Perioperative complications in obese patients.
A thesis on risk reducing strategies.
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Abstract


Aspiration of gastric content and delayed or failed intubation are the leading causes of anesthesia-related mortality and morbidity. In the recovery period, airway obstruction with subsequent hypoxia is a relatively common cause of morbidity, and is highly associated to the amount of opioids administered, especially in obese patients.

The overall aim of this thesis was to study these risk factors for airway complications and postoperative hypoxia in obese patients, and to evaluate possible strategies for their prevention.

In Study I, intubation times and incidence of failed intubation in obese patients were compared between direct laryngoscopy and videolaryngoscopy with the Stortz® C-MAC™. In Studies II and III, the effect of esmolol vs. remifentanil on the esophageal junction, and the possible analgesic properties of low-dose esmolol vs. placebo were evaluated using high-resolution manometry and the cold pressor test, respectively. Finally, in Study IV, the possible opioid-sparing effect of esmolol after laparoscopic gastric bypass surgery was evaluated.

The use of videolaryngoscopy did not shorten intubation times, however appeared to reduce the incidence of failed intubation. Our results also show that esmolol has a favorable profile, compared to remifentanil, with regard to the protection against passive regurgitation and aspiration of gastric content. No analgesic effect of low-dose esmolol was however demonstrated. The intraoperative administration of esmolol instead of remifentanil also did not reduce the requirement of morphine for treatment of post-operative pain.

The use of Stortz® C-MAC™ may be recommended for intubation of obese patients. Further studies are however required to clarify the possible role of esmolol in anesthesia.

Keywords: Intubation time, videolaryngoscopy, obesity, esophagogastric junction, remifentanil, esmolol, high-resolution manometry, pulmonary aspiration, postoperative pain, postoperative opioid-sparing.

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ABBREVIATIONS

AIC: Akaike Information Criterion
AUC: Area under the curve
BIS: Bispectral index
BPM: Beats per minute
CD: Crural diaphragm
CPT: Cold pressor test
DL: Direct laryngoscopy
ECG: Electrocardiography
EGJ: Esophagogastric junction
EPT: Esophageal pressure topography
HRM: High resolution manometry
IBW: Ideal body weight
IDS: Intubation Difficulty Scale
IQR: Inter quartile range
LBW: Lean body weight
LES: Lower esophageal sphincter
LMM: Linear mixed model
MAC: Minimal alveolar concentration
MAP: Mean arterial pressure
MRI: Magnetic resonance imaging
NAP4: Fourth National Audit Project
NO: Nitric oxide
NRS: Numeric rating scale
NSAID: Non-steroidal anti-inflammatory drug
OIH: Opioid-induced hyperalgesia
OSAS: Obstructive sleep apnea syndrome
PEEP: Positive end-expiratory pressure
PONV: Post operative nausea and vomiting
TBW: Total body weight
TCI: Target-controlled infusion
TTI: Time to intubation
VIP: Vasoactive intestinal peptide
VL: Videolaryngoscopy
LIST OF ORIGINAL STUDIES

This thesis is based on the following papers, which will be referred to in the text by their roman numerals.


II. Effects of esmolol on the esophagogastric junction: a double-blind, randomized, crossover study on 14 healthy volunteers.

III. Does the beta-receptor antagonist esmolol have analgesic effect? A randomized, placebo-controlled crossover study on healthy volunteers undergoing the cold pressor test.

IV. The effect of intraoperative esmolol infusion compared to remifentanil on opiate requirement after laparoscopic gastric bypass surgery: a randomized pilot study.
Ander F, Magnuson A, Ahlstrand R, de Leon A Manuscript

Study I is reprinted with permission from Minerva Anesthesiologica.
Study II and III are reprinted with permission from Wolters Kluwer.
INTRODUCTION

Background
Since the Eighties, the prevalence of overweight and obese people has steadily increased, and continues to do so. Today, approximately two in ten people are obese, whereas more than half of the subjects in western countries are overweight or obese (1). This places high demands on anesthesiologists since obesity is a major risk factor for anesthesia-related complications and death (2).

The National Audit Project was established to estimate the incidence of major airway management complications in hospitals in the UK, and to perform qualitative analyses. The total number of events related to general anesthesia, reported in the audit, was 133 whereas the approximate number of anesthetics given during the same period was 2.9 million giving a minimum rate of 133/2.9 million, i.e. approximately 1/22 000 general anesthetics (2).

In the Fourth National Audit Project (NAP4), aspiration of gastric content was the primary event in 23 cases, and the most common cause of death. It also complicated several other primary events, such as difficult intubation (2). Other authors report the incidence of pulmonary aspiration, defined as the inhalation of oropharyngeal or gastric content into the lower airway (3), to be a much more common event (3-6/10 000 general anesthetics) (4-6). Even though obvious major regurgitation of gastric content in the perioperative period is a relatively uncommon event (5, 6), lesser degrees of passive regurgitation can occur at any time during the perioperative period and may cause silent aspiration and subsequent postoperative complications (2, 5, 7).

Apart from pulmonary aspiration, delayed and failed intubation was identified as the second most common primary airway problem during anesthesia (2). In the recovery period, airway obstruction, proportionally, was a relatively common cause of morbidity (2), a complication that in obese patients is highly associated with the amount of opioids administered in the postoperative period (8).

In the NAP4, 42% of the patients suffering from anesthesia-related complications were obese (BMI of > 30 kg/m2) (2), a rate that is almost double the prevalence of obesity in the general population (1), making obesity a clear risk factor for perioperative airway complications.
Perioperative challenges in the obese patient

Anesthetic management of the obese patient is a challenge. Patients with obesity, especially if they suffer from obstructive sleep apnea syndrome (OSAS), may be difficult to ventilate with a mask (9-11), due to anatomic abnormalities caused by fat deposition in the pharyngeal region (12). In addition, several studies have shown obesity to be an independent risk factor for difficult intubation (13-15), though this is somewhat controversial (16). Characteristics associated with obesity, such as large neck circumference, may be prognostic for difficult tracheal intubation (17, 18). Furthermore, large neck circumference is also a risk factor for the combination difficult mask ventilation and difficult laryngoscopy (11).

Not only may airway management in obese patients be challenging and time-consuming, during extended periods of apnea in conjunction with difficult tracheal intubation, oxygen desaturation develops rapidly in the obese patient (19, 20). This is due to the reduced functional residual capacity and increased oxygen consumption in obese patients (21). A swift and safe strategy for airway management in obese patients is thus especially important.

As identified in the NAP4, difficult and prolonged intubation is a risk factor for pulmonary aspiration (2), and preservation of lower esophageal sphincter tone is important if one is to avoid passive regurgitation (4). In this context, our research group has previously shown that obese patients exhibit lower esophagogastric junction (EGJ) pressures compared to lean patients (22), possibly making obese patients prone to passive regurgitation.

The final aspect of this thesis concerns the negative postoperative effects of opioids, which may reduce the tone in the upper airway, induce airway obstruction (23), and aggravate OSAS (24). Furthermore, morphine together with its metabolite morphine-6-glucuronide depresses ventilation and ventilatory responses to hypoxemia and hypercapnia (25). Consequently, hypoxemia after laparoscopic bariatric surgery, with or without OSAS (8), and nocturnal respiratory depression are directly related to the amount of opioids administered in the postoperative period (26). A multimodal strategy to minimize the postoperative use of opioids has been emphasized (27, 28).
The esophagogastric junction

The esophagogastric junction (EGJ) is the high-pressure zone of the distal esophagus, and is also the main barrier against reflux of gastric content into the esophagus. It comprises two superimposed sphincters; the intrinsic lower esophageal sphincter (LES) and the extrinsic crural diaphragm (CD) (29) (Figure 1).

Figure 1. Anatomy of the EGJ. Reproduced with permission from Mittal RK and Balaban DH. The esophagogastric junction. N Engl J Med 1997;336:924-932, Copyright Massachusetts Medical Society.

The LES, which consists of smooth muscle cells, is responsible for the tonic pressure of the EGJ (30), and its contraction creates the end-expiratory sphincter pressure in the resting state (31). The LES is under both myogenic and neural control. The main regulatory mechanism acting on the LES is, however, centrally mediated by parasympathetic cholinergic signaling via the Vagus nerve (Figure 2) (29, 32, 33).
The LES is also innervated by sympathetic splanchnic nerves (34). Furthermore, several neurotransmitters and hormones decrease the LES tone, including nitric oxide (NO), vasoactive intestinal peptide (VIP), beta-adrenergic agonists, dopamine and prostaglandin E, whereas muscarinic receptor agonists, substance P, and alpha-adrenergic agonists increase the tone (34).

