muscle) esophagus, with resulting shortened distal latency, increased contractile vigor and numerically increased IRP.
Introduction

Remifentanil is an ultra-short acting mu opioid receptor (MOR) agonist, used during anaesthesia for its centrally depressing and anti-nociceptive effects. Many individuals, including healthy volunteers, complain of dysphagia during administration of remifentanil\(^1,2\). Recent descriptions of the effects of remifentanil and other MOR agonists on swallowing function have revealed attenuated oropharyngeal\(^3,4\) and laryngeal\(^5\) (sensory function, increased pulmonary aspiration\(^5\), decreased distal esophageal latency\(^6,7\) and decreased esophagogastric junction (EGJ) relaxation\(^6-11\). Esophageal pressure topography (EPT) revealed a shortened distal latency and increased distal intrabolus pressure during remifentanil administration\(^7\). The integrated relaxation pressure in 4 seconds (IRP4), a measure of EGJ relaxation, increased but remained well within physiological limits. Patients on chronic opioids frequently have evidence of EGJ obstruction and likely related distal esophageal hypercontractility\(^6\). The mechanisms of the observed esophageal changes and the origin of the sensation of dysphagia are incompletely understood.

The use of computer-based analyses of high-resolution impedance manometry recordings enables us to relate pressure-flow phenomena to their functional consequences, including the completeness of impedance-based bolus passage and bolus-based esophageal distention and related pressures\(^12\). Separate evaluation can be undertaken of the proximal and distal esophagus, as well as the EGJ with the intention to relate pressure-flow phenomena to physiology, pathophysiology, and symptoms\(^12,13\). Esophageal pressure flow analysis has not been performed during administration of remifentanil and offers the opportunity to enhance our understanding of changes in esophageal physiology induced by opioids.

Bolus-flow phenomena are important in determining successful bolus passage through the hollow organs of the gastrointestinal tract such as the tubular esophagus. This is of particular interest as the human esophagus consists of proximal striated and distal smooth muscle, with potentially different effects in relation to such physiological events as bolus-based distention. Our group has previously
described the concept of the ‘neuromechanical loop’ in which bolus distention causes oral contraction and aboral relaxation of circular muscle with the subsequent movement of content then generating the new mechanical stimulus that activates intramuscular tension receptors reinitiating the sequence\textsuperscript{14,15}. Page and colleagues described attenuated responses in mucosal and tension receptors following MOR agonism in the ferret esophagus, meaning a greater stimulus is needed to invoke the same neuro-mechanical response\textsuperscript{16}. It can thus be hypothesised that the increased intrabolus pressure observed during remifentanil exposure represents retained bolus due to decreased EGJ relaxation\textsuperscript{7}. In this study we sought to further characterise the effect of MOR on esophageal segment physiology using state of the art methods. We therefore conducted novel pressure-impedance analyses on manometric recordings from healthy volunteers before and during remifentanil administration. The aim of this study was to determine how mechanisms of compartmentalised bolus transport and esophageal emptying are affected by exposure to remifentanil.
Methods and Materials

Subjects

Data from eleven healthy young participants (mean age 23±3 yrs, 7 male), collected at the Department of Anaesthesiology, University Hospital in Örebro, Sweden, were analysed. All participants were previously enrolled in a double-blind, randomized, placebo-controlled; cross-over study of opioid drugs on pharyngeal swallowing and all gave informed consent. The protocol of this study was reviewed and approved by the Central Ethics Review Board in Uppsala, Sweden. None of the participants smoked, reported any current or past symptoms of dysphagia or upper gastrointestinal diseases, or took any medications that could affect pharyngeal or esophageal function. Exclusion criteria for this study included potential pregnancy, current breastfeeding, or previous participation in a medical study.

