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A NOVEL DRUG AND DEVICE IN ANESTHESIA

WITH FOCUS ON BREATHING AND UPPER AIRWAY PHYSIOLOGY

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By Åse Lodenius, MD

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“Every breath you take
Every move you make
...
I’ll be watching you”

The Police
ABSTRACT

Anesthesia-related airway complications are associated with hypoxia due to inability to secure or maintain the airway with subsequent insufficient ventilation and gas exchange. This thesis has explored the impact on airway integrity and respiratory regulation of two anesthetic compounds frequently used for sedation and a novel principle for oxygenation in patients at risk of hypoxia, in order to further improve patient safety during sedation and induction of anesthesia.

Using a crossover study design, sedation with dexmedetomidine and its effect on regulation of breathing was investigated and compared to sedation with propofol in healthy young men. An impairment of both peripheral and central regulation of breathing, with a similar magnitude of effect during dexmedetomidine and propofol sedation, was found. Incidentally, upper airway obstruction and apneas were discovered which led to investigations on upper airway collapsibility. Pharyngeal critical closing pressure was measured during dexmedetomidine sedation and compared to sedation with propofol at low and moderate infusion rate of sedative drug. A difference in passive pharyngeal closing pressure between dexmedetomidine and propofol could not be demonstrated at either infusion rate of sedation. Clinically significant episodes of apnea during induction of sedation with both drugs were displayed in the two studies, but to a somewhat more pronounced degree with dexmedetomidine.

High-flow nasal oxygenation during apnea using THRIVE (transnasal humidified rapid-insufflation ventilatory exchange) was evaluated describing the change of arterial blood gases and pH that it induces in patients undergoing elective laryngeal surgery in general anesthesia. Oxygenation proved to be well maintained and a lower rate of rise of arterial carbon dioxide than in earlier studies of apneic oxygenation was confirmed, permitting an extended safe apneic period. Since THRIVE maintained oxygenation during apnea for at least 30 minutes it might be of benefit during rapid sequence induction of anesthesia. Therefore, THRIVE and its effect on peripheral oxygen saturation was compared to traditional preoxygenation with a facemask in rapid sequence induction in 80 patients presenting for emergency surgery. In the facemask group 12.5% of patients desaturated below 93% vs. none in the THRIVE group.

In conclusion, sedation with dexmedetomidine impairs regulation of breathing, affects upper airway collapsibility and induces apnea to a similar extent as propofol sedation. High flow nasal oxygenation using THRIVE maintains oxygenation and causes a slow rise in arterial carbon dioxide. This enables extension of the apnea time and indicates possible benefit when used for oxygenation during airway management.

Keywords: anesthesia, sedation, hypnotics and sedatives, airway management, pharynx, airway obstruction, hypoxia, hypercapnia, artificial respiration, pulmonary gas exchange, postoperative complications
LIST OF SCIENTIFIC PAPERS

I. Sedation with Dexmedetomidine or Propofol Impairs Hypoxic Control of Breathing in Healthy Male Volunteers. A Nonblinded, Randomized Crossover Study.
Åse Lodenius, Anette Ebberyd, Anna Hårdemark Cedborg, Eva Hagel, Souren Mkrtchian, Eva Christensson, Johan Ullman, Mika Scheinin, Lars I. Eriksson, Malin Jonsson Fagerlund.

II. Comparison of Upper Airway Properties during Dexmedetomidine and Propofol Sedation. A Nonblinded, Randomized Crossover Study.
In manuscript.

Ida- Maria Gustafsson*, Åse Lodenius*, Jonas Tunelli, Johan Ullman, Malin Jonsson Fagerlund.
* These authors contributed equally

IV. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) vs. facemask breathing pre-oxygenation for rapid sequence induction in adults: a prospective randomised non-blinded clinical trial.
Åse Lodenius, Joanna Piehl, Anders Östlund, Johan Ullman, Malin Jonsson Fagerlund.
**LIST OF ABBREVIATIONS**

<table>
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<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>EMGgg</td>
<td>Electromyography of the genioglossus muscle</td>
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<td>ETCO₂</td>
<td>End-tidal carbon dioxide</td>
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<td>ETO₂</td>
<td>End-tidal oxygen</td>
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<td>FRC</td>
<td>Functional residual capacity of the lung</td>
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<td>GABA</td>
<td>γ-aminobutyric acid</td>
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<td>HVR</td>
<td>Hypoxic ventilatory response</td>
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<td>HCVR</td>
<td>Hypercapnic ventilatory response</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<td>PaCO₂</td>
<td>Partial pressure of arterial carbon dioxide</td>
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<td>PaO₂</td>
<td>Partial pressure of arterial oxygen</td>
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<td>PCO₂</td>
<td>Partial pressure of carbon dioxide</td>
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<td>PO₂</td>
<td>Partial pressure of oxygen</td>
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<td>Pcrit</td>
<td>Pharyngeal critical closing pressure</td>
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<td>REM</td>
<td>Rapid eye movement</td>
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<td>RSI</td>
<td>Rapid sequence induction</td>
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<td>SpO₂</td>
<td>Blood oxygen saturation</td>
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<td>TcCO₂</td>
<td>Transcutaneous carbon dioxide</td>
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<td>THRIVE</td>
<td>Transnasal Humidified Rapid-Insufflation Ventilatory Exchange</td>
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1 INTRODUCTION

1.1 Background

General anesthesia enables surgery to be performed by inducing reversible loss of consciousness. A well-known side effect of general anesthetics is interference with the respiratory system that typically compromises the integrity of the airway and respiratory regulation. A primary objective in anesthesia is, therefore, to secure the airway and safeguard continuous ventilation and gas exchange in the anesthetized or sedated patient to prevent respiratory adverse events.

Airway complications have been a concern since the early start of anesthesia as was demonstrated by the tragic death of Hannah Greener, a healthy 15-year-old girl who underwent chloroform anesthesia for minor surgery in 1848. While this was the first published case of death attributed to anesthesia, respiratory complications continue to be common in the postoperative period and are associated with perioperative morbidity.

Anesthesia-related serious complications are frequently associated with hypoxia due to an inability to secure and maintain the airway with subsequent insufficient ventilation and gas exchange. Importantly, the incidence of anesthesia-related airway complications has declined since the early 1970s. This is most likely due to an array of advancements made over time such as improved monitoring, the introduction of novel equipment and a focus on airway management as a specific area of interest within anesthesia that merits special consideration. In brief, continuous development of drugs with a more favorable pharmacodynamic and pharmacokinetic profile, monitoring equipment (pulse oximetry, capnography) and novel optical tools for intubation, e.g. the flexible fiberscope and the video laryngoscope, have changed perioperative care and the way by which we manage the airway. Both retrospective and prospective studies have evaluated the failure rate of airway management and increased our knowledge in this field forcing us to alter strategies.

Several algorithms have been created and revised to give a better structure for actions to be undertaken when difficulties in airway management are anticipated or met in clinical practice. Nevertheless, although reduced in number airway complications still occur and can ultimately cause serious damage, such as death and hypoxic brain injury, among our patients.

This thesis has explored the impact on airway integrity and respiratory regulation of two anesthetic compounds frequently used for sedation and a novel principle for oxygenation in patients at risk of hypoxia, in order to further improve patient safety during sedation and induction of anesthesia.
1.2 Upper airway physiology

Breathing consists of inspiration and expiration moving air into and out of the lungs in repetitive cycles. Inspiration is accomplished by contraction of the diaphragm, intercostal and some of the neck muscles. Expiration is mainly passive but is enhanced during exercise or with increased minute ventilation when the abdominal wall and intercostal muscles generate active expiration.

During inspiration, in order to accomplish air flow into the lungs, a sub-atmospheric pharyngeal pressure must be generated, which creates a tendency for the upper airway to collapse. The upper airway (above the larynx) consists of a collapsible part (the pharynx) placed between two rigid parts (the nose and the trachea). Collapse is likely to occur in the pharyngeal segment of the airway. The pharyngeal critical closing pressure (Pcrit), the pressure at which the airway collapses and airflow is zero, can be used as a measure of upper airway collapsibility (Figure 1).

![Starling resistor model of the upper airway](https://example.com/figure1.png)

**Figure 1.** Starling resistor model of the upper airway. A collapsible (pharyngeal) segment placed between two rigid structures (the nasal and tracheal segments). \( P_{\text{upstream}} = \text{pressure upstream} \), \( P_{\text{downstream}} = \text{pressure downstream} \), \( R_{\text{upstream}} = \text{resistance upstream} \), \( R_{\text{downstream}} = \text{resistance downstream} \). From British Journal of Anaesthesia 91(1):31-9. Illustration used with permission from Elsevier.