The crural diaphragm consists of skeletal muscle fibers and is mainly innervated by the phrenic nerves. Its relaxation is also mediated by swallowing, distension of the esophagus, and transient LES relaxation (29).

EGJ pressure varies during the respiratory cycle and is lowest at the end of expiration (29). Theoretically this is the point in the respiratory cycle when the risk for regurgitation is at its highest (29). However, only the so-called “inspiratory EGJ augmentation”, which is the difference between

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Figure 2. EGJ innervation. Reproduced with permission from Mittal RK and Bala-ban DH. The esophagogastric junction. N Engl J Med 1997;336:924-932, Copyright Massachusetts Medical Society.
inspiratory and expiratory EGJ pressures, and is the enhancement of EGJ pressure caused by contraction of the crural diaphragm during inspiration, has independently been related to objectively confirmed gastroesophageal reflux disease (GERD) (endoscopy or pH-positive) (35). Preserved inspiratory EGJ augmentation is indicative of crural diaphragm integrity (35).

Several drugs used during anesthesia and analgesia, including propofol (22) and remifentanil (22, 36), reduce the barrier efficiency of the esophagogastric junction. Some beta-receptor agonists have been shown to decrease the tone in esophageal muscle strips (37), whereas some beta-receptor antagonists have been shown to induce contraction (38).

**Remifentanil**

Remifentanil is a selective μ-receptor agonist that provides intense analgesia with rapid onset and short duration (39). These unique pharmacokinetic properties make it ideal for anesthetic use, and it is therefore widely used for sedation in the anesthetic- and intensive care setting, and as an analgesic and sympatholytic agent during general anesthesia.

Concerns regarding possible adverse-effects, however, have been raised. Our own research group has demonstrated that healthy volunteers experience swallowing difficulty when exposed to remifentanil (36) and that remifentanil can induce pulmonary aspiration in healthy volunteers, probably due to the negative effect on pharyngeal motor function (40). Furthermore, we have shown that remifentanil induces relaxation of the lower esophageal sphincter and reduces barrier efficiency of the esophagogastric junction (22, 36), possibly increasing the risk for passive regurgitation if used during sedation and anesthesia.

Several studies have also demonstrated that high-dose remifentanil may cause opioid-induced hyperalgesia (41-45), as well as opioid tolerance (46, 47), which theoretically could increase postoperative morphine consumption.

**Esmolol**

Esmolol is a beta-1 adrenoreceptor antagonist with rapid onset and short duration (48-50). The elimination half-time is approximately 7-9 minutes (48, 50), which together with the short onset time makes the drug ideal for intraoperative use when rapid adjustment of sympathetic tone is required. Historically, the drug has mostly been used to control hypertension and
tachyarrhythmia (48, 51). It may also be used to attenuate the sympathetic response to laryngoscopy and tracheal intubation (52-54).

New and interesting areas of use have been found (55). The addition of esmolol to an anesthetic regimen may reduce the intraoperative requirement of volatile anesthetics (56-59) and opioids (60). Furthermore, it may also reduce the need for rescue treatment with analgesics postoperatively (58, 59, 61-63). There are even data suggesting that esmolol may possess an inherent analgesic effect (64-68), a property that could possibly broaden the use of esmolol in anesthesia.

The dose of esmolol used intraoperatively depends on the indication. When administered to attenuate the sympathetic stress reaction to tracheal intubation, various dosing strategies have been proposed (69-71). Figueredo et al. came to the conclusion that 500 μg · kg⁻¹ · min⁻¹ over 4 minutes, followed by a continuous dose of 200-300 μg · kg⁻¹ · min⁻¹ was the most appropriate dose (71). In order to reduce the requirements of intraoperative anesthetic agents, doses of 0.5 mg/kg followed by 30-50 μg · kg⁻¹ · min⁻¹ have been used (56, 58), whereas doses as little as 1 mg/kg followed by 5-15 μg · kg⁻¹ · min⁻¹ has been shown to have a significant postoperative opioid-sparing effect after laparoscopic cholecystectomy (61). Any advantage of intraoperative esmolol should be weighed against the risk of unintentional hypotension, a risk that may be reduced by using low-dose infusions, titrating the dose to a hemodynamic endpoint (72).
**Possible analgesic and opioid-sparing mechanisms of esmolol**

The following possible mechanisms of an anti-nociceptive effect of esmolol have been suggested:

1. Functional magnetic resonance imaging (MRI) has demonstrated that the hippocampus may play a role in nociception (73), possibly mediated via stress-related secretion of noradrenaline (74), a process that could potentially be attenuated by the antagonism of beta-receptors.

2. Tanahashi et al showed that esmolol blocks tetrodotoxin-resistant Na\(^+\) channels in rat spinal dorsal root ganglia possibly attenuating afferent signals in the spinal cord (75).

3. Yasui et al demonstrated that esmolol modulates neurotransmission in the trigeminal nucleus of the substantia gelatinosa in the spinal cord of rats, suggesting facilitation of the pain inhibitory system (76).

4. Noradrenaline increases heat-induced hyperalgesia in skin that has been sensitized by capsaicin (77), which suggests that beta-receptor antagonists could be used to modify peripheral inflammatory reactions.

Based on these assumptions, the postulated anti-nociceptive action of esmolol could thus be explained by modulation of pain signals at central, spinal and peripheral levels.

In addition to the postulated direct action on pain, it has also been suggested that the perioperative opioid-sparing effect of esmolol could be related to one, or more of the following secondary effects:

1. Synergy with coadministered drugs (56, 60, 62, 78, 79).

2. Altered elimination of coadministered opioids, due to a reduction in cardiac output and hepatic blood flow, leading to prolonged duration of action (80).

3. Prevention of opioid-induced hyperalgesia (OHI). Since the attenuation of sympathetic activation following beta-receptor blockade may reduce, or exclude intraoperative opioid requirements (61, 81), the development of OHI may be prevented (41, 43, 46, 82).
AIMS

The overall aim of this thesis was to study known risk factors for airway complications and postoperative hypoxia in obese patients, and to evaluate possible strategies for the prevention of these.

The specific aims were:

I To compare time-to-intubation (TTI) when obese patients are intubated using videolaryngoscopy (Storz® C-MAC™ with the standard Macintosh® blade) with that using direct laryngoscopy (Macintosh® blade).

To see if videolaryngoscopy (Storz® C-MAC™) reduces the incidence of failed intubation, compared to direct laryngoscopy (Macintosh® blade) for tracheal intubation in obese patients.

To compare videolaryngoscopy (Storz® C-MAC™) with direct laryngoscopy (Macintosh® blade) regarding the perceived difficulty in intubation.

To see if choice of intubation technique influences the occurrence of sore throat in the postoperative period.

II To evaluate and compare the effects of esmolol and remifentanil on EGJ-pressures when administered as single drugs in healthy volunteers, and to test the hypothesis that esmolol, in contrast to remifentanil, does not affect inspiratory EGJ augmentation.

III To see if low dose esmolol, in the absence of opioids or anesthetics, has an analgesic effect, when testing pain using the cold pressor test (CPT).

To evaluate the effect of esmolol in attenuating the sympathetic stress response during CPT, and to see if esmolol causes any of the side-effects (swallowing difficulty, nausea, respiratory depression and desaturation) associated with opioid treatment.
IV To compare total doses of morphine required for rescue treatment for postoperative pain when esmolol is administered instead of remifentanil during anesthesia for laparoscopic gastric bypass surgery.

To compare the incidence and severity of postoperative nausea and vomiting and need for antiemetic treatment, between patients receiving esmolol and those receiving remifentanil during laparoscopic gastric bypass surgery.
SUBJECTS AND METHODS

Approvals
All studies were approved by the Regional Ethics Committee in Uppsala, Sweden (Dnr 2012/015, 2014/372, 2012/070, 2014/373). Studies involving esmolol (II-IV) were also approved by the Medical Products Agency. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and registered in either of the central databases, ClinicalTrial.gov or European Clinical Trials Database (EudraCT).

If eligible, all patients and volunteers were given verbal and printed information on the details of the study in question, and signed consent was obtained before enrolment. A total of one hundred patients (thirty-one men, sixty-nine women) and twenty-eight healthy volunteers (nineteen men, nine women) were enrolled in the four studies.