Intervention

Intravenous target controlled infusion was used to administer remifentanil with an effect-site concentration of 3 ng/ml (Minto Model, Alaris PK syringe pump, Alaris Medical Nordic AB, Sollentuna, Sweden). The infusion pump uses a 3-compartment model described by Minto\textsuperscript{17,18} (variates are lean body mass and age) to calculate dose administration. The system delivers a brief, rapid infusion to reach the targeted effect size concentration without overshoot, followed by a series of decreasing infusion rates to maintain the targeted concentration.

High-Resolution Impedance Manometry

Manometry and impedance data were recorded using a 4.2mm diameter catheter housing 36 circumferential pressure sensors that were spaced 1 cm apart and 18 x 2 cm long impedance segments (Manoscan™, Sierra Scientific Instruments, Inc., LES Angeles, CA). Catheter calibration was performed in accordance with manufacturer specifications, before the catheter was placed transnasally so that sensors straddled the entire esophagus and esophagogastric junction (EGJ).
Participants rested for a period of 5 minutes to accommodate to the catheter in situ. Participants then ingested ten 10ml saline boluses on command, once every 20 seconds before and 15 min and 30 min following commencement of remifentanil administration. In the present study, we compare data recorded at baseline to those recorded at 30 min following the commencement of remifentanil infusion as the steady state plasma concentration is rapidly achieved by target controlled infusion systems and we previously demonstrated that the pharmacodynamic effects at 15 min and 30 min did not differ.

**EGJ Metrics**

Bolus flow through the EGJ was determined as described by Lin et al.19. In brief, the method consists of creating a virtual e-sleeve at the EGJ to simultaneously measure pressure and impedance data in a custom Matlab program (Mathworks, Natick, MA). The pressure and impedance data were used to determine the direction of flow and a flow gradient, by using the proximal pressure sensor and a referenced gastric pressure. Lin et al.19 determined criteria for bolus flow (bolus presence in the EGJ and flow permissive pressures) through comparison of measured data with radiologically determined EGJ bolus flow. Bolus flow was determined to be halted when the crural diaphragm pressures were above that of the pressure just proximal to the level of the sphincter within the zone of the bolus presence time. Bolus presence above the LES is expressed here as bolus presence time (BPT). Distention impedance and pressure were determined for the EGJ in the same way as that for the esophagus described below. The EGJ nadir pressure was also measured as a discreet value.

**Pressure Flow Analysis**

Swallows were analysed using purpose designed software (based in MATLAB version 8.5.0.197613 - R2015a; The MathWorks Inc, Natick, US), which automatically interpolated (Piecewise Cubic Hermite Interpolating Polynomial) the pressure and impedance data to increase the dataset to a 1mm spatial resolution.
Five space-time landmarks were determined on the plot as follows (see also Figure 1):

1. Swallow onset determined by the onset of upper esophageal sphincter (UOS) relaxation.
2. The temporal position of the peak esophageal pressure at the oral margin of the proximal esophagus.
3. Position of mid-point of the transition zone between striated and smooth muscle esophagus, defined as the lowest pressure between proximal and distal esophageal pressure sequences or the distal margin of the proximal esophageal contraction in the case of large peristaltic breaks.
4. The proximal margin of the LES high-pressure zone post-swallow.
5. The distal margin position of the LES high-pressure zone, defined by lowest position of the distal edge of the high-pressure zone pre and/or post swallow.

These landmarks guided the calculation of values for a range of esophageal and EGJ variables.

**Esophageal Pressure Flow Variables**

Swallow function variables during PFA were determined for the whole esophagus and esophagus proximal to, but excluding the transition zone (proximal esophagus) and esophagus from the (transition zone to the proximal margin of the LES high-pressure zone (distal esophagus). As it has been determined that nadir impedance correlates with maximal luminal cross-sectional area as measured radiologically\(^{20,21}\) or via ultrasound\(^{22}\), the following PFA variables were derived: (i) Distention impedance, determined as the mean nadir impedance for the respective esophageal segment. (ii) Distention pressure, an intrabolus pressure variable, measured at the point of maximal luminal distention and averaged for the esophageal segment. (iii) Peak pressure, the mean value of maximum contractile pressures along the length of the esophageal segment. (iv) The time between peak distention (nadir impedance) and peak pressure, termed the distention contraction latency (DCL). (v) The mean distention contraction latency, as the time between nadir impedance and peak pressure DCL, determined per esophageal segment. (vi) The total length of breaks in the 20mmHg
isocontour, measured as 20mm isocontour defects (ICD). (vii) Impedance ratio, determined for the complete distal esophagus as the mean value of the ratio of nadir impedance to the impedance at peak pressure. A higher ratio implies relatively more bolus retention as the drop in impedance is determined by the presence of bolus.