Pharyngeal and laryngeal muscles display both tonic and phasic contraction to maintain airway patency and regulate air flow. Obstruction of the airway is counteracted by simultaneous reflex contraction of pharyngeal dilating muscles activated during inspiration. This reflex contraction is rapidly initiated by mechanoreceptors in the pharynx and larynx that respond to sub-atmospheric pressure and by activation of central neurons in the brainstem. The bilateral genioglossi muscles play an important role in maintaining air...
passage in the oropharyngeal region and are often monitored by electromyography (EMG) as an indicator of muscle tone in the upper airway. Genioglossus activity is enhanced in the supine position keeping the airway anatomy intact, preventing the tongue from falling towards the posterior pharyngeal wall. When inspiration is initiated and a negative pressure is generated, EMG activity in both the tensor palatini and the genioglossus, the most influential dilating muscle, increases in about 20 msec and pharyngeal muscle activity is initiated even prior to the start of inspiratory airflow.

During sleep, a reduced central drive lowers upper airway muscle activity due to a decrease in both cortical influence and chemosensitivity. Muscle tone is sleep stage dependent with partial depression during non-rapid eye movement (REM)-sleep and more profound depression during REM-sleep. Chemoreception, such as hypercapnia, promotes the excitatory drive to neurons regulating upper airway patency and arousal from sleep, thereby stabilizing airway dynamics and preventing further upper airway collapse.

1.3 Upper airway patency and anesthesia

Many drugs administered during sedation and anesthesia reduce airway patency increasing the risk of airway obstruction and oxygen desaturation. Patients also have various propensity to upper airway occlusion due to anatomic features, increasing obesity in the population with concomitant obstructive apnea syndrome, pathology of the airway or neuromuscular disorders among other conditions. Therefore, vigilance is especially required during sedation if patients rely on spontaneous ventilation or at anesthesia induction when airway mechanics can change drastically.

Adding to the central effects seen during sleep, anesthesia also reduces upper airway muscle tone by direct effects on laryngeal neural activity depressing upper airway reflexes. The loss of upper airway muscle tone leads to airway obstruction usually at the level of the soft palate. Furthermore, muscles of the upper airway are more affected than the diaphragm during both sleep and anesthesia. When inspiration is attempted during spontaneous ventilation a negative intraluminal airway pressure increases the risk of complete collapse due to upstream obstruction. Animal studies have shown a differential suppression of activity in the upper airway compared to the diaphragm during administration of halothane, thiopental, and diazepam.

General anesthetics such as inhaled and intravenous anesthetic drugs typically increase the collapsibility of the upper airway. Propofol sedation is associated with an inhibition of dilating upper airway muscle activity (reduced EMG), an increase in pharyngeal critical closing pressure and decreased inspiratory flow during maintenance airway pressure. A reduction of the anteroposterior diameter of the pharynx during propofol anesthesia has also been displayed with magnetic resonance imaging. In the same manner, inhalational sedation with isoflurane decreased muscle activity in the genioglossus muscle and increased...
the pharyngeal critical pressure at which the airway occludes. In a recent study, sevoflurane sedation induced a dose-dependent impairment of upper airway closing pressure (Pcrit) and reduction of both tonic and phasic genioglossus muscle activity measured by EMG. In addition to muscle deactivation and these structural changes, functional impairment and dyscoordination of the pharynx during swallowing have been demonstrated with subhypnotic doses of sevoflurane, isoflurane and propofol.

Various other drugs used for sedation or as part of general anesthesia such as benzodiazepines (diazepam, midazolam), opioids, residual effects of neuromuscular blocking agents and also neostigmine, used for reversal of neuromuscular block, have been shown to impair upper airway patency. This has been proven by decreased neuromuscular activity, a reduced cross-sectional diameter of the pharynx or pharyngeal dysfunction. The exception to this rule is ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, that appears to induce less compromise of the airway than γ-aminobutyric acid (GABA)-acting sedative agents.

Of interest when considering awake intubation due to anticipated difficulty with airway management is the fact that topical anesthesia can cause upper airway obstruction. Total obstruction of the airway in patients with a compromised airway has been reported. Reduced maximum air flows and genioglossus activity with increased collapsibility have been seen when using topical anesthesia.

Upper airway patency in the anesthetized is also affected by body posture. During anesthesia in the supine position, the soft palate falls towards the posterior pharyngeal wall occluding the nasopharynx, presumably due to interference with the tensor palatini, palatoglossus and/or palatopharyngeus muscles decreasing the anteroposterior diameter of the pharynx. The tongue and epiglottis are displaced posteriorly. Neck flexion (chin towards chest) in both the supine and prone position, mouth opening, and the Trendelenburg position increase the risk of airway obstruction caused by loss of longitudinal tension of the upper airway.

1.4 Control of breathing

Control of breathing serves to regulate respiration to match changes in ventilatory and metabolic demand as generated by voluntary movement, speech, singing, physical exercise or emotional stress and disease (e.g. anxiety, fever, and infection). Breathing can be controlled by voluntary action within certain limits but is also affected by involuntary acts such as sleep, sneezing, coughing, vomiting, swallowing or hiccup (Figure 2).

Control and regulation of breathing are primarily based on brain stem chemoreceptor sensing of carbon dioxide (CO₂) and pH and to a lesser extent peripheral chemoreceptors sensing of oxygen (O₂) and CO₂. The central chemoreceptors are located in the ventrolateral part of the medulla. CO₂ easily passes the blood-brain barrier, hydrates to carbonic acid which then
ionizes to give rise to hydrogen ions (H⁺), yet the mechanism by which H⁺ causes stimulation of chemoreceptors has not been revealed 38.

A rise in partial pressure of CO₂ (PCO₂) stimulates increased breathing, both tidal volume and respiratory rate, and is termed the hypercapnic ventilatory response (HCVR). There is a linear correlation between PCO₂ and the ventilatory response above an apneic threshold necessary to stimulate breathing. If hyperventilation reduces PCO₂ below the apneic threshold apnea might occur. As the PCO₂ level increases maximal ventilation will eventually be reached when muscle fatigue and CO₂ narcosis will follow. An accentuated response, a steeper slope of the hypercapnic ventilatory response, is seen when there is a concomitant reduction in partial pressure of O₂ (PO₂). Human peripheral chemoreceptors are located in the carotid bodies, bilaterally placed in the bifurcation of the carotid arteries. The main stimuli is a fall in arterial partial pressure of O₂ (PₐO₂), not oxygen saturation, but the carotid body also responds to an increased PₐCO₂ and a decreased pH. When hypoxia occurs, neural afferent signals are conveyed by the carotid sinus nerve to the respiratory center in the medulla 39,40. There is a non-linear correlation between PₐO₂ and minute ventilation. The relationship between oxygen saturation (SpO₂) and minute ventilation is linear with a negative slope which provides the usual base for assessing the hypoxic ventilatory response (HVR).

There is a wide inter-individual response to hypoxia 39,41. The HVR is also influenced by circadian rhythm, gender, hormonal status (such as pregnancy and menstrual phase) and psychological factors and can also vary within subjects between days 39,42. HVR is decreased during sleep related to sleep stage 43. An altered modulation of the hypoxic response in the central nervous system has been suggested as an explanation for this.

Chronic hypoxia, due to high altitude or hypoxemic disease for example, or chronic intermittent hypoxia, such as in obstructive sleep apnea, gives rise to hyperplastic carotid bodies and an exaggerated hypoxic ventilatory response 39,44,45.

Hypoxia also has a direct effect on the respiratory center. Severe medullary hypoxia depresses the neurons and ultimately causes apnea 39.
Figure 2. Inputs to breathing. Multiple inputs are capable of regulating breathing. During sleep, many inputs are diminished (dashed red lines) or absent (solid red lines). From Principles and Practice of Sleep E-Book, 6th ed. Illustration used with permission from Elsevier.

Chemoreceptive neurons convey excitatory respiratory drive to the central pattern generator located in the medulla in the brainstem. The central pattern generator also receives input from peripheral mechanoreceptors in the pharynx, larynx and the lungs adjusting the breathing pattern to meet the demands. Respiratory control is coordinated by the pons but is affected by many other areas of the central nervous system.