Study I

Patients
In Study I, eighty adult patients with ASA status I-III and body mass index BMI >35 kg/m² were enrolled. Exclusion criteria were: age < 18 years; previous difficult intubation; anticipated difficult intubation not related to obesity (Mallampati IV, small interincisal opening, reduced neck movement and short thyreomental distance); and head and neck surgery.

Study protocol
Immediately prior to induction of anesthesia, patients were randomly assigned to one of two groups; direct laryngoscopy (DL) (n=40) or video-laryngoscopy (VL) (n=40).

Throughout anesthesia, standard monitoring (electrocardiography, pulse oximetry, non-invasive or invasive blood pressure measurement and neuromuscular transmission) was employed.

Patients were placed in the reverse Trendelenburg position with a small pillow under the head and shoulders. After a period of oxygenation (with 100% oxygen and 5cm H₂O PEEP) by facemask, anesthesia was induced using a bolus dose of propofol and a target-controlled infusion (TCI) (83) of remifentanil. Rocuronium was given for muscle relaxation, and manual mask ventilation using 100% oxygen was performed for two minutes.
Thereafter orotracheal intubation was performed using either the Stortz® C-MAC™ videolaryngoscope or a standard Macintosh® laryngoscope (HEINE, Herrsching, Germany and Karl Storz, Tuttingen, Germany) according to group allocation. Both devices were equipped with the classic Size 3, Macintosh blade (Figure 3). All intubations were performed by one of two anesthesiologists experienced in the use of both devices used in the study (> 50 intubations with each device). Following intubation, anesthesia and surgery were performed according to routine practice at our department.

Figure 3. The size 3 Macintosh® laryngoscope™ compared to the Stortz® C-MAC™.
Methods

Time-to-intubation
The primary outcome, time-to-intubation (s), was measured from the moment the anesthetist took the laryngoscope handle until end-tidal CO$_2$ was registered on the ventilator monitor.

Perceived difficulty in intubation
The secondary outcome, perceived difficulty in intubation (NRS), was graded on an eleven-point numeric rating scale (0-10) by the anesthetist directly after intubation.

Postoperative sore throat
The secondary outcome, postoperative sore throat, was evaluated using a verbal four-point scale (0 = no sore throat, 1 = mild sore throat (less severe than a cold), 2 = moderate sore throat (similar to a cold), and 3 = severe sore throat (84)) at 1, 24, 72, and 96 hours after surgery (if a sore throat was present at the previous evaluation).

The Stortz® C-MAC™ videolaryngoscope
Video-assisted laryngoscopy was introduced to help overcome some of the problems associated with the difficult airway (85) and has been shown to improve intubating conditions in morbidly obese patients (86, 87). The common feature of all video-assisted devices is the presence of a camera applied to the blade. Otherwise, the various types of videolaryngoscopes available today have their own specific characteristics.

The Stortz® C-MAC™ is equipped with a size 3 (or 4) Macintosh metal blade with a CMOS digital camera positioned at the distal third. The view from the camera includes the tip of the blade, allowing visual guidance of the tip into the vallecula (88). It can be used for both direct laryngoscopy and indirect videolaryngoscopy.

Compared to other video devices, the Stortz® C-MAC™, has been shown to reduce intubation time in difficult airway cases (89), including tracheal intubation of obese patients (90).
Study II

Volunteers
In Study II, fourteen healthy volunteers with body mass index < 30kg/m² and without symptoms of gastroesophageal reflux disease were enrolled and randomized to either of two intervention sequences (a. esmolol followed by remifentanil, and b. remifentanil followed by esmolol). Exclusion criteria were: gastroesophageal reflux disease; ongoing treatment with a benzodiazepine or cardiovascular medication; allergy to drugs used in the study; pregnancy and breastfeeding; abnormal electrocardiography (ECG); or participation in another medical trial.

Study protocol
Study sessions were preceded by a 6-hour fast and subjects were monitored with ECG, pulse oximetry and non-invasive blood pressure measurement.

Measurement of esophageal pressure was performed using a manometric catheter that was placed transnasally after topical application of local anesthetic (Lidocaine 100mg/ml, AstraZeneca, Södertälje, Sweden). Correct positioning was verified by visualization of pressure landmarks between the pharynx and the stomach. After a 5-minute stabilization period, baseline EGJ pressure registration was performed with the volunteer in the supine position.

Sequence a: Intervention began with the administration of an intravenous bolus of esmolol (1mg/kg) over 1 minute followed by an infusion of 10μg · kg⁻¹ · min⁻¹ over a 15-minute period. Following a twenty-minute wash-out period, an intravenous bolus dose of normal saline was administered over 1 minute to resemble the bolus dose of esmolol, after which a target-controlled intravenous infusion of remifentanil was started (Minto model programmed after ideal weight) (83), with a targeted effect-site concentration of 4ng/ml, and continued for 15 minutes. Sequence b: The order of interventions was reversed but otherwise administration was identical (Figure 4).
Recording of EGJ pressures was performed continuously throughout the study session but only analyzed at baseline (T0), after 2 minutes (T2), and after 15 minutes of infusion of esmolol or remifentanil (T15). Since different dosing strategies were chosen for esmolol and remifentanil, primary comparisons were performed between esmolol at T2 and remifentanil at T15. These points in time reflected the expected peak effect of esmolol (T2) (54), and the steady state levels of remifentanil and esmolol (T15) (50, 83).

Methods

High-resolution solid-state manometry

Esophageal motor function can be assessed using a variety of techniques. However, manometry is considered the gold standard, and provides direct evaluation of the contractile performance of the esophagus. There are two main esophageal manometry recording systems; solid-state and the water-perfused assemblies. Both systems have specific strengths and weaknesses.

In the water-perfused system, the intraluminal esophageal pressure is transmitted to external pressure transducers via catheter lumens perfused with sterile water (91). Since the pressure transducers are located outside the catheter, these assemblies can incorporate a large number of recording points, producing high-resolution recordings (92). In general, however, they are not suitable for ambulatory manometry.

In contrast, solid-state assemblies such as the one used in the second study of this thesis, have pressure transducers incorporated within the actual catheter, which enables the transmission of rapidly changing pressures.
pressures. Pressure transducers convert mechanical pressure information from sensors on the surface of the catheter to electrical signals that are processed and transferred for storage in a computer (93). The solid-state catheters are relatively easy to set up and use, and the closely spaced sensors enable continuous measurements from the pharynx to the stomach, regardless of catheter position relative to the moving anatomical structures. Apart from portability, however, solid-state catheters are fragile, less comfortable, and considerably more expensive than water-perfused assemblies (93).

In the second study of this thesis, manometric recordings were performed using the high-resolution manometric system ManoScan 360 A-100 (Sierra Scientific Instruments, Inc., Los Angeles, CA, USA). The system uses a 4.2mm solid-state manometric catheter that has 36 circumferential sensors spaced at 1-cm intervals.
Esophageal pressure topography
The data acquired by high-resolution manometry (HRM) is presented as esophageal pressure topography plots (Figure 5). The plot is a display method where pressure is encoded in color (high pressure orange and red, low pressure green and blue) (92). The esophageal pressure topography plot offers an intuitive and rapid interpretation of data, enables correct positioning of the manometric catheter, and since the presentation of data is performed in real time, problems can be solved as they appear during data acquisition (93, 94). The position of catheter sensors is displayed on the vertical axis and time on the horizontal axis (95).

Figure 5. Pressure topography plot of a high-resolution solid-state manometry recording. Distance from the nares is indicated on the vertical axis. Orange/red corresponds to high pressures, blue to low pressure. I = inspiration, E = expiration. UES = upper esophageal sphincter, EGJ = esophagogastric junction.
Analysis procedures
In Study II, the Manoview analysis software (Sierra Scientific Instruments) was used to analyze the effect of esmolol on esophageal pressure and to compare it with remifentanil. The analysis procedure began by identifying the distal high-pressure zone of the esophagus. The secondary outcomes were: inspiratory EGJ pressure, defined as the highest pressure during a normal respiratory cycle; and expiratory pressure defined as the EGJ pressure at the midpoint between two adjacent inspiratory pressures in a normal respiratory cycle (95). The mean of two values was derived when calculating inspiratory and expiratory EGJ pressures. The primary outcome, inspiratory EGJ augmentation, was defined as the difference between inspiratory and expiratory EGJ pressures (35). EGJ pressures were related to intragastric pressure such that the inspiratory and expiratory EGJ pressures reflected the actual barrier function of the EGJ.
Study III

Volunteers
In Study III, 14 healthy volunteers with body mass index < 30kg/m² were enrolled and randomized to one of three intervention sequences. Exclusion criteria were: ongoing treatment with cardiovascular medication, benzodiazepines or analgesics; allergy to drugs used in the trial; pregnancy and breastfeeding; or participation in another medical trial.