**Esophageal Pressure Topography**

Esophageal Pressure Topography was determined as by Chicago Classification Criteria²³. Swallow onset was defined as the onset of relaxation in the upper esophageal sphincter (UOS) high-pressure zone. The integrated relaxation pressure in 4 seconds (IRP4) was determined as the lowest contiguous or non-contiguous pressure in the lower esophageal sphincter (LES) high-pressure zone in the ten seconds following swallow onset. IRP4 is referenced to intragastric pressure. Contraction deceleration point (CDP) was determined as the inflection in peristaltic velocity within the distal esophagus 2-3 cm from the EGJ. This inflexion is indicative of the formation of the phrenic ampulla associated with distal esophageal bolus clearance. The time from swallow onset to the CDP was termed the distal latency (DL), measured in seconds. Peristaltic velocity was determined by drawing a line parallel to the 30mmHg isocontour starting at the CDP and extending proximally.

**Statistical analysis**

Bonferroni-adjusted paired t-tests were used to compare outcome variables measured before and during exposure to remifentanil. These are presented here as mean ± standard error (t-statistic) with a p-value <0.05 indicating statistical significance.
Results

The total cumulative dose of remifentanil administered in our volunteers ranged from 346 to 487 µg. Two of the subjects reported a subjective sensation of dysphagia during the infusion, while some other subjects reported nausea. Most of the subjects described feeling sedated. All the side-effects rapidly disappeared on stopping the infusion.

An overview of esophageal pressure topography and impedance of five consecutive swallows at baseline and at 30 minutes during remifentanil infusion are depicted as Figure 2.

The main effects are demonstrated in Figures 3-5 with mean values shown in Tables 1 and 2.

Bolus flow through the EGJ

Effects on bolus flow as measured through bolus flow time and bolus presence time are pictured in Figures 3, 4 and Table 1. Both BFT and BPT were markedly reduced during administration of Remifentanil (Table 1).

Pressure Flow Analysis

Effects of Remifentanil on pressure flow analysis are shown in Table 1. Peristalsis remained intact and of an equivalent vigor in the distal esophagus. There were reduced peak pressures in the proximal (striated) esophagus. There was evidence of increased intrabolus distension pressures throughout the esophagus. Additionally, IBP slope increased significantly in the distal esophagus only from 1.1± 0.6 mmHg/s pre to 3.9±0.9mmHg/s during remifentanil exposure (P = 0.03). Esophageal luminal cross-sectional area, inferred by distension impedance, remained unchanged throughout the esophagus. Distention-contraction-latency time (DCL) was significantly shorter during remifentanil exposure in the distal esophagus only (Figure 5B&C).

Esophageal Pressure Topography
Effects of Remifentanil on EPT metrics are shown in Table 2. No subjects fulfilled Chicago classification diagnosis for motor abnormalities prior to commencing the remifentanil infusion.