Chemoreceptor stimulation produces arousal from sleep but during non-REM sleep these reflexes are depressed and minor fluctuations in PCO₂ can, therefore, cause apnea and periodic breathing. In REM-sleep breathing frequency is not under control of chemoreceptors but maintained by input from an unknown part of the brain.
1.5 Control of breathing and anesthesia

Respiratory depression is a common side effect of many of the drugs used in general anesthesia or sedation either by direct action on the respiratory center or by impairment of the ventilatory response induced by chemoreceptors. Consequently, spontaneous arousal and resolution of upper airway obstruction that normally occurs with hypoxia or hypercapnia may be diminished. There is a dose-dependent depression of ventilatory response and high doses administered quickly can induce apnea. Still, sub-anesthetic or sedative levels of drugs in anesthesia are generally regarded to have pronounced effects on control of breathing. During sedation, with the patient relying on spontaneous ventilation, respiratory monitoring is usually limited, consisting of peripheral oxygen saturation and possibly respiratory rate. In procedural sedation or in presence of well-functioning regional anesthesia there may also be a lack of counteracting surgical stimuli. Therefore, it should come as no surprise that airway safety may be compromised during sedation and that it may persist even when only a fraction of the anesthetic dose of the drug remains, as for instance in the post-operative period, putting the patient in a vulnerable position.

Propofol is the most frequently used intravenous anesthetic today. Its hypnotic action is mediated by binding to the GABA\(_A\)-receptor. It causes respiratory depression and at higher doses apnea. Propofol sedation reduces the HVR in humans as well as in experimental carotid body models \(^{48-51}\). Sedation with propofol also reduces the ventilatory response to hypercapnia due to interference with the central chemoreflex loop \(^{51,52}\).

Volatile anesthetics reduce both peripheral carotid body O\(_2\) and CO\(_2\) chemosensitivity. Animal studies have revealed that volatile anesthetics reduce the carotid body HVR \(^{53}\). In humans inhalational anesthetics reduce the acute HVR about 50% in sub-anesthetic doses and at higher doses even more \(^{54}\). The depression of ventilatory response was most profound with halothane followed by enflurane, isoﬂurane and sevoﬂurane \(^{55}\). Inhalational anesthetic agents also decrease the HCVR proportionally to alveolar concentration and at deep levels of sedation, the hypercapnic reaction is almost abolished \(^{56-59}\). However, low doses of inhaled anesthetics (<0,2 MAC) cause almost no reduction of the hypercapnic response in humans \(^{59}\). Hence, lingering effects of inhalational anesthetics may compromise the airway even if spontaneous breathing has resumed at emergence of anesthesia.

Other classes of drugs used in anesthesia with an impact on regulation of breathing are opioids, benzodiazepines, and neuromuscular blocking agents. Opioids are powerful analgesics but also have respiratory depression as a well-known side effect, reducing both respiratory rate and tidal volume \(^{60}\). Benzodiazepines, frequently used during sedation, cause a dose-dependent reduction of resting ventilation and a decreased ventilatory response to hypoxia and hypercapnia \(^{61-63}\). Non-depolarising muscular blocking agents have been shown to reduce the HVR by approximately 30% at a partial muscular block, train-of-four ratio 0.7, via inhibition of nicotinic transmission of the chemoreceptor in the carotid bodies \(^{64-68}\).
1.6 Dexmedetomidine

Dexmedetomidine (Dexdor®) is a highly selective α2-adrenergic agonist with sedative and analgesic-sparing effects. As initially used for decades in veterinary medicine, it was registered for human use in the United States in 1998 and in Europe in 2011 with an indication for sedation in the intensive care unit. In the US dexmedetomidine (Precedex®) is also approved for procedure-related sedation in non-intubated patients since 2003.

Dexmedetomidine primarily targets noradrenergic neurons in the central nervous system to produce hypnosis that qualitatively resembles natural non-REM sleep. While receiving sedation patients remain easily arousable and cooperative.

In contrast to other sedative agents, dexmedetomidine has been perceived to preserve respiratory drive and has therefore been promoted as an alternative intravenous sedative agent. Such statements have in general been based on observations that oxygen saturation is well preserved and the arterial CO₂ level only slightly increased during resting ventilation when dexmedetomidine sedation is administered. This has been demonstrated with a wide variety of dose when given to both healthy volunteers and patients. For this reason, dexmedetomidine is increasingly used as a sedative when preservation of spontaneous breathing is important as in the intensive care when the airway is not secured with an endotracheal tube, during procedural sedation or during awake intubation when airway pathology is present.

As expected, a sedative drug that potentially lacks negative respiratory side effects would substantially add to patient safety in a wide variety of clinical settings. However, the impact of dexmedetomidine on regulation of breathing had not been fully evaluated, e.g. the human regulation of breathing during hypoxia when sedated with dexmedetomidine had not been investigated. The theoretic background to suspect an influence on the HVR consisted of reports of α2-adrenoceptor expression in the carotid body in various species. However, conflicting results regarding α2-adrenergic agonist action on the hypoxic response generated in the carotid body from animal studies in vivo had been presented. Administration of the prototypical α2-adrenergic agonist clonidine inhibits breathing in various species and reduces both the hypoxic and the hypercapnic ventilatory response in humans. Therefore, it seems reasonable to believe that dexmedetomidine could display similar properties. There are also discrepancies regarding the impact of dexmedetomidine in hypercapnic ventilatory response during dexmedetomidine sedation. While Belleville and co-workers found the hypercapnic ventilatory response to be reduced a more recent study demonstrated no effect of dexmedetomidine on the hypercapnic ventilatory response. The diverging results between the two studies may be explained by CO₂-induced arousal during hypercapnia in the latter study.

Regarding the effect of dexmedetomidine sedation on upper airway patency little was known. Episodes of upper airway obstruction after intravenous dexmedetomidine and oral or epidural administration of the closely related α2-adrenergic agonist clonidine have been reported in humans. In addition, systemic administration of clonidine has been shown to cause airway obstruction in animals with both glottis closure and narrowing of the hypopharynx. Magnetic resonance imaging had demonstrated a reduction of the upper airway diameter.
and a need for airway maneuvers or artificial airways during sedation with dexmedetomidine has been described indicating that airway obstruction may occur \textsuperscript{89-91}.

Hence, while dexmedetomidine may have beneficial pharmacodynamics there was a growing body of information suggesting that dexmedetomidine-induced sedation might interfere with regulation of breathing and upper airway patency. These potential hazardous side-effects needed to be explored and characterized with regard to frequency and underlying mechanisms to ensure safe oxygenation and gas exchange during sedation.
1.7 Respiration and gas exchange

Respiration serves to ensure adequate oxygenation and removal of CO$_2$. Oxygen (O$_2$) is brought into the lungs as a result of active inspiration that creates a negative pressure within the thoracic cage. Inspired air is humidified and cleared from pathogens and irritants before reaching the terminal bronchioles and alveoli where gas movement takes place by diffusion rather than tidal ventilation. When reaching the alveoli oxygen diffuses from the alveolus to the capillary, a distance of approximately 0.5 µm, via plasma across the red blood cell membrane$^{47}$. Oxygen is mainly transported with hemoglobin within the red blood cells (about 20 ml/100 ml of blood), a minimal part remaining in free solution in plasma (about 0.3 ml/100 ml of blood), down its concentration gradient to the mitochondria of cells where it is consumed. Approximately 250 ml of O$_2$ is consumed each minute in a normal adult.

There are no large oxygen stores in the body. The main part of body oxygen, about 850 ml out of 1550 ml in total, is contained in the blood and can supply barely three minutes of metabolism in the resting state. Therefore, if the oxygen level is reduced in the lung, due to reduced breathing, hypoxia follows quickly. In fact, when breathing air a 90 second apnea period is enough to induce hypoxia$^{47,92}$.

Reduced breathing causes the CO$_2$ levels to rise and blood pH to fall. Changes in PCO$_2$ and pH produce a shift in the O$_2$-hemoglobin dissociation curve (the Bohr effect). An increased PCO$_2$ and decreased pH results in a weaker O$_2$-hemoglobin bond and facilitates O$_2$ release in the periphery. Conversely, a low PCO$_2$ and high pH induce a tighter binding of O$_2$ to hemoglobin which facilitates the upload of O$_2$ to hemoglobin in the lungs.