Study protocol
Each volunteer went through three study sessions at least three days apart. In Session A: Esmolol (Brevibloc©; Baxter Healthcare Ltd, Thetford, Great Britain) was administered as a bolus dose of 0.7mg/kg over 1 minute followed by an infusion of 10μg·kg⁻¹·min⁻¹ over 30 min. Session B: remifentanil (Remifentanil Teva®; TEVA Pharmaceuticals Works Private Limited Company, Gödöllö, Hungary) was administered as an infusion of 0.2μg·kg⁻¹·min⁻¹ over 30 min. The infusion of remifentanil was preceded by a bolus of saline over one minute to resemble the bolus administration of esmolol. Session C: Saline was administered as a one-minute bolus followed by a 30-minute infusion.

During each study session, continuous monitoring of vital signs was performed throughout the experiment and documented at five-minute intervals.

Experimental pain testing was performed using the cold pressor test (CPT) described in detail below (96, 97). The device used for the CPT consisted of a 10-litre plastic container filled with ice water with a target temperature of 0.0 to 1.0°C. During each CPT, the right hand was immersed in the ice water mixture to above the wrist. Pain intensity levels (NRS) and heart rate were measured immediately before, and at fifteen-second intervals during immersion. Non-invasive blood pressure measurements were performed as frequently as possible. Voluntary hand withdrawal was possible at any time during the test, and the test was terminated after 2 minutes if withdrawal had not already taken place.
Methods
The primary outcome, cold pain intensity was evaluated using NRS-max and was defined as the maximum NRS-score experienced during the CPT(98). Cold pain tolerance was defined as the time (s) from immersion to spontaneous withdrawal (99), or termination of the test, whichever was the case.

During each study session, a cold pressure test was performed prior to intervention, at the very end of the 30-minute intervention period, and 20 minutes after the termination of the intervention.

Apart from cold pain intensity and cold pain tolerance, hemodynamic changes (blood pressure, heart rate) during CPT, and the occurrence of side-effects defined as oxygen saturation $\leq 92\%$, respiratory rate $\leq 8$ /min, difficulty in swallowing, and nausea were also assessed.

The cold pressor test (CPT)
The cold pressor test was originally developed as a standardized procedure to induce a cardiovascular response in humans (100), and was later developed for analgesic evaluation of by Wolff et al. in 1969 (101). It is considered to be a suitable modality for experimental testing of somatic pain (102, 103). The method has become more and more popular in pain studies (97, 104, 105), and has been shown to provide good test reliability (106, 107) and retest stability (108). The autonomic response to the CPT is also well documented (96, 109).

During the procedure, one hand is immersed in cold water for 1-2 minutes. The outcome measured is one or several of the following: time to onset of pain, pain intensity, and pain tolerance (time to withdrawal) (110). Since tolerance and pain intensity vary with water temperature (107), a constant water temperature during a series of tests is most important.

Numeric rating scale (NRS)
During the CPT, the subject was asked to rate pain intensity every 15 seconds on an eleven-point scale, range 0-10, 0 = no pain, 10 = worst pain imaginable (111, 112).

Difficulty in swallowing.
Subjects were asked to perform dry swallowing and to assess any difficulty on a four-point scale (0 = no difficulty, 1 = mild difficulty, 2 = moderate difficulty, 3 = severe difficulty).
Study IV

Patients
In Study IV, a small pilot study comparing morphine consumption after laparoscopic gastric bypass surgery when esmolol respective remifentanil was administered intraoperatively, 20 patients with body mass index (BMI) > 35kg/m² were enrolled. Exclusion criteria were: chronic treatment with beta-receptor antagonists; calcium-antagonists, or opioids; allergy to drugs used in the trial; pregnancy and breastfeeding; electrocardiogram with conduction block; or participation in another medical trial.

Study protocol
As part of the preoperative preparation, patients received 1.3g paracetamol orally and were randomly allocated to either of the two study groups. On arrival at the operating theater, heart rate, blood pressure, oxygen saturation, and depth of anesthesia (BIS) monitoring was applied.

General anesthesia was induced using propofol, and muscle relaxation was achieved using rocuronium. Esmolol or remifentanil was administered depending on group allocation. Esmolol was administered as an intravenous bolus of 1mg/kg ideal weight (IBW) followed by an intravenous infusion with an initial dose of $10\mu g \cdot kg^{-1} \cdot min^{-1}$. Remifentanil was administered as a target controlled intravenous infusion (TCI) with a targeted effect-site concentration of 4ng/ml prior to tracheal intubation (83), being reduced to 2ng/ml after tracheal intubation. Anesthesia was maintained using sevoflurane titrated to keep the BIS value between 40 and 60. The esmolol infusion was titrated in increments of $5\mu g \cdot kg^{-1} \cdot min^{-1}$, and the remifentanil infusion by increments of 1ng/ml effect-site concentration to maintain the heart rate and blood pressure ± 25% of baseline values. Intraoperative bradycardia (heart rate < 40BPM) and hypotension (MAP < 60mmHg) were treated with predetermined doses of atropine (0.5mg) and phenylephrine (0.1mg) or ephedrine (5mg) respectively.

During surgery, the antiemetic and analgesic regimen was complemented with betamethasone (8mg) and parecoxib (40mg), and bupivacaine (5mg/ml, 20ml) was infiltrated prior to skin incision and insertion of the laparoscopic ports. Morphine (0.1mg/kg, max 10mg) and ondansetron (4mg) were administered towards the end of surgery.

All patients received full dose oral paracetamol as postoperative analgesia. Whenever rescue treatment for postoperative pain was needed, morphine was administered intravenously (2.5mg) according to a written
prescription. Intravenous ondansetron (4mg) was administered to treat persistent nausea (> 5min) or vomiting, and if insufficient, droperidol (1mg) was given. Follow-up was terminated 24 hours after surgery.

**Method**

The primary endpoint was defined as the total morphine consumption at 2 hours postoperatively, whereas the total morphine consumption at 24 hours was considered a secondary endpoint. The level of nausea (0 = no nausea, 1 = mild nausea, 2 = moderate nausea, and 3 = severe nausea) and the total number of antiemetic doses at 2 and 24 hours postoperatively were also considered secondary endpoints. Perioperative hemodynamic data, BIS-values, anesthetic agent requirement, and the need for atropine and vasopressors were analyzed in order to compare the intraoperative performance of the two infusions.
**Statistical Analyses**

In Study I the primary outcome was time-to-intubation (TTI). Mean difference(s) between the two study groups was analyzed using the unpaired Students T-test. Since the Shapiro-Wilk test indicated that the primary outcome did not follow a normal distribution, a non-parametric analysis (Mann-Whitney U-test) was also applied, and median intubation times were reported.

The cut off for failed intubation was set at 60s. Patients who were not intubated within 60s were regarded as TTI 60s in the statistical evaluation. Since some patients were not intubated within 60s the Kaplan-Meier method and log rank test were also used to describe and compare the primary TTI outcome. Correlation between TTI and sequence of inclusion in the videolaryngoscope group was performed to rule out any possible learning effect. This analysis was performed using the Spearman’s two-tailed correlation test.

The perceived difficulty in intubation also violated the normality assumption and was thus analyzed using the Mann-Whitney U-test.

Occurrence of sore throat was initially graded on a 4-point scale (0-3). However, since it was a relatively rare event, the results were analyzed as presence or not of sore throat. Fisher’s exact test was used for this analysis, as well as for the analysis of the rate of successful intubation.

In Study II, the effects of esmolol on EGJ metrics at time-points T2 and T15 were compared to remifentanil at T15 using a linear mixed model for repeated measurements. Period (1, 2); sequence (1: esmolol first/remifentanil second and 2: remifentanil first/esmolol second); and group (esmolol, remifentanil); with baseline EGJ (T0) as covariate were fixed factors in the LMM.

Compound symmetry was used as covariance structure, since it showed the best AIC (Akaike Information Criteria). Each manometric value represents a mean of two measurements.

In order to evaluate any possible carry-over effect of either intervention, the mixed model analyses were repeated after stratification according to intervention sequence. The Shapiro-Wilk test was used to verify the normality assumption for the residuals of the mixed model.