The most marked effect of Remifentanil exposure was a reduced distal latency (Table 2; Figure 5A). In addition, there was a strong trend approaching significance for increased peristaltic velocity in the smooth muscle esophagus, likely associated with the shortening of distal latency. There were no statistically significant differences in peristaltic vigor as measured through DCI. EGJ relaxation pressures as measured by IRP4 were not significantly different during remifentanil exposure overall, even though the IRP4 was increased numerically in 6 of the subjects.
Discussion

In this study we evaluated the pharmacodynamic effects of the mu opioid receptor (MOR) agonist remifentanil on esophageal bolus transport and emptying mechanisms. Remifentanil induced a pattern of changes in esophageal function with the net effect of increasing bolus flow resistance during compartmentalised transport and esophageal emptying. The main effects of remifentanil were on esophageal body distension pressures and motility with some contrasting effects localised in the proximal and distal regions of the esophagus, which have differing underlying physiology. In the proximal striated muscle esophagus, remifentanil i) increased distension pressures and ii) weakened contractility. In the distal smooth muscle esophagus, remifentanil i) reduced swallow-contraction latency, ii) reduced distension-contraction latency and iii) increased distension pressures, but (iv) did not weaken contractility or impair bolus clearance. In the EGJ, remifentanil (i) did not significantly alter relaxation residual pressures, however (ii) EGJ bolus flow time was shorter in concert with (iii) a shorter period of bolus presence within the distal esophagus. Altogether, these findings suggest that remifentanil exposure primarily alters timing of smooth muscle peristalsis and duration of EGJ opening.

Remifentanil effects on proximal esophageal motility

The central nervous system, via brainstem based central pattern generators of swallowing, initiates and controls proximal striated muscle peristalsis via sequential activation of motor neurone pools within the nucleus ambiguus\textsuperscript{25}. Central sensory relay occurs in the nucleus tractus solitarius (NTS)\textsuperscript{26}, and motor outputs are modulated in response to sensory input for different bolus characteristics\textsuperscript{27,28}. In our study, remifentanil exposure reduced proximal esophageal contractility, suggesting either central effects leading to attenuated motor neurone activation or, alternatively, peripheral effects at the striated neuromuscular junction. Central modulation may occur at the level of the NTS as it has been shown to contain MOR\textsuperscript{29,30}. However, one might expect that besides reduced contractile vigour, modulation of central pattern generator activity in the NTS would also
result in altered contractile sequence, which was not the case in our study. Similarly, Storr and colleagues\textsuperscript{31} demonstrated that exposure to the MOR endogenous ligands Endomorphin-1 and -2 induced a reduction in the contractile response of rat striated muscle esophagus to electrical field stimulation (EFS) \textit{in vitro}. In contrast to the effects on amplitude, the timing of the proximal contractile sequence was unaffected by remifentanil. This suggests that, like in the pharyngeal contraction sequence\textsuperscript{3,4}, the centrally determined neural \textit{timing sequence} governing velocity of propagation of proximal esophageal contraction remains unchanged by opioids and that the observed effects are more likely due to peripheral MOR effects.

\textit{Remifentanil effects on distal esophageal motility}

In contrast to the lack of effect on the proximal peristalsis pattern, remifentanil exposure markedly altered the timing of distal peristalsis below the transition zone. Specifically, remifentanil caused distal peristalsis to become more rapidly propagated, hence reaching the EGJ earlier (shorter latency), whilst at the same time the distal contractile amplitude was unchanged. As distal smooth peristalsis is controlled via activation of the enteric nervous system\textsuperscript{24,32,33}, we propose that our findings are consistent with peripheral MOR agonism causing an excitatory-inhibitory ‘imbalance’ due to a selective reduction of nitric oxide (NO) release by inhibitory neurons. Such effects would be in keeping with the clinical observation of an increased incidence of spastic motor disorders of the distal esophagus in chronic opioid users, reported by Ratuapli \textit{et al.}\textsuperscript{7}