Carbon dioxide is the end product of aerobic metabolism that takes place in the mitochondria. CO$_2$ is a small molecule that passes easily from the cytoplasm to the blood. CO$_2$ is predominantly carried in blood as bicarbonate but also as carbamino compounds formed with hemoglobin or plasma proteins and to a small degree (less than 1%) as carbonic acid in solution in plasma$^{47}$. In the lungs, CO$_2$ diffuses easily from the pulmonary capillaries with the higher PCO$_2$ to the alveoli and is actively transported from the lung with alveolar ventilation. Blood leaving the alveoli has the same PCO$_2$ as the alveoli.

As O$_2$ is delivered in peripheral tissue the hemoglobin becomes reduced (oxygen-free). Reduced hemoglobin is more effective in carrying CO$_2$ (the Haldane effect) and also has an increased buffering capacity. Increased PCO$_2$ generates an increased carbamino carriage of CO$_2$ by hemoglobin, which is enhanced by a lowered O$_2$ saturation that is likely to occur at the same time. An increased PCO$_2$ will also cause a decreased pH, i.e. increase in hydrogen ions (H$^+$), that is buffered by the reduced hemoglobin.

Average CO$_2$ production in an awake and resting adult of 70 kg is approximately 200 ml/min for a male and 160 ml/min for a female$^{93}$. CO$_2$ elimination is equal to its production in steady state. During acute hypoventilation, a substantial part of the CO$_2$ that is produced is diverted into body stores. Since the total amount of CO$_2$ in the body is very large it takes several minutes for CO$_2$ levels to change when ventilation is abruptly decreased. The rate of rise of arterial CO$_2$ when there is no ventilation is about 0.6 kPa/min$^{94}$.
During apnea with an intact circulation oxygen uptake continues (approximately 250 ml/min) and CO₂ output decreases as the alveolar gas reaches equilibrium with venous blood. If no gas is delivered from the outside and air was being inhaled prior to apnea hypoxia would supervene within 90 seconds. If 100% oxygen was administered prior to apnea the apneic period can be substantially prolonged before desaturation occurs. If the airway is kept patent ambient gas is drawn by mass movement down the trachea replacing the O₂ that passes to blood minus the smaller amount (initially about 20 ml) of CO₂ passing into the alveoli. Supplying air to the patent airway will slowly increase the fraction of nitrogen in the lungs as O₂ is being consumed and hypoxia will occur within a few minutes. If, instead, the gas supplied is 100% oxygen hypoxia can be put off for several minutes since the alveolar PO₂ is only reduced by the rise of CO₂ (approximately 0.6 kPa/min). Apneic oxygenation or “diffusion respiration” providing 100% O₂ prior to apnea and a continuous flow of 100% O₂ to a patent airway can maintain oxygen saturation in humans for more than 60 minutes.

1.8 Oxygenation during anesthesia induction

A significant and feared problem during induction of anesthesia is failure to secure the airway thereby not being able to oxygenate the patient. To prevent apnea-induced hypoxia during induction of anesthesia, preoxygenation with 100% oxygen is currently standard of care. This maneuver serves the purpose of replacing nitrogen with oxygen within the functional residual capacity (FRC) of the lungs thereby increasing the oxygen reserve, ultimately allowing more time for the airway to be secured before hypoxemia develops. This is emphasized during rapid sequence induction (RSI) of anesthesia when ventilation is avoided until endotracheal intubation is successfully completed and the airway is secured. This, in turn, means that the patient relies on his/her oxygen reserve during the entire intubation procedure.

Traditional preoxygenation consists of breathing 100% oxygen via a tight-fitting facial mask with a high fresh gas flow. In healthy subjects, preoxygenation prolongs the time to desaturation < 90% with several minutes (Figure 3).

![Figure 3. Time to hemoglobin desaturation with initial FAO₂ = 0.87 and an occluded airway (VE =0) in various types of patients. FAO₂ = alveolar fraction of oxygen; SaO₂ = arterial oxygen saturation; VE = minute ventilation. From Anesthesiology 1997;87:979-82. Published with permission from Wolters Kluwer Health, Inc.](image-url)
Because some patients desaturate in spite of preoxygenation with 100% O\textsubscript{2} several novel concepts of continuous O\textsubscript{2} delivery during intubation has been described and evaluated over the years.

1.9 Apneic oxygenation

“Respiration without respiratory movements” was described by Robert Hooke already in 1667 in a report of an experiment conducted in a dog that was revived and kept alive for more than an hour (Figure 4). The chest was opened and two bellows where connected to the trachea blowing air continuously through the lungs, letting it out through small slits made by “pricking all the outercoat of the lungs with the slender point of a very sharp pen-knife” 97.

Figure 4. Account of Mr. Hooke’s experiment of keeping a dog alive from the Philosophical Transactions of the Royal Society of London. Image downloaded with courtesy from the Royal Society of London.

Following this experiment, dating centuries back, several studies on apneic oxygenation took place from the early 20th century and onwards 95,98-101. H:son Holmdahl performed extensive work on “apneic diffusion oxygenation”, presented in his thesis in 1956. This thesis describes prolonged periods of apneic oxygenation in both animals and humans and its effect on gas exchange, pH, and the circulation, providing important information until this date 100.

These early studies showed that if the airway is kept open at all times, denitrogenation has been performed and 100% oxygen is administered, oxygen saturation can be maintained for a time period with apneic oxygenation of up to 60-65 minutes 95,98,99,101. The limiting factor for the time period possible to use apneic oxygenation is the increase in arterial CO\textsubscript{2} level and the accompanying decrease of pH that ultimately will challenge the circulation. This was demonstrated in the Frumin study from 1959 where the arterial pH of several participants was severely lowered and two participants experienced cardiac arrhythmia.
In 1988 Teller and co-workers conducted a small study with 12 subjects during apnea comparing no additional oxygen vs. additional 3 L/min of pharyngeal O₂ insufflation in anesthetized and paralyzed patients. Patients not receiving additional oxygen kept the peripheral oxygen saturation above 92% for about 6-7 min while patients receiving additional oxygen via pharyngeal insufflation kept saturation at approximately 98% for at least 10 minutes, the maximum time allowed before resuming ventilation. More recently, others have shown that oxygen administered with low to moderate flow, 3-15 L/min, nasally with prongs or a catheter during intubation increases the time to desaturation and lowers the incidence of desaturation during rapid sequence induction (RSI) intubation.

As a further extension of this concept, Patel and Nouraei published a landmark study in 2015 presenting a technique delivering a very high flow (30-70 L/min) of nasal oxygen termed transnasal humidified rapid-insufflation ventilator exchange (THRIVE) using Optiflow™ (Fisher & Paykel Healthcare, Auckland, New Zealand). In this pivotal study, the THRIVE technique provided extended time to secure the airway in high-risk patients with known airway pathology scheduled for pharyngo-laryngeal procedures. No patient desaturated below a SpO₂ of 90% and the increase in CO₂ level was considerably lower than the one reported in older studies. The mechanisms for this slower accumulation of CO₂ has not been entirely clarified but it suggests partial washout of CO₂ and opens for a possibility of extending the time with apneic oxygenation when using THRIVE without approaching a harmful PCO₂ and pH.

The same oxygenation concept, using the high-flow nasal catheter with 100% oxygen, was also evaluated for preoxygenation in intensive care patients. This was performed as a before-and-after study using traditional preoxygenation and thereafter changing clinical practice to use of Optiflow™ during preoxygenation in the intensive care unit (ICU), resulting in improved oxygenation in these patients. Patients undergoing fiberoptic intubation during light sedation supported with oxygenation using Optiflow TM were also examined. In all 50 included patients, with complex pharyngeal and laryngeal anatomy, the oxygenation improved measured as SpO₂ during this procedure.

1.10 A high-flow nasal oxygenation device

The use of heated and humidified high-flow oxygen is well established in the intensive care. The technique presents an alternative way to support ventilation in patients with preserved spontaneous breathing in respiratory failure or after extubation. With a flow of 30-70 L/min, the high-flow oxygen delivery device Optiflow™ accomplishes a continuous positive airway pressure of about 1 cmH₂O/10 L/min of flow and increases end-expiratory lung impedance suggesting an increase in functional residual capacity during spontaneous breathing. While the first description of the THRIVE technique provided a novel way by which apneic oxygenation could be maintained during airway management, the study was strictly observational and provided preliminary clinical information. The study gained attention as this new technique found its way to the operating room but left a gap of knowledge regarding gas exchange and pH progression that had not been characterized so far.
Based on the facts presented above it seemed that the THRIVE concept of apneic oxygenation could provide an alternative to traditional ventilation or jet ventilation during laryngeal surgery of short duration when an endotracheal tube would obscure the view of the surgical field. It could also serve well as an alternative technique for preoxygenation during RSI intubation, thereby extending the time to oxygen desaturation if the time to intubate is prolonged.