In Study III, the primary outcome (pain intensity score) was evaluated using a linear mixed model for repeated measurements. In this set of data, the unstructured covariance structure was applied. Intervention (esmo-
lol/remifentanil/placebo), time of CPT (before, during, and after drug administration), sequence of intervention, and the interaction-variable intervention*time, were fixed factors in the mixed model. Analysis of hemodynamic data was performed in a similar manner, except that this was adjusted for baseline values. In both cases, the Shapiro-Wilk test was used to verify the normality assumption of the residuals from the mixed model.

Correlation between NRS-max and NRS-AUC was measured using Pearson’s correlation coefficient (r). The Kaplan-Meier method was used to visualize cold pain tolerance, and the log rank test was used to compare times to hand withdrawal.

Fisher’s exact test was used to analyze categorical data (side-effects). Initially, we aimed to evaluate the degree of swallowing difficulty and nausea, each on a 4-point scale. However, since few volunteers suffered from these side-effects, only the occurrence or not of swallowing difficulty or nausea, regardless of severity, are reported.

As in Studies II and III, total morphine consumption at 2 and 24 hours after surgery in Study IV, were also evaluated with a linear mixed model for repeated measurements. In these sets of data the unstructured covariance structure, was applied. Intervention (esmolol/remifentanil), time, and the interaction-variable intervention*time, were fixed factors in the mixed model.

The Shapiro-Wilk test was used to verify the normality assumption of the residuals from the mixed model. Since the residuals were not entirely normally distributed due to some outliers (one in each group), the outcome was also transformed logarithmically (log + 1) and analyzed again with a linear mixed model, as above. The mixed model was also repeated with duration of surgery as one of the fixed factors, since this variable differed between the two groups and was considered a possible confounder. The three sets of analyses led to the same conclusion.

A similar linear mixed model was also used to analyze perioperative monitoring data (BIS, end-tidal sevoflurane concentration, minimal alveolar concentration (MAC), heart rate, and systolic- and diastolic blood pressure), though using the autoregressive covariance structure. Like the primary outcome, the residuals of the monitoring data were analyzed using the Shapiro-Wilk test. Some of the residuals did not follow the assumption of normality, also due to outliers. The mixed model was therefore supplemented with a non-parametric test (Mann-Whitney U-test) when appropriate. Only data up to 90 minutes after induction of
anesthesia were analyzed. Data from the esmolol-group after 90 minutes were sparse due to the shorter duration of surgery in this group.

Secondary outcomes (incidence of PONV and number of doses of antiemetic) and intraoperative variables (drug dosage, duration of anesthesia and surgery) were analyzed using the Chi² test for trend, Fisher’s exact test or Mann-Whitney U test when applicable.

In all studies, a p-value < 0.05 was considered statistically significant. In case of multiple comparisons, p-values were corrected using the Bonferroni-Holm method (113). Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, USA) and STATA release 14 (College Station, TX: StataCorp LP) when applicable.
RESULTS

Study I
In Study I we examined whether or not the use of videolaryngoscopy (Storz® C-MAC™) decreases the time to intubation compared to direct laryngoscopy (Macintosh®). We were unable to demonstrate any such effect. Mean intubation time (TTI) was 25.0s (SD 8.3) in the videolaryngoscopy (VL) group and 26.7s (SD 14.7) in the direct laryngoscopy (DL) group, whereas the median intubation time (TTI) was 23.2s (25th to 75th interquartile range; 20.8 to 26.5s) and 22.0s (25th to 75th interquartile range; 18.6 to 25.3s) respectively.

Time-to-intubation using the Kaplan-Meier method is presented in Figure 6. No significant difference between groups was observed, \( p = 0.89 \) (log rank test). The correlation between the TTI (VL group) and the sequence of enrolment revealed no learning effect.

Even though no difference in time-to-intubation was seen, orotracheal intubation was successfully performed within 60s in all patients in the VL group, whereas 5 patients in the DL group were not intubated during this period of time. All 5 patients were eventually intubated using direct laryngoscopy with a different sized blade (n = 1) or by using the Storz® C-MAC™ (n = 4). The proportion of successful intubations within 60s was 39/39 in the VL group and 34/39 in the DL group (\( p = 0.055 \)). Despite there being no failed intubations in the VL group, no difference in perceived difficulty in intubation was seen.

Figure 6. Time-to-intubation. Statistical analysis was performed using the log-rank test. Patients not intubated at time 60s were regarded as 60s in the statistical evaluation.
The incidence of sore throat in the present study was low. No patient in either group reported any degree of sore throat at follow-up twenty-four hours after extubation.

**Study II**

In Study II we compared the effect of esmolol as a bolus dose (1mg/kg) and followed by low-dose infusion (10μg · kg⁻¹ · min⁻¹) with the effect of remifentanil (4ng/ml) on inspiratory EGJ augmentation, inspiratory EGJ pressure, and expiratory EGJ pressure. Data are presented in Table 1, and visualized in Figure 7.

When comparison between esmolol 1mg/kg (T2) and remifentanil 4ng/ml (TCI) (T15) was made, no statistically significant difference between interventions on inspiratory EGJ augmentation was seen. Compared to esmolol, however, remifentanil influenced both inspiratory and expiratory EGJ pressures negatively (Table 1, Figure 7). Similar results were seen when the effect of low dose esmolol (10μg · kg⁻¹ · min⁻¹) (T15) was compared with remifentanil 4ng/ml (T15) (Figure 7).
Table 1. Comparison between effects of remifentanil at T15 and esmolol at T2 on EGJ metrics evaluated with linear mixed model for all subjects (n=14). Outcomes are compared between remifentanil at T15 and esmolol at T2. Adjustments are made for period (1, 2), sequence (1, 2), and group (esmolol/remifentanil) as fixed factors, and the EGJ baseline measurement (T0) as a covariate in the linear mixed model. Measures of effect are expressed as mean difference (95% CI). All values denote pressure (mmHg). *P-values are corrected for multiple testing using the Bonferroni-Holm method when applicable.
Figure 7. Box plots showing pressure in the esophagogastric junction (EGJ) in 14 volunteers. A = inspiratory EGJ augmentation, B = inspiratory EGJ pressure, C = expiratory EGJ pressure. T0 = baseline, T2 and T15 = 2 and 15 minutes after bolus administration of esmolol/saline (during infusion of esmolol/remifentanil). Each box plot is defined by median (line within the box), quartiles (box range), and min-max (whiskers) if no outliers are present. Outliers are indicated by a circle if more than 1.5 box-lengths from the box and an asterisks (*) if more than 3 box-lengths from the box.
Study III

In Study III we examined the possible analgesic effect of esmolol, administered as a single drug in a bolus dose of 0.7mg/kg followed by a continuous infusion of 10μg·kg⁻¹·min⁻¹, by comparison with saline using the cold pressor test. Any possible effect on pain was evaluated by maximal pain intensity using NRS-max and the NRS-area under the curve (NRS-AUC), and by cold pain tolerance using time to withdrawal. We also examined the effect of remifentanil on pain score and pain tolerance compared to saline.

We found that esmolol did not affect the maximal pain intensity score compared to saline (Table 2), whereas remifentanil caused a significant reduction in the pain intensity score (Table 2). Mean pain intensity scores (NRS-max and NRS-AUC) were similar in the CTPs performed after interventions, as in the CPTs performed before (Table 2) suggesting stable pain test properties and the absence of conditioning by the previous test and the development of hyperalgesia.

The cold pain tolerance results during interventions are visualized in the Kaplan-Meier figure, showing the cumulative proportion of hand withdrawals due to pain during the CPT (Figure 8). No difference between esmolol and saline regarding pain tolerance was seen, p = 1.0. During remifentanil infusion, on the other hand, all subjects tolerated the 120-second test.

Compared to saline, remifentanil caused significantly more episodes of respiratory depression (episodes of desaturation and low respiratory rate) than did esmolol. Otherwise, no significant differences in side-effects and hemodynamic changes were seen.
### Table 2. NRS-max and NRS-AUC during the cold pressor tests before, during, and after interventions.

During each study session, cold pressor tests were performed before, during, and after interventions. NRS-max and NRS-AUC denote maximal values registered during the cold pressor tests, and are expressed as mean (SD). Effects of esmolol and remifentanil (NRS-max, NRS-AUC) during cold pressor tests are compared with placebo and adjusted for sequence of intervention using linear mixed model, see statistics section for details. Measures of effect are expressed as mean difference (95% CI). P-values are corrected for multiple testing using the Bonferroni-Holm method.