Normally propagated primary peristalsis of the smooth muscle esophagus results from vagally mediated activation of nitricergic inhibitory neurons, followed by activation of cholinergic excitatory neurones. Along the esophageal body, the relative density of inhibitory innervation increases distally and so does the latency period from swallow to muscle contraction, producing the orderly and distally propagating peristaltic behaviour that is typically seen in healthy subjects\textsuperscript{24}. Via its effects on the CNS, remifentanil may in theory attenuate the vagal preganglionic nerve activation with the knock-on effect of altered post-ganglionic neurotransmitter release. However, as this effect would
impact equally on both inhibitory and excitatory pathways, the overall timing of the distal peristalsis would not be expected to change, but perhaps rather its overall contractile amplitude be attenuated. We therefore propose that the main effects of MOR agonism are most likely via peripheral mechanisms, in particular reduced peripheral NO release by antagonising NO-synthase production\textsuperscript{33}. Reduced peripheral NO release best explains our latency findings as they are akin to the effects of the NO synthase inhibitor nitro-L-arginine methyl ester hydrochloride (L-NAME) which induces a similar rapid peristaltic sequence pattern in healthy volunteers\textsuperscript{34}. An alternative peripheral mechanism may be remifentanil-induced disruption of sensory mechano-receptor mediated peripheral circuits that modulate peristalsis in relation to luminal stimuli, most notably bolus-based distension\textsuperscript{35}. Whilst impairment of sensory modulation of peristalsis may in part explain the elevated distension pressures seen, it would also attenuate both inhibitory and excitatory pathways and therefore seems an unlikely mechanism governing the imbalance suggested by shorter distention contraction latency. This is further supported by the observation that in the lower gut, opioids abolish, rather than modify, propagation of distension-induced peristalsis by completely interrupting neuroneuronal and neuroeffector transmission\textsuperscript{35,36}.

**Remifentanil effects on lower esophageal sphincter and EGJ**

Using manometry with circumferential or unidirectional pressure sensing, we can only assess the sum effect of MOR agonism on LES tone and relaxation, which is complete relaxation of a shorter duration. We lack the resolution to appreciate the radial asymmetry or assess striated and smooth muscle components separately. Importantly bolus transit through the LES is not affected by remifentanil (Fig 1 & 2), and the rapid propagation of the distal contraction continues to the LES and leads to increased intrabolus pressure above the LES. The bolus traverses the sphincter more rapidly due to the greater pressure differential between the distal esophagus and intragastric pressure. There are several potential explanations for the increased IRP4 seen in the majority of subjects in our study and previously observed during MOR agonist administration\textsuperscript{7}. Firstly, in our study sphincter relaxation is of a shorter duration than the four seconds included in calculating IRP.
Secondly increased intrabolus pressures will also increase IRP. Lastly, it is possible that remifentanil may have differential effects on striated and smooth muscle and/or the different smooth muscle components of the LES, or differential central and peripheral neural inhibition.

Nitric oxide is the main neural inhibitor involved in swallow-induced LES relaxation\(^{37-41}\). The LES is complex and consists of both external striated (diaphragmatic crus) and internal smooth muscle components. Furthermore, the smooth muscle consists of three different components with differing responses to neurotransmission from locally projecting myenteric fibers. Clasp and sling smooth muscle fibers react differently to neural excitation and inhibition\(^ {42,43}\), while the distal esophageal circular muscle forms a third separate smooth muscle component of the LES, similar in response to sling fibres\(^ {43}\). Both clasp and sling fibers relax in response to NO. However, this relaxation is much more pronounced in the clasp fibers\(^ {40,41}\), so that modulating effects of remifentanil attenuating NO release are likely to affect this component of the LES to a greater degree. Technology with the ability to assess LES pressure symmetry or striated and smooth muscle components separately may be able to elucidate the effects of remifentanil or other MOR agonists on the LES to a greater extent.