While the technique held a promise of increased safety during apnea a more detailed evaluation before considering it for implementation in our clinical environment in routine practice seemed warranted.

1.11 Current controversy and lack of knowledge

Dexmedetomidine has been described as a sedative drug with minimal or no impact on respiratory control, although a more detailed evaluation on the impact on regulation of breathing and upper airway collapsibility in humans has so far been limited. From recent observations, there is increasing evidence that dexmedetomidine may affect regulation of breathing and may be associated with airway obstruction and periods of centrally evoked apnea.

High flow nasal oxygenation with the THRIVE technique has the potential to increase safety by extending the apneic period when used either as a means of oxygenating during surgery of shorter duration or during tracheal intubation, owing to its slower rate of rise in PCO$_2$ while maintaining oxygen saturation. Compared to traditional preoxygenation that ends when laryngoscopy and intubation are initiated, THRIVE provides continuous oxygen supply throughout the procedure. Therefore, it rather provides “oxygenation” than “preoxygenation” and may entail a paradigm shift in our way of managing the airway in the future, especially if difficulty is anticipated.
2 AIMS

The overall aim with this thesis was to evaluate clinical aspects of a drug, dexmedetomidine, and device, a high-flow nasal oxygenation device using the Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) technique, by characterizing the impact on respiration, gas exchange and upper airway patency.

The specific aims were

• To investigate how the hypoxic and hypercapnic regulation of breathing is affected by sedation with dexmedetomidine and to compare it to sedation with propofol

• To evaluate upper airway collapsibility during sedation with dexmedetomidine and to compare it to sedation with propofol

• To investigate changes in arterial pH, PO$_2$, and PCO$_2$ over time when using high-flow nasal oxygenation with THRIVE for apneic oxygenation during general anesthesia in laryngeal surgery

• To compare oxygenation during rapid sequence induction of anesthesia using oxygenation with THRIVE or preoxygenation with the traditional tight occluding facemask
3 MATERIAL AND METHODS

3.1 Ethics

The Stockholm Regional Ethics Committee approved Studies I, III and IV. Study II was approved by the Sir Charles Gairdner Hospital Human Research Ethics Committee, Nedlands, Western Australia. All studies were performed in accordance with the 2008 and 2013 Declaration of Helsinki on Human Research and Good Clinical Practice.

3.2 Participants

Study I: Healthy male volunteers were recruited by advertisement on the campus of Karolinska Institutet and at the Department of Anesthesiology, Surgical Services and Intensive Care, Karolinska University Hospital Solna (Figure 5).

Study II: Volunteers were recruited among staff and patients at the West Australian Sleep Disorders Research Institute, Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia and by advertisement among students at the University of Western Australia, Perth, Western Australia.

Study III: Adult patients presenting for elective laryngeal surgery at the Ear, Nose and Throat operation ward were enrolled in the study during preoperative anesthetic evaluation.

Study IV: Adult patients presenting for emergency surgery at the Function Unit, Trauma and Emergency Surgery, Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm where RSI of anesthesia was required were enrolled in the study during preoperative anesthetic evaluation.

All participants in the studies gave written informed consent prior to entering the studies.
Figure 5. The lab in Study I. From the left Malin Jonsson Fagerlund, supervisor, in control of the anesthesia machine delivering air, Anette Ebberyd keeping track of the protocol and the Collect software on the computer. A volunteer sedated and monitored with Datex and bispectral index score (BIS) that is seen on the top right side. Åse Lodenius to the far right.

3.3 Spirometry
In Study I airflow and airway pressure were measured with a spirometer (D-lite™, Datex-Ohmeda AS/3™, GE Medical Systems Madison, WI, USA). The spirometer measures total pressure and static pressure at a known resistance with laminar flow, calculating dynamic pressure, i.e. pressure difference (ΔPressure). Inspiratory and expiratory airflow (L/min) was calculated every 40 msec (Constant * ΔPressure = Flow). Technical specifications state that the measuring range is 1.5 to 100 L/min. Airflow was recorded at 100 Hz using the manufacturer’s software solution (Datex-Ohmeda S/5™ Collect). Inspiratory and expiratory tidal volumes were automatically calculated through integration. The accuracy of flow measurement has been tested by comparing measured inspiratory volumes to inspiration with high-precision calibration syringes (Hans Rudolph, P&A Medical, Bolton, UK) of varying sizes (300, 500, 800 and 1100 ml). The accuracy of measured inspiratory volume was 96-100% of the known calibrated volume, i.e. measurement is made with a precision of ± 4-7 ml. The breathing system was calibrated with high precision syringes before each experiment.

In Study II a similar set up was employed using a pneumotachograph (Korr Medical Technologies, Salt Lake City, UT, USA). The pneumotachograph was calibrated with a 3 L syringe and a device delivering flow with a known velocity in two directions. Calibrations of flow and inspired volume were performed before each experiment.
3.4 Respiratory movements

Respiratory movements were monitored as a sign of breathing effort with thoracic and abdominal inductance pneumography/impedance with bands placed around the thorax and abdomen in both Study I (Bio-Radio™, Great Lakes Neuro Technologies, Valley View, OH, USA) and Study II (Respitrace, Ambulatory Monitoring, Ardsley, NY). The technique is based on sinusoidally arranged coils embedded in soft elastic bands that are placed around the thorax and abdomen. During breathing the volume of the rib cage and abdomen changes and these changes are transduced to electrical signals to detect the movement.

3.5 Pressure measurements

In Study II a four-sensor pressure transducer catheter (CTO-4; Gael Tec, Dunvegan, Isle of Skye, Scotland, UK) was passed via a nostril into the esophagus to measure pharyngeal and esophageal pressures for measurement of respiratory effort. The catheter was placed with the tip in the mid-esophagus and its position controlled by visual inspection of the oropharyngeal pressure transducer 1-2 cm below the soft palate. Pressure transducers 4 cm above and below the oropharyngeal transducer also measured retropalatal and hypopharyngeal pressures, respectively. The pressure transducers were calibrated prior to subject set-up with two known pressures.

3.6 The hypoxic ventilatory response test

Hypoxia induces an increase in minute ventilation within seconds, a response generally known as the acute hypoxic ventilatory response (HVR). The HVR consists of three phases (Figure 6). The initial phase is a rapid rise in minute ventilation, due to increased tidal volume and respiratory frequency, that is maintained for 5-10 minutes before the second phase, the hypoxic ventilatory decline, is initiated. The third phase of the HVR is seen if isocapnic hypoxia is kept (hypoxia at an unchanged arterial carbon dioxide level) where ventilation continues to rise in a second peak for several hours.

Figure 6. The hypoxic ventilatory response during isocapnia and poikilocapnia. From Nunn’s Applied Respiratory Physiology, 7:th Edition, 2012, Copyright Elsevier. Illustration used with permission from Elsevier.
In poikilocapnic conditions where carbon dioxide level is allowed to fluctuate as a result of the increased breathing (i.e. the level of CO₂ is decreased) ventilatory decline resides within 20-30 minutes before reaching a plateau above resting ventilation at normoxia.

The isocapnic HVR test is employed in order to study peripheral chemosensitivity and by maintaining isocapnia the effect of hypoxia is separated from interaction with CO₂.

In the isocapnic HVR test in Study I, 0.2 % CO₂ was added in inspired air to stimulate background central drive at baseline before initiating the hypoxic test. Hypoxic ventilation was induced manually by switching abruptly from room air to a hypoxic mix of O₂ and N₂. The fraction of inspired O₂ was approximately 0.08 to 0.12 kPa targeting a SpO₂ of 80%. During the hypoxic test, we manually adjusted the additional CO₂ with a micro flowmeter to keep ETCO₂ constant. The peak hypoxic ventilation was then averaged for 3 minutes after 3 minutes of hypoxia.