<table>
<thead>
<tr>
<th></th>
<th>Placebo n = 14</th>
<th>Esmolol n = 14</th>
<th>Remifentanil n = 14</th>
<th>Esmolol vs. Placebo p-value</th>
<th>Remifentanil vs. Placebo p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS-max</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>8.6 (1.3)</td>
<td>8.6 (0.6)</td>
<td>8.2 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During</td>
<td>8.4 (1.3)</td>
<td>8.5 (1.4)</td>
<td>5.4 (2.1)</td>
<td>0.83</td>
<td>-3.1 (-4.4 to -1.8) &lt; 0.001</td>
</tr>
<tr>
<td>After</td>
<td>8.6 (1.3)</td>
<td>8.5 (1.2)</td>
<td>8.4 (1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS-AUC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>864 (165)</td>
<td>871 (117)</td>
<td>818 (163)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During</td>
<td>824 (196)</td>
<td>824 (187)</td>
<td>494 (200)</td>
<td>-0.5 (-1.6 to 0.6)</td>
<td>1.0 -340 (-501 to -179) &lt; 0.001</td>
</tr>
<tr>
<td>After</td>
<td>833 (166)</td>
<td>843 (163)</td>
<td>813 (184)</td>
<td></td>
<td></td>
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</tbody>
</table>
Figure 8. Cold pain tolerance (s) during the 120s cold pressor test. The Kaplan-Meier figure shows the cumulative proportion of hand withdrawal, due to pain. The log rank test was used to compare time to withdrawal for the primary and secondary hypothesis (esmolol and remifentanil vs. placebo). P-values are corrected for multiple testing using the Bonferroni-Holm method.
Study IV

In Study IV we examined if the intraoperative administration of esmolol instead of remifentanil reduces total morphine consumption at 2 and 24 hours postoperatively. Contrary to our hypothesis, no such effect was seen. Instead, morphine consumption was slightly less in the remifentanil group at both 2 and 24 hours, though this was not statistically significant (Table 3).

We also examined the incidence and severity of PONV, and the consumption of antiemetic agents due to PONV to see if these are reduced by the intraoperative administration of esmolol instead of remifentanil. No difference between groups with regards to PONV and the requirement of antiemetics was seen.

Data from intraoperative monitoring of vital signs and consumption of anesthetic agents, vasopressors and atropine were analyzed in order to compare the intraoperative effects of the interventions. Analyses showed that the requirement of propofol for induction of anesthesia was significantly higher in the esmolol group compared to the remifentanil group. Likewise, the end-tidal sevoflurane concentration required for adequate maintenance of anesthesia was significantly higher in the esmolol group during the initial period of anesthesia (Figure 9).

Heart rate, though in the normal range, was significantly higher in the esmolol group during the initial period of anesthesia (Figure 9). No difference in blood pressure between groups was seen. Despite apparent hemodynamic stability, four of 10 patients in the esmolol group, compared to one in the remifentanil group, required intraoperative treatment with atropine for bradycardia (not statistically significant due to small sample size) (Table 4).

The duration of surgery was significantly longer in the remifentanil group even though patients were randomly assigned (Table 4).
Table 3. 2- and 24-hour total postoperative morphine consumption. Data expressed as mean (SD). Measures of effect are expressed as mean difference (95% CI), and are compared using the linear mixed model. A p-value < 0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th></th>
<th>Esmolol n = 10</th>
<th>Remifentanil n = 10</th>
<th>Esmolol vs Remifentanil</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>8.0 (4.8)</td>
<td>6.0 (6.5)</td>
<td>2.0 (-3.4 to 7.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>24 hours</td>
<td>10.1 (5.9)</td>
<td>6.8 (8.5)</td>
<td>3.3 (-3.6 to 10.2)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Table 4. Perioperative data. Duration of anesthesia, duration of surgery, and intraoperative drug administration. Continuous data are expressed as median and inter-quartile range (IQR). The doses of ephedrine, phenylephrine and atropine are expressed as number of patients receiving 0/1/2 or ≥3 doses. Comparisons between groups were performed using Mann Whitney U-test, Chi² test for trend and Fisher’s exact test when applicable. A p-value < 0.05 was considered statistically significant.
Figure 9. Monitoring data. Panel a. BIS-level b. End-tidal sevoflurane concentration (%) c. Minimal alveolar concentration (MAC) d. Heart rate (BPM) e. Systolic blood pressure (mmHg), f. Diastolic blood pressure (mmHg). Data presented as mean (SD). Comparisons between interventions were performed using a linear mixed model for repeated measurements. * denotes p < 0.05 after adjustment for multiple testing using the Bonferroni-Holm method. The time axis corresponds to the chronological time from induction of anesthesia. Several procedures in the esmolol group took less than 90 minutes. Therefore, only data up to 90 minutes are presented. Few measurements of MAC and sevoflurane concentration were available at 0 and 5 minutes after induction of anesthesia.
DISCUSSION

The overall aim of this thesis was to study known risk factors for airway complications and postoperative hypoxia in obese patients, and to evaluate possible strategies for the prevention of these.

Intubation time and “failed intubation”

The use of the Storz® C-MAC™ improves visualization of the larynx during tracheal intubation of obese patients (87). When comparing the Storz device with direct laryngoscopy (Macintosh) in obese patients, two experienced anesthesiologists were unable to reduce the intubation time when the C-MAC™-device was used for tracheal intubation. However, intubation was equally rapid with the Storz® C-MAC™, even though this is not our first instrument of choice in everyday practice.

There are several reasons why the Storz® C-MAC™ was chosen for this study. First of all, the Storz® C-MAC™ is the videolaryngoscope we use at our department for the management of difficult intubation, and we are thus experienced in using the devise. Another reason was that even though the Storz® C-MAC™ is widely used, considerably fewer studies report on its performance than that of other devices.

Maassen et al compared three videolaryngoscopes (GlideScope®, McGrath®, and Storz® V-MAC™) and found that the V-MAC™, a predecessor to the C-MAC® equipped with the Macintosh® blade, performed better than the other two in terms of intubation time, number of intubation attempts, and user satisfaction (90). Intubation time in the videolaryngoscopy group in our study was somewhat longer than that reported by Maassen et al (90). The slight difference in intubation times between the two studies can be explained by different definitions of outcome; the capnography transit delay time was included in the TTI in our study, whereas this was not included in the Maassen study. Both Maassen et al and Andersen et al, who compared the Glidescope® with Macintosh® direct laryngoscopy, reported significantly longer intubation times with the Glidescope® (90, 114).

When it comes to predicting the risk for difficult intubation in obese patients, there are conflicting opinions (13-16, 115). Some authors advocate the use of neck circumference as a predictive factor (17, 18, 116, 117), whereas others recommend a combination of various anatomical characteristics (14, 116, 118, 119). In Study I of this thesis, patients with a large neck circumference were not excluded from enrolment. However, we did
exclude patients with high Mallampati grade, narrow mouth opening, short thyreomental distance and reduced neck movement: all factors associated with difficult intubation, especially in the obese surgical populations (13, 18). Despite these exclusions, the incidence of “failed intubation” in the direct laryngoscopy group was fairly high (120). Direct comparison between studies, however, is difficult since the characteristics of patients and the definition of failed intubation vary. In the present study, the definition of failed intubation was based on the time-to-intubation, with a cut-off at sixty seconds. The actual time to successful intubation for four of the five patients in the DL group that were not intubated at 60s, was considerably longer than this predetermined cut-off, suggesting that the outcome definition was not the reason for the relatively high incidence of “failed intubation” in our study compared to others. Rather, we regard the patients with “failed intubation” in our material as genuinely difficult to intubate.

**Perceived difficulty in intubation.**

Various scales have been proposed for grading difficulty in intubation. Adnet et al used the visual analog scale (0-100) when validating the Intubation Difficulty Scale (IDS). They were able to demonstrate a high correlation between VAS and IDS, meaning that the subjective perception of difficulty in intubation correlates well to the objective measures. (121) It is interesting that even though intubation took more than 60s for several patients in the direct laryngoscopy group, no difference between groups was seen as regards difficulty in intubation. Few intubations, both with direct and indirect laryngoscopy, were seen as challenging, which is reflected by the similarly low median difficulty in intubation value. However, the interquartile range was somewhat larger in the direct laryngoscopy group, consistent with the occurrence of difficult/failed intubations in this group of patients.