**Limitations**

We acknowledge that this study has some limitations. For example, the additional use of opioid receptor antagonism, such as naloxone, would have added to the findings in our study. Of note, previous studies have failed to demonstrate a reversal of the effects of remifentanil by either naloxone or methylnatrexone\(^ {1,7}\), however a supratherapeutic dose of naloxone may be needed to reverse the effects of remifentanil\(^ {44}\). When considering remifentanil as a model for mu-opioid agonism, we acknowledge that the pharmacokinetics of remifentanil is markedly different from that of longer acting mu-opioids and thus any inference that longer acting mu-opioid agonists will have similar effects are only an assumption. Furthermore, we did not study the pharmacodynamics of remifentanil in our study. Whilst we did not directly correlate impedance based bolus flow in the esophagus or at the EGJ with simultaneous radiology, we note previous studies\(^ {46}\) validating nadir impedance as a marker of bolus distension and the bolus flow time to quantify the period of
esophageal emptying\textsuperscript{19,47}. Swallowing maneuvers, including multiple rapid swallows, were not performed, but would have had utility in determining the level at which (whether centrally or peripherally) swallowing inhibition, leading to a shortened distal latency, originates\textsuperscript{13}. Finally, we did not assess bolus volume effects or compare different bolus viscosities which may reveal altered sensory modulation of swallow features.

\textit{Conclusion}

In summary, we reported on remifentanil induced changes in the proximal and distal esophagus, as well as at the EGJ. Proximally, there was a reduction in esophageal contractility and increased intrabolus pressures, a known correlate of bolus perception\textsuperscript{13}. Distal changes in distention pressure and latency were in keeping with a reduction of descending deglutitive inhibition and, at the EGJ, there was a reduced duration of trans-sphincteric bolus flow. Overall, although the changes in esophageal motility during liquid swallows did not generate symptoms of dysphagia, these observed changes may become more relevant when swallowing boluses of solid consistencies, when undertaking provocative challenges such as multiple rapid swallows, and/or if evaluated in individuals with minor esophageal motor disorders. This study has important implications for the interpretation of upper gastrointestinal symptoms, particularly considering a recent trend towards large numbers of opioid prescriptions\textsuperscript{47}. 
ACKNOWLEDGMENTS

Author Contributions

CC contributed to study concept and design, analysed data, wrote the manuscript and is the guarantor of the article. TO contributed to study concept and design, analysed data and wrote the manuscript; SD contributed to data interpretation and critical revision of manuscript; JS performed the research, data analysis and critically revised the manuscript. All authors approved the final version of the manuscript.

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Conflicts of interest: TO is the recipient of an Australian National Health and Medical Research Council Senior Research Fellowship (APP1079715). TO also holds an Australian Patent (2011301768) in relation to the analytical methods described. This patent is not commercialised. TO has no other conflicts of interest to disclose. CC and SD have no conflicts of interest to declare.
REFERENCES


TABLE 1. Pressure flow analysis of esophagogastric junction (EGJ) and Esophageal Metrics prior to (Baseline) and 30 minutes during administration of Remifentanil (at 30 minutes).

<table>
<thead>
<tr>
<th>AIMplot Derived Metrics</th>
<th>Baseline</th>
<th>Remifentanil</th>
<th>t-statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20mmHg ICD cm Impedance Ratio</td>
<td>2.6 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>-0.033</td>
<td>0.974</td>
</tr>
<tr>
<td><strong>Proximal Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distension Impedance Ohms</td>
<td>237 ± 17</td>
<td>248 ± 12</td>
<td>-0.941</td>
<td>0.371</td>
</tr>
<tr>
<td>Distension Pressure mmHg</td>
<td>2.6 ± 1.3</td>
<td>5.3 ± 0.9</td>
<td>-3.234</td>
<td>0.010</td>
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<tr>
<td>Peak Pressure mmHg</td>
<td>65 ± 4</td>
<td>45 ± 6</td>
<td>3.803</td>
<td>0.004</td>
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<tr>
<td>Distension-Contraction Latency sec</td>
<td>2.2 ± 0.2</td>
<td>2.1 ± 0.1</td>
<td>1.459</td>
<td>0.179</td>
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<tr>
<td><strong>Distal Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distension Impedance Ohms</td>
<td>197 ± 13</td>
<td>196 ± 11</td>
<td>0.040</td>
<td>0.969</td>
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<td>Distension Pressure mmHg</td>
<td>3.1 ± 0.8</td>
<td>8.6 ± 1.7</td>
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<td>Peak Pressure mmHg</td>
<td>59 ± 8</td>
<td>69 ± 11</td>
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<td>Distension-Contraction Latency sec</td>
<td>4.7 ± 0.2</td>
<td>3.5 ± 0.1</td>
<td>6.196</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>EGJ</strong></td>
<td></td>
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<tr>
<td>Nadir Pressure mmHg</td>
<td>2.4 ± 0.9</td>
<td>2.2 ± 0.8</td>
<td>0.168</td>
<td>0.871</td>
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<tr>
<td>Distension Impedance Ohms</td>
<td>157 ± 12</td>
<td>136 ± 19</td>
<td>1.920</td>
<td>0.087</td>
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<tr>
<td>Distension Pressure mmHg</td>
<td>-0.1 ± 1.5</td>
<td>2.5 ± 1.8</td>
<td>-0.551</td>
<td>0.155</td>
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<tr>
<td>Bolus Presence Time sec</td>
<td>7.5 ± 0.5</td>
<td>5.1 ± 0.5</td>
<td>4.771</td>
<td>0.001</td>
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<tr>
<td>Bolus Flow Time sec</td>
<td>5.0 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>0.694</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ICD = isobaric contour defect, cm = centimetre, mmHg = millimetre of mercury, sec = seconds.