The HVR can be calculated as ∆VE / ∆SpO₂.

\[
HVR \ (L/min/\%) = \frac{(VE \ challenge - VE \ control)}{(SpO₂ \ challenge - SpO₂ \ control)} = \frac{∆VE}{∆SpO₂}
\]

\[
VE = \text{minute ventilation; } SpO₂ = \text{peripheral saturation of oxygen}
\]

3.7 The hypercapnic ventilatory response test

Hyperventilation, with a typical increase in respiratory rate and tidal volume, is rapidly induced by stimulation of both peripheral and central chemoreceptors that results in increased discharge in the phrenic nerve and augmented breathing.

The ventilatory response to CO₂ consists of two components. Peripheral chemoreceptors provide the initial, rapid response and central chemoreceptors provide most of the steady-state response with a somewhat slower onset\(^\text{37}\). Steady-state at 75% of the maximum ventilatory response is reached within a few minutes. If hypercapnia is sustained, the minute ventilation continues to increase for the following hour\(^\text{116}\). To evaluate these two components the initial quick response must be separated from the second slower response. This can be done with brief (milliseconds) hypercapnic periods. During a single step increase of CO₂, only the initial part (about 2 minutes) can be used to determine the peripheral component of ventilatory response.

In Study I the hypercapnic ventilatory response was evaluated with a single step increase in CO₂ by an instant addition of 5% CO₂ to the inspired air for 8 minutes. The minute ventilation was averaged for the last 3 minutes of the 8-minute test period thus evaluating mainly the central chemoreceptor response to hypercapnia.
The HCVR can be calculated as $\Delta VE / \Delta PCO_2$.

$$HCVR (L/min/mmHg) = (VE \text{ challenge} - VE \text{ control}) / (PETCO_2 \text{ challenge} - PETCO_2 \text{ control}) = \Delta VE / \Delta PETCO_2$$

$VE = \text{ minute ventilation}; \ PETCO_2 = \text{ partial pressure of end-tidal carbon dioxide}$

3.8 Measurement of pharyngeal critical closing pressure

The upper airway can be described as a collapsible segment (pharynx) placed between two rigid segments (nose and trachea) and as having the function of a Starling resistor (Figure 1)\textsuperscript{13,117}. Air flow is determined by the relation between pressures upstream ($P_{\text{upstream}}$) and downstream ($P_{\text{downstream}}$) as well as the pressure surrounding the collapsible pharyngeal part. If $P_{\text{upstream}} > \text{tissue pressure} > P_{\text{downstream}}$ the flow rate will depend upon the gradient between $P_{\text{upstream}}$ and tissue pressure and be independent of $P_{\text{downstream}}$ (which is equal to inspiratory effort).

When $P_{\text{upstream}}$ is lowered flow limitation will occur which can be identified by no increase in flow rate in spite of increased inspiratory effort (lowering of $P_{\text{downstream}}$). Reducing the $P_{\text{upstream}}$ further will result in proportionate reductions of maximum flow rate.

Reducing the $P_{\text{upstream}}$ below tissue pressure will cause occlusion of the airway and no flow. The upstream pressure at which there is no flow is the critical closing pressure ($P_{\text{crit}}$). $P_{\text{crit}}$ assesses structural properties of the upper airway and provides an objective value of collapsibility of the airway. A high $P_{\text{crit}}$ is indicative of a more collapsible airway. If greater than atmospheric pressure the airway will occlude if it is open to air. A negative value indicates that the airway is resistant to collapse and that a negative pressure needs to be applied to induce obstruction/occlusion. In general, normal individuals have a negative $P_{\text{crit}}$ (less than $-8 \text{ cmH}_2\text{O}$), individuals who snore a less negative $P_{\text{crit}}$ (about $-4 \text{ cmH}_2\text{O}$), and in obstructive sleep apnea patients, the $P_{\text{crit}}$ is at or above atmospheric pressure\textsuperscript{117-119}.

$P_{\text{crit}}$ measurement in Study II: A nasal mask was fitted to the study subject. A pneumotachograph, an expiratory port and a custom-made pressure source device capable of delivering both positive and negative pressures, from -20 to +20 cmH$_2$O were connected to the nasal mask. Nasal mask pressure ($P_{\text{mask}}$) was measured continuously via a sample port connected to a pressure transducer. Stable breathing was established with a CPAP level (“maintenance pressure”) sufficient to abolish inspiratory flow limitation. Airflow limitation was recognized by appearance of a plateau in the inspiratory flow profile or a failure to increase flow despite increased inspiratory effort (a decrease in esophageal pressure). $P_{\text{mask}}$ was rapidly reduced from maintenance pressure to a range of positive and, if necessary, negative pressures to induce variable degrees of inspiratory flow limitation over a 5-breath sequence before return to maintenance pressure. A minimum of three pressure drops to levels associated with flow limitation were obtained. $P_{\text{crit}}$ was derived from the extrapolation of the
linear Pmask - plateau flow rate relationship obtained during these pressure drops to zero flow (Figure 7). Pmask at zero flow = Pcrit.

Figure 7. Calculation of pharyngeal critical closing pressure (Pcrit) ie the mask pressure at zero air flow by linear regression.

3.9 Statistics

All studies

Continuous data are reported as means with standard deviation (±SD) (Study I-IV) or medians and interquartile range (IQR) (Study IV). Categorical data are expressed as median (range) or frequencies (proportions). A p-value of <0.05 was considered statistically significant. Statistical analyses were undertaken using Statistica 13 (StatSoft, Sweden) in Study I, Prism 7.0 (GraphPad, Software Inc., La Jolla, CA, USA) in Study III and IBM SPSS Statistics version 24 software (IBM, Armonk, New York, USA) in Study II and IV. Graphs were made using IBM SPSS Statistics (Study IV) or Prism 7.0 (GraphPad, Software Inc.) (Study I-III).

Study I

A comparison of means of the primary outcome variable was made using repeated measures ANOVA with two within factors: Time and Treatment/Drug. Time in Study I was defined to three occasions: 1. baseline before sedation, 2. during sedation and 3. recovery from sedation. Treatment being the two study drugs: dexmedetomidine and propofol. If significant differences were revealed by ANOVA pairwise comparisons were made. Sphericity was checked with Mauchly’s test and if found to be significant the p-value was adjusted.

A paired samples t-test was used when comparing the means of one variable between the two study groups, sedated with dexmedetomidine or propofol.
Study II

The primary outcome variable, Pcrit, was compared between the two study groups using repeated measures ANOVA with two within factors: Time and Drug. Time being defined as the two sedation levels that were aimed for: low infusion rate and moderate infusion rate. Drug being the two drugs studied, dexmedetomidine and propofol. The Winsorizing method was employed to replace very negative Pcrit values, a sign of an airway highly resistant to collapse, as a means of reducing the effect of extreme outliers when comparing groups. Repeated measures ANOVA was also employed for other variables with continuous data at varying time intervals. A paired samples t-test or a Wilcoxon signed-rank test was used when comparing the means of one variable measured at one occasion between the two study groups, sedated with dexmedetomidine or propofol. A Sign test was employed to compare categorical ordinal data between groups.

Study III

An independent samples t-test was used to compare partial pressure of arterial CO$_2$ (PaCO$_2$) between normal ventilation and hyperventilation.

Study IV

Continuous variables were compared with an independent samples t-test or Mann-Whitney U-test as appropriate. The Mann-Whitney U test was employed for the primary outcome variable, median lowest SpO$_2$ during intubation. Categorical variables were compared using the Pearson Chi-square test.
4 SUMMARY OF RESULTS

Study I

In Study I we investigated the effect of light to moderate sedation with dexmedetomidine and its effect on HVR and HCVR in healthy young men, and compared it to sedation with propofol, in a randomized crossover study design.

We found that dexmedetomidine sedation reduced both the hypoxic and hypercapnic ventilatory responses (Figure 8), indicating that dexmedetomidine sedation interacts with both peripheral and central regulation of breathing. The magnitude of effect by dexmedetomidine was similar to that of propofol sedation at equipotent levels of sedation, as assessed by clinical bedside testing.

Figure 8: Hypoxic and hypercapnic ventilatory responses during dexmedetomidine or propofol sedation. During sedation with dexmedetomidine and propofol, the hypoxic (A) and the hypercapnic (B) ventilatory responses were reduced. Data analyzed with repeated measures ANOVA followed by planned comparison between baseline and sedation for both drugs. n=9 for HVR and n=10 for HCVR. * P<0.05, **P<0.01. HVR=Hypoxic ventilatory response, HCVR=Hypercapnic ventilatory response.