**Sore throat**

The force applied during videolaryngoscopy is significantly lower than that using the direct technique (122-125). With this in mind, we compared the presence of postoperative sore throat, a fairly common complication of tracheal intubation (126). The incidence of sore throat was very low (127-129), and no significant difference between groups was observed at any time. We have no explanation for this. However, the sample size of the
study was not chosen with regard to this secondary outcome. Furthermore, the means of evaluation was fairly crude, not taking into account factors that may affect the development of post-intubation sore throat, including controlled cuff pressure (130), cuff shape (127) and intra- and postoperative analgesia. Interpretation of the results of this secondary outcome should therefore be made with some caution.

**Effects of remifentanil and esmolol on EGJ pressure**

No effect on the primary outcome, inspiratory EGJ augmentation, was seen. The lack of effect on inspiratory EGJ augmentation in Study II, however, may be explained by the equally negative effect of remifentanil on both inspiratory and expiratory EGJ pressures, whereas esmolol had no effect on either of these (Figure 7).

Inspiratory EGJ augmentation is defined as the difference between inspiratory and expiratory EGJ pressures, and is interpreted as amplification of the EGJ by the contraction of the crural diaphragm during inspiration (29). The EGJ pressure reaches its nadir at the end of expiration (29), and this is therefore considered to be the point during the respiratory cycle when the risk for regurgitation is at its highest (4). Though a barrier pressure above 0mmHg should theoretically be enough to prevent passive regurgitation, no study has shown this to be the case. However, since Pandolfino et al were able to associate an inspiratory EGJ augmentation of < 10mmHg with objectively confirmed gastroesophageal reflux disease (GERD) (endoscopy or pH-positive) (35), we choose inspiratory EGJ augmentation as our primary outcome.

As Pandolfino et al suggested, the inspiratory EGJ augmentation might certainly predict regurgitation in patients with spontaneous breathing, without influence of sedation. In the context of anesthesia, however, when the amplitude of the inhalation diminishes, the diaphragm relaxes and apnea occurs, the main protection against passive regurgitation is instead the tonic contraction of the lower esophageal sphincter (30). In hindsight, it might therefore have been prudent to document the end-expiratory EGJ pressure as primary outcome instead of the inspiratory EGJ augmentation. As reported in Paper II, in contrast to remifentanil, the end-expiratory EGJ pressure was preserved during administration of esmolol, which is consistent with previous studies showing that beta-antagonism induce esophageal smooth muscle contraction (38).
**Dosing and timing**

As described in the introduction of this dissertation, esmolol has gained popularity in the clinical anesthesia because of its ability to attenuate the sympathetic stress response to tracheal intubation (52-54, 71). Figueredo et al. found 500μg · kg⁻¹ · min⁻¹ over 4 minutes, followed by a continuous dose of 200-300μg · kg⁻¹ · min⁻¹ to be the most appropriate dose (71), though several other dose strategies have been used (69, 70).

In studies indicating that the intraoperative use of esmolol may reduce the requirement of volatile anesthetic agents (56-59), and the intraoperative and postoperative requirement of opioids (58, 59, 61-63), a considerably lower dose of esmolol than that required to attenuate the stress response to tracheal intubation was used.

In order achieve dose strategies similar to those used in the above mentioned studies, yet avoiding the risk of unintentional hypotension (72), we chose to administer a bolus dose of esmolol 1mg/kg over 1 minute followed by a fixed infusion of 10μg · kg⁻¹ · min⁻¹ in Study II.

The effect of esmolol on EGJ pressures at 2 and 15 minutes after the bolus dose was compared to the effect of remifentanil on EGJ pressures after a 15-minute infusion. This can be regarded as a comparison of high-and low-dose esmolol with a steady state dose of remifentanil.

**Analgesic and opioid-sparing effects of esmolol**

Several studies have indicated that esmolol may possess inherent analgesic properties (64-68), though this is debatable. Davidson et al. showed that treatment with high-dose esmolol reduced sensitivity to painful formalin injection in the hind leg of rats (68). In addition, Ono et al. demonstrated that intrathecal administration of esmolol had antinociceptive effects in a rat model for postoperative pain (67). Pretreatment with esmolol in humans has been shown to reduce the incidence of pain associated with propofol injection (65, 66) and sub-paralyzing doses of rocuronium (64). The postulated analgesic effect has been attributed to modulation of pain signals at central, spinal and peripheral levels (74-77).

Several clinical trials also suggest that the intraoperative administration of low-dose esmolol could reduce the need for opioids as recue treatment for postoperative pain (58-61). The mechanisms underlying such an opioid-sparing effect, however, are unclear.
In Study III we used the cold pressor test (a pain model) to test our hypothesis that a very low dose of esmolol (10μg·kg⁻¹·min⁻¹) has an analgesic effect. No such effect was seen and the hypothesis was rejected.

The reason for the lack of effect was possibly due to the very low esmolol dose, and this could be clarified in a dose titration study. Our results, however, indicate that the supposed postoperative opioid-sparing effect of esmolol is more likely to be secondary to other factors rather than an inherent analgesic property. The design of Study III, where esmolol was administered alone, does not, however, allow us to comment on these mechanisms.

Factors that have been suggested to underlie the supposed postoperative opioid-sparing effect of esmolol include synergism with coadministered anesthetic agents and opioids, altered pharmacokinetics of coadministered opioids, and the avoidance of opioid-induced hyperalgesia (OIH) (42, 56, 60, 62, 78-80, 131). However, in view of the short elimination half-time of esmolol (50), we consider that synergy is not a likely explanation. Neither can alteration in the pharmacokinetics of intraoperatively administered opioids provide the full explanation, since two previous studies have demonstrated considerable reduction in the need for opioids after anesthesia for laparoscopic cholecystectomy when esmolol was administered together with an anesthetic agent, in the absence of an analgesic agent (61, 81). Moreover, in neither of these studies was the intraperative dose of remifentanil in the comparison group high enough to raise the suspicion that opioid-induced hyperalgesia due to remifentanil was the reason for the lower opioid-consumption in the esmolol group (41, 42, 46, 61, 81).

Multimodal analgesic strategies are known to reduce the need for rescue treatment with opioids in the postoperative period (132). In Study IV, patients in both study groups received paracetamol before surgery, and NSAID, betamethasone and a single dose of morphine intraoperatively. Compared to previous studies on the requirement of opioids after laparoscopic gastric bypass surgery (133, 134), the postoperative consumption of morphine in this pilot study was relatively low in both groups. We have therefore reason to believe that the lack of opioid-sparing effect of esmolol in Study IV was attributable to the multimodal analgesic strategy already implemented intraoperatively.

The non-significant difference in secondary outcomes (incidence and severity of PONV, requirement of antiemetic treatment) between the
esmolol and remifentanil groups was probably due to the similarly low opioid consumption.

**Intraoperative depth of anesthesia and hemodynamic stability**

Compared to the remifentanil group, significantly higher doses of propofol and sevoflurane were required in the esmolol group to obtain a similar depth of anesthesia as measured with BIS. Despite similar depth, the heart rate was slightly higher in the esmolol group compared to the remifentanil group during the early phase anesthesia (Figure 9), suggesting either inferior sympathetic blockade with esmolol, or that the dose was too low.

Despite apparent hemodynamic stability in both groups, more patients in the esmolol group required atropine during anesthesia. We therefore highlight the awareness of the risk of hypotension previously reported by others (72).
Limitations

Study I
In Study I, all intubations were performed by either of two anesthetists with a relatively large experience in videolaryngoscopy. This may possibly have contributed to the relatively short intubations times. However, it does not entirely reflect the reality of everyday practice in our department, where the level of experience in videolaryngoscopy amongst colleagues varies.

The required sample size of the two study groups was calculated with regard to the primary outcome (time-to-intubation) only. The sizes of the group in this study thus provide only limited power to detect small differences regarding the secondary outcomes.

Study II
Study II was designed as a crossover study that included one single study session per volunteer, so that one study drug was administered after the other, separated by a 20 minute wash-out period. Optimally, the wash-out period should be long enough to naturally rule out any possible carry-over effect. The wash-out period in this study was somewhat short to totally rule out any remaining effect of esmolol when administered prior to remifentanil, taking the elimination half-life of esmolol into account (50, 135). However, the clinical effect of esmolol has been shown to be very short, with complete recovery from beta-blockade within twenty minutes (135), suggesting that the wash-out period chosen was adequate for our purpose.

In order to the possibility of a carry-over effect, the output was stratified on the basis of intervention sequence and analyzed separately. The stratified analysis confirmed that remifentanil reduced EGJ pressure compared to esmolol, regardless of whether esmolol was administered before or after remifentanil.