TABLE 2. Esophageal Pressure Topography Metrics prior to (Baseline) and 30 minutes during administration of Remifentanil (Remifentanil).

<table>
<thead>
<tr>
<th>Manoscan OPT Metrics</th>
<th>Baseline</th>
<th>Remifentanil</th>
<th>t-statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractile Front Velocity mmHg/sec</td>
<td>3.8 ± 0.4</td>
<td>5.2 ± 0.4</td>
<td>-2.238</td>
<td>0.060</td>
</tr>
<tr>
<td>Distal Latency sec</td>
<td>7.5 ± 0.2</td>
<td>5.2 ± 0.4</td>
<td>9.013</td>
<td>0.001</td>
</tr>
<tr>
<td>Distal Contractile Integral mmHg.s.cm</td>
<td>1104 ± 248</td>
<td>1533 ± 480</td>
<td>-0.979</td>
<td>0.356</td>
</tr>
<tr>
<td>Integrated Relaxation Pressure mmHg</td>
<td>11.6 ± 2.4</td>
<td>10.7 ± 2.7</td>
<td>0.237</td>
<td>0.822</td>
</tr>
</tbody>
</table>

mmHg/sec = millimetre of mercury per second, sec = seconds, mmHg.s.cm = millimetre of mercury per second per centimetre, mmHg = millimetre mercury.
FIGURE LEGENDS

FIGURE 1. Esophageal pressure topography (A), esophageal contour plot (B) and peak distention and contraction used during pressure flow analysis (C). Five user defined landmarks are used for analysis, namely (1) swallow onset, (2) orad onset of peak pressure wave – both time and space, (3) midpoint of transition zone, (4) proximal margin of the EGJ high-pressure zone and (5) distal margin of the EGJ high-pressure zone. Inter contour defect (ICD) and distention contraction latencies (DCL) are pictured. During pressure flow analysis mean values are determined for the proximal (P) and distal (D) esophagus. Flow through the EGJ is analysed separately.

FIGURE 2. Example esophageal body pressure and impedance topography plots for consecutive swallows in a healthy subject prior to (A) and during (B) remifentanil administration.

FIGURE 3. Distal latency (A) and distention contraction latency for the proximal (B) and distal (C) esophagus during remifentanil.

FIGURE 4. EGJ bolus flow in healthy volunteers following remifentanil. Reduced bolus presence and flow times are observed during remifentanil using the methodology described by Lin et al.17.

FIGURE 5. Overlay of esophageal body topography and distention timing. From these data it is apparent that timing and velocity remains constant in the proximal esophagus with reduced distention contraction latency and increased velocity in the distal esophagus during remifentanil.