An incidental finding of upper airway obstruction and apnea during dexmedetomidine sedation was done during Study I that evoked the idea of Study II.
Study II

Upper airway collapsibility was evaluated measuring passive pharyngeal critical closing pressure (Pcrit) during sedation with dexmedetomidine and compared to sedation with propofol in a randomized crossover study design. The sedative drugs were administered in two different set doses, at low and moderate infusion, aiming for Pcrit measurement at light and deep sedation with dexmedetomidine or propofol.

<table>
<thead>
<tr>
<th>Participants (n = 10)</th>
<th>Dexmedetomidine</th>
<th>Propofol</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Moderate</td>
</tr>
<tr>
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<td>&lt; -15</td>
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</tr>
<tr>
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<td>2.3</td>
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</tr>
<tr>
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</tr>
<tr>
<td>6</td>
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</tr>
<tr>
<td>10</td>
<td>&lt; -15</td>
<td>&lt; -15</td>
</tr>
</tbody>
</table>

Table 1: Obtained Pcrit values for all participants during low and moderate infusion of dexmedetomidine or propofol aiming for light and deep sedation. When no flow limited breaths or a profoundly negative Pcrit, indicative of a highly resistant airway, was found Pcrit is described as < -15 cmH2O. Airway measurements in participant #8 were only made during dexmedetomidine sedation.

No systematic difference in passive pharyngeal closing pressure between dexmedetomidine and propofol could be demonstrated at either infusion rate of sedation (p = 0.72) (Table 1).

Three participants also displayed clinically significant episodes of apnea lasting for up to 70 seconds during induction of sedation with both drugs (Figure 9).
We investigated the change of arterial blood gases and pH over time during apneic THRIVE oxygenation in patients undergoing elective laryngeal surgery of short duration in general anesthesia, also evaluating if PaCO$_2$ was consistent with transcutaneous CO$_2$ (TcCO$_2$) and ETCO$_2$. Patients were randomized to hyperventilation or normoventilation during preoxygenation as an attempt to extend the apnea time by lowering PCO$_2$ voluntarily prior to anesthesia induction.

Oxygenation was maintained for all patients and none had a SpO$_2$ below 91%. The mean (SD) increase in arterial CO$_2$ level was 0.24 (0.05) and end-tidal CO$_2$ was 0.12 (0.04) kPa/min. Hyperventilation lowered PaCO$_2$ initially but there was no difference in PaCO$_2$ or TcCO$_2$ after five minutes. Transcutaneous and arterial CO$_2$ levels correlated well. No difference could be seen between the two modes of CO$_2$ measurement. THRIVE functioned as sole means of oxygenation for the duration of 30 minutes but monitoring of CO$_2$ levels and pH is recommended.
Study IV

In 80 patients randomized for preoxygenation with either THRIVE or traditional facemask during rapid sequence induction of anesthesia, a comparison was made regarding the median lowest \( \text{SpO}_2 \) during intubation and number of patients desaturating below 93%.

![Graph showing lowest \( \text{SpO}_2 \) during intubation vs apnea time with THRIVE and facemask preoxygenation.]

**Figure 10.** For each subject, the lowest peripheral oxygen saturation \((\text{SpO}_2)\) attained vs apnea time during intubation when using THRIVE or facemask preoxygenation. \((\text{THRIVE} = \text{transnasal humidified rapid-insufflation ventilator exchange})\).

There was no significant difference in median lowest \( \text{SpO}_2 \) during intubation between groups \((p = 0.097)\). Five patients (12.5%) desaturated below 93% in the facemask group vs none in the THRIVE group \((p = 0.019)\) (Figure 10) indicating a possible benefit with THRIVE oxygenation during rapid sequence induction.

**SUMMARY**

We have established that dexmedetomidine affects regulation of breathing, upper airway collapsibility and can induce apnea at a clinically relevant level of sedation. Using a crossover blinded study design in volunteers, we further show that the reduced ventilatory responses to hypoxia and hypercapnia as well as upper airway collapsibility were affected to a similar degree during dexmedetomidine as propofol sedation.

A high flow nasal oxygenation device has been demonstrated to maintain oxygenation and cause a slower rise in arterial PCO\(_2\) than earlier studies making it possible to extend safe apnea time. It could, therefore, serve well for shorter surgery and opens for the possibility of increased safety when used for preoxygenation if apnea is prolonged due to difficulty to intubate.
5 DISCUSSION

In this thesis, we show that dexmedetomidine, an anesthetic compound described as having minimal effect on respiration and the upper airway, reduces the control of breathing and affects upper airway patency to a similar extent as propofol. Moreover, high-flow nasal oxygenation with the THRIVE technique has been demonstrated to constitute a feasible way of oxygenating patients during apnea and to reduce the number of patients desaturating compared to facemask preoxygenation when used in RSI anesthesia. Thus, using THRIVE during apnea enables a shift towards continuous oxygenation during airway management rather than preoxygenation alone.

In more detail, we have for the first time in humans shown that dexmedetomidine sedation impairs regulation of breathing to an extent similar to propofol (Study I). This was done in a crossover design using propofol as an active comparator. Although this finding was unexpected, when looking at clonidine, another $\alpha_2$-agonist, it was found to be in line with previous observations made during sedation, in either humans or other species but in contrast to an unaffected oxygen chemosensing reflex in dogs \cite{78,81,82}. While there may be species-dependent differences in the effect of anesthetic agents on the carotid body, it seems reasonable to suggest that the observation in humans of an interference with regulation of breathing during hypoxia most likely is due to an interaction with $\alpha_2$-adrenergic signaling in the carotid body \cite{120}. There is experimental support for this view based on the presence of $\alpha_2$-adrenoceptors in carotid body of cats and rabbits and a reduction of hypoxic response by $\alpha_2$-agonists \cite{77,78}. Finally, unpublished data from our own laboratory have also confirmed the presence of $\alpha_2$-adrenoceptors in the human carotid body.

Dexmedetomidine sedation also interferes with central regulation of breathing to a similar extent as propofol sedation. This was illustrated by a similar reduction in hypercapnic ventilatory response by the two drugs at an equipotent level of sedation. Propofol has previously been shown to reduce the ventilatory response to both hypoxia and hypercapnia at sedative doses and our findings in Study I thus confirm these previous observations \cite{48,51,121}.

Possible mechanisms for the reduced ventilatory responses during hypoxic and hypercapnic challenges, other than affecting the chemoreceptors, may consist of a direct action on the respiratory regulatory system in the brainstem or secondary effects to sleep induced by the drug. Sleep in itself is known to reduce the chemoreceptor reflexes \cite{38,47}. The oxygen sensing reflex has been found to be reduced related to sleep stage with a more profound reduction during REM sleep than non-REM sleep in men \cite{43,122}. Dexmedetomidine-induced sedation resembles natural recovery sleep, therefore, the impairment of respiratory regulation might originate from the induced sleep rather than direct effects of chemoreceptors \cite{71}. The model of hypoxic ventilatory test used in Study I does not allow for determination of whether peripheral chemosensitivity or central conversion of input from chemoreceptors into ventilator output is affected. Yet, the magnitude of the reduced ventilatory response was
similar to that of propofol sedation, a drug widely used for sedation with a different molecular target than dexmedetomidine, that was used as a comparator in Study I. Propofol primarily interacts with central GABA-ergic signaling and in addition interferes with cholinergic hypoxic sensing in the carotid body 49.

While examining the hypoxic and hypercapnic ventilatory responses during dexmedetomidine and propofol sedation we made an incidental finding that many of the volunteers displayed signs both of an obstructed airway and apnea when sedated with dexmedetomidine. We also found that airway obstruction had previously been reported during administration of dexmedetomidine and another α2-adrenergic agonist, clonidine 72,74,82,85,123,124. These facts led us to conduct Study II in which we examined upper airway collapsibility during dexmedetomidine sedation, using propofol as a comparator.

In Study II, Pcrit during dexmedetomidine sedation at two different sedation levels was examined for the first time in adults. The study was conducted in a crossover design comparing dexmedetomidine to propofol sedation. No systematic difference in upper airway collapsibility between dexmedetomidine and propofol sedation was found which is in accordance with findings from drug-induced sleep endoscopy using either dexmedetomidine or propofol. In these examinations, no difference in anatomic site or degree of airway obstruction could be seen with the two drugs 125-127. Previous magnetic resonance imaging studies have shown modest but statistically significant reductions in upper airway dimensions but less need for airway maneuvers and artificial adjuncts to keep a patent airway during sedation with dexmedetomidine compared to propofol sedation 89-91.