Study III
The dose of esmolol used in this study was based on the doses that significantly reduced the postoperative requirement of rescue treatment with opioids in previous studies. We therefore consider the very low dosage used in this study not to be a limitation.

The use of volunteers with no ongoing surgical pain or coadministered drugs could instead be considered a major limitation of this study. However, in this controlled experiment using the cold pressor test as a surro-
gate for perioperative pain, we were able to study the postulated analgesic effect of esmolol *per se*, without the interference of other factors.

Furthermore, the cold pressor test is considered a reliable method for the experimental testing of nociceptive pain (102-104), and is a standardized and well-documented procedure, that offers good test reliability (97, 105-107). However, since various tests of experimentally induced pain have, in some cases, exhibited low intermodality correlation (136, 137), the study may have benefited from the addition of another experimental modality of pain.

Another limitation of Study III is the somewhat skewed gender distribution amongst the volunteers, since men and women differ in their perception of pain (135, 138). However, the crossover design enabled each volunteer to act as his/her own control. The skewed gender distribution should not therefore have introduced any bias, and is not considered a major problem.

**Study IV**

Since no previous studies have explored the effect of esmolol on analgesic requirement after laparoscopic gastric bypass surgery, or for that matter, surgery on obese patients, Study IV was designed as a pilot study, thus the small sample size. The sizes of the groups in this study however provide only limited power to detect small differences between groups. In addition, during analyses, the small sample size increased the risk that the assumption of normality was set aside due to one or several outliers.
Clinical implications

Since videolaryngoscopy using the Stortz® C-MAC™ appeared to reduce the risk for failed intubation in the Study I, its use in obese patients may therefore be recommended in order to improve success rates and reduce the risk for complications.

Aspiration in conjunction with anesthesia is a relatively rare event that is related to various factors. One factor that may be important in the perioperative period is the preservation of EGJ barrier function. Theoretically, a barrier pressure above 0mmHg should be sufficient to prevent passive regurgitation. In Study II, we observed relatively high EGJ pressures (Figure 7), well above zero during both interventions. The measurements were performed in healthy volunteers, and the study drugs were administered separately and without the addition of a sedative drug. Conditions are different in the clinical setting where, for example, anesthetic agents being used, and this could have important implications, especially in obese patients known to have lower barrier pressures than lean patients (22). In these cases, the lack of effect of esmolol on the EGJ should be an advantage over remifentanil.

Since we were not able to demonstrate an analgesic effect of esmolol in the experimental setting, further studies are needed to establish its use in pain management. The results from Study IV imply that the sole use of esmolol as an adjunct to an anesthetic agent in order to reduce postoperative analgesic requirement after laparoscopic gastric bypass is not motivated. Even so, esmolol could possibly have a part to play in an intraoperative multimodal strategy intended to reduce the amount of short-acting opioids given intraoperatively. In order to find out, further studies on the perioperative applicability of esmolol are required.
Future perspectives
In a Cochrane report from 2014, it is suggested that more primary research is needed to investigate optimal intubation techniques in obese patients, and that studies should be performed in order to detect differences in complications and in success rates (139). Study I contributes new knowledge in this field. However, a larger randomized study evaluating several commonly used airway devices should shed more light on this issue.

Most drugs used in sedation and anesthesia reduce the barrier function of the esophagogastric junction negatively. The results from Study II however indicate that esmolol does not. This does however not mean that all questions are answered. It would instead be valuable to study the effect of esmolol on EGJ function when co-administered with an anesthetic agent such as propofol. More volunteer studies are thus needed.

With respect to passive regurgitation, the absent effect of esmolol on EGJ barrier function might favor the use of esmolol, rather than remifentanil. However, we were not able to show an analgesic effect of low-dose esmolol, a feature that possibly could broaden the scope of the drug. An experimental dose titration study, where the effect of esmolol is compared with placebo in the relief of pain could possibly contribute with further knowledge on whether or not esmolol possesses inherent analgesic properties.

The postoperative requirement of rescue morphine treatment in Study IV of this thesis was relatively low compared to previous studies, most probably due to the multimodal analgesic strategy that was implemented in the design of the pilot study. In addition, despite that numerous clinical and experimental studies have demonstrated the advantages of perioperative administration of esmolol, no opioid-sparing effect was demonstrated. We have no reason to suspect that esmolol should have a different effect in obese patients, compared to lean. However, to shed light over the possible advantages of the perioperative use of esmolol in obese patients, more studies are required in this patient group.
CONCLUSIONS

• Tracheal intubation of obese patients can be performed equally fast using either direct laryngoscopy or the Stortz® C-MAC™ videolaryngoscopy.

• The use of the Stortz® C-MAC™ videolaryngoscope appears to reduce the incidence of failed intubation.

• Even though failed intubation occurred in the direct laryngoscopy group, no difference in perceived difficulty in intubation was seen.

• Postoperative sore throat was a minor problem in our study and was not related to the method of laryngoscopy.

• No difference in inspiratory EGJ augmentation between interventions was seen. However, remifentanil, in contrast to esmolol, reduced both inspiratory and expiratory esophagogastric junction barrier pressure negatively, thereby maintaining inspiratory EGJ augmentation.

• In view of its effect on the esophagogastric junction, esmolol may have an advantage over remifentanil in the perioperative setting.

• In the absence of adjuvant opioid or anesthetic agent, no analgesic effect of low-dose esmolol was seen during experimental pain testing with the cold pressor test. The opioid-sparing effect of esmolol is instead probably secondary to other factors, rather than an inherent analgesic property.

• Low-dose esmolol did not attenuate the sympathetic stress induced by the cold pressor test.
• Low-dose esmolol did not cause opioid-related side-effects such as desaturation, low respiratory rate, swallowing difficulty, or nausea in healthy volunteers.

• The intraoperative use of esmolol, instead of remifentanil, did not reduce the requirement of morphine as rescue treatment for pain after laparoscopic gastric bypass surgery. The multimodal analgesic strategy that was used in the study may have contributed to the unexpectedly low requirement for postoperative analgesia.

• The intraoperative use of esmolol instead of remifentanil did not reduce the incidence of PONV, nor the consumption of antiemetic agents after laparoscopic gastric bypass surgery.
Risken för allvarlig komplikation i samband med sövning är idag relativt låg. På grund av anatomiska och fysiologiska skillnader löper emellertid patienter med fetma och grav övervikt större risk att drabbas av allvarlig händelse under och efter anestesi. Den vanligaste orsaken till anestesi-relaterad död är aspiration, följt av förlängd eller misslyckad intubation. I det postoperativa förloppet är syrebrist hos den gravt överviktige patienten starkt kopplad till opioidbehandling.

I den här avhandlingen har vi i fyra delarbete därför studerat riskfaktorer för luftvägsrelaterad komplikation vid anestesi till gravt överviktiga patienter, men också försökt att utveckla strategier för att förhindra uppkomsten av desamma.

I Studie I visade vi att intubation kan genomföras lika snabbt med videolaryngoskopi (Stortz® C-MAC™) som med direktlaryngoskopi, och att risken för misslyckad intubation verkar kunna reduceras.

I Studie II visade vi att beta-1-antagonisten esmolol, till skillnad från opioiden remifentanil inte påverkar den övre magmunnens barriärfunktion negativt. Mätningar gjordes med esofagusmanometri.

I Studie III undersökte vi om lågdos esmolol har smärtstillande egenskaper. Någon analgetisk effekt kunde emellertid inte påvisas då s.k. cold pressor test användes som smärtmodell. Remifentanil reducerade som förväntat upplevd smärtintensitet, men ökade också förekomsten av sväljningssvårigheter och respiratoriska biverkningar.

I det avslutande arbetet studerade vi om behovet av morfin för smärtlindring efter laparoskopisk gastric by-pass kirurgi kunde reduceras genom att ersätta behandling med remifentanil mot esmolol under kirurgin. Trots att flera tidigare studier visat att esmolol haft betydande opioid-sparande effekt i samband med annan tittthålskirurgi (cholecystectomi) kunde vi inte påvisa någon sådan effekt i vår pilotstudie.

Användandet av Stortz® C-MAC™ i samband med sövning av gravt överviktiga patienter verkar således kunna minska risken för misslyckad intubation. Esmolol har en gynnsam profil i jämförelse med remifentanil avseende bevarandet av den övre magmunnens funktion och skydd mot passiv regurgitation och aspiration. Eftersom varken smärtlindrande eller opioidsparande effekter kunde påvisas behöver ytterligare studier göras för att klargöra läkemedlets eventuella roll inom anestesi till patienter med grav övervikt och fetma.

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