Propofol, on the other hand, is a drug well known to reduce upper airway patency 21,22. An earlier study of upper airway collapsibility by Eastwood and colleagues showed a more consistent, but modest, increase of Pcrit with an increased level of propofol sedation than that seen in Study II 21. The participants of the Eastwood study were recruited independent of vulnerability to upper airway collapse and, although not reported, may have had more homogenous anatomical airway features and propensity to airway collapse than participants in Study II, which may have influenced the result.

In Study I and II, clinically significant periods of apnea occurred during both dexmedetomidine and propofol sedation. This is actually in line with previous findings of irregular breathing and apnea that have been reported during administration of dexmedetomidine and clonidine 72,85,123,124. Alpha2-adrenoceptors are widely distributed in the central nervous system including parts associated with respiratory control 39. Stimulating these receptors reduces the firing rate of central neurons and causes disturbance in respiratory pattern that is not dependent on the carotid body. This suggests an effect on central α2-adrenoceptors, that affects the rhythm of breathing, increasing the likelihood that dexmedetomidine exerts a similar effect in these locations 83,128. In both studies, apnea periods occurred during administration of the bolus dose with both dexmedetomidine and
propofol in the same two vs. three participants, perhaps indicating that sensitivity to a rapid rise of plasma concentration of drug varies between individuals.

In Study I we aimed for a light to moderate level of sedation as assessed by sedation scale, verified by bispectral index score (BIS), in order to mimic a clinical situation. The sedation level was found to be in agreement according to clinical assessment between groups but BIS levels were found to be higher during dexmedetomidine sedation than propofol sedation which diverges from earlier studies showing BIS values to be lower at clinically assessed equal sedation levels [129]. A comparison of regulation of breathing was therefore found to have been evaluated at equivalent sedation levels in Study I but the effect of deep sedation has not been examined.

In Study II we aimed to evaluate airway collapsibility at two different sedation levels but in order not to disturb airway measurements clinical assessment of sedation level had to be limited. Instead, after administration of the initial bolus dose sedation was administered in two different set doses of drug, low and moderate infusion, aiming for light and deep sedation. Sedation was more profound and BIS levels were significantly lower during propofol than dexmedetomidine sedation at both infusion rates and differed also in sedation scale score during moderate infusion rate. Despite this difference in level of sedation, we found a similar degree of airway collapsibility during dexmedetomidine and propofol sedation. However, we cannot rule out a further increased airway collapsibility during dexmedetomidine sedation at a deeper level of sedation, corresponding to the BIS levels achieved in the propofol group. On the basis of this, close respiratory supervision during sedation when the patient relies on spontaneous breathing is of utmost importance and should be extended until recovery considering the long-lasting effects of dexmedetomidine.

In the studies we have conducted, there is surprisingly little difference both in the effect of central and peripheral regulation of breathing and in airway collapsibility when comparing dexmedetomidine and propofol sedation. Regarding the character of sedation, the participants in Study I were slightly more arousable during dexmedetomidine sedation but in agreement with the longer elimination half-life, took longer to mobilize from bed to sitting position and revert to ordinary daily life. Subjectively, when given a choice all participants in both Study I and II would have preferred sedation with propofol. Hence, when considering these facts the description of dexmedetomidine as an ideal sedative drug for procedural sedation or use in an outpatient setting must be challenged.

In both Study I and II a randomized crossover design and standardized settings were applied, thus comparing regulation of breathing and airway collapsibility with each participant serving as his or her own control. A crossover study design diminishes between-subject variability, including the well-known large inter-individual variation in HVR, and with only the sedative drug differing between examinations, the number of participants can be reduced. In order to minimize the effect of previous exposure interfering with the study results participants in both Study I and II were randomized to the order in which drugs were administrated. However, the crossover design carries a risk of losing participants during conduction of the study. One
subject in each of Study I and II did not participate in the second part of the examination. It is possible that these subjects represent individuals who find these situations more stressful and that inclusion of data emanating from such individuals might influence the result.

In Study III high-flow nasal oxygenation with the THRIVE technique was used as the sole mode of ventilation during laryngeal surgery and a description of arterial gas exchange and pH over time was reported for the first time with this new technique. We showed that oxygenation is well maintained for up to 30 minutes in normal to light overweight patients with moderate systemic disease and that the rate of increase in PaCO$_2$ is lower than in earlier studies of apneic oxygenation making it possible to prolong the apneic period in a safe fashion. The increase in end-tidal CO$_2$ was in good agreement with the rate of rise found in the Patel and Nouraei study (Figure 11) $^{106}$.

Figure 11. The rate of rise of carbon dioxide levels under different apnea conditions. Figure adapted from Patel and Nouraei 2015. 1. airway occlusion 2-4. classical apneic oxygenation low flow of O$_2$ 5. low-flow O$_2$ (0.5 L/min) intra-tracheal cannula 6-7. THRIVE O$_2$ 40-70 L/min. 8. high-flow O$_2$ (45 L/min) intra-tracheal cannula. THRIVE = transnasal humidified rapid-insufflation ventilatory exchange. Red diamond = arterial carbon dioxide partial pressure (PaCO$_2$), blue square = end-tidal carbon dioxide partial pressure (ETCO$_2$) 94,95,99,106,107,130-132.
Transnasal humidified rapid-insufflation ventilatory exchange constitutes an alternative to jet-ventilation or mechanical ventilation with a tracheal tube and provides excellent conditions for surgery not obscuring the surgical field. However, an addition to standard perioperative monitoring is necessary in order to control PCO$_2$ levels and pH since end-tidal CO$_2$ levels cannot be measured during THRIVE oxygenation. Transcutaneous and arterial CO$_2$ levels were found to correlate closely in Study III and offer alternative ways of monitoring. Keeping CO$_2$ levels and pH under control is strongly recommended if THRIVE is to be employed as sole mode of ventilation during surgery in order not to challenge the circulation which has proven to be a risk in earlier studies of prolonged apnea$^{95,100}$.

The first prospective randomized controlled study regarding patients requiring RSI intubation for surgery was conducted in 2016 in parallel with Study IV and published in 2017$^{133}$. Arterial partial pressure of oxygen during intubation was compared in 40 patients randomized to pre-oxygenation with either the traditional tight occluding facemask or THRIVE. When comparing PaO$_2$ between groups THRIVE was found not to be inferior to traditional facemask preoxygenation but a benefit for THRIVE could not be demonstrated. In Study IV we compared SpO$_2$ during intubation in 80 emergency surgery patients randomized to either facemask or THRIVE preoxygenation. We found no difference between groups regarding our primary outcome, median lowest SpO$_2$, but a lower incidence of patients desaturating below the predefined limit in the THRIVE group compared to the group preoxygenated with facemask, indicating that this novel technique might be of benefit when employed during RSI induction.

There are conflicting results from studies using THRIVE for pre-oxygenation in patients who are critically ill showing both a higher median level of lowest SpO$_2$ during intubation and a decreased number of patients desaturating whereas in other studies no improvement was found$^{108,134-138}$. The lack of improvement possibly reflects the underlying lung pathophysiology in the critically ill patient population resulting in lower FRC and increased V/Q mismatch combined with higher O$_2$ consumption that cannot be overcome with a high fraction of inspired O$_2$$^{139-141}$. Critically ill patients may therefore not have the same benefit of pre-oxygenation with the THRIVE concept. Nevertheless, since comparable levels of desaturation occurred even in severely hypoxemic patients this implies that high-flow nasal catheter is not an inferior alternative for pre-oxygenation even in this category of patients$^{138}$. Recently, apneic oxygenation used during intubation was evaluated in a meta-analysis approach that found evidence for a reduced risk of hypoxemia in patients being intubated for reasons other than respiratory failure but a lack of benefit in patients with respiratory failure$^{142,143}$ . Hence, there is increasing evidence of benefit using high-flow nasal oxygenation for preoxygenation but further investigation is essential to define subgroups that might require alternative modes of preoxygenation, such as maintaining non-invasive ventilation.

Studies referring to apneic oxygenation with high-flow nasal oxygenation use different methods and rates of oxygen flow varying from 5-70 L/min of oxygen. When evaluating high-flow nasal oxygenation the rate of oxygen flow, therefore, needs to be taken into
consideration since it may affect the result. Heated and humidified oxygen with a flow of 30-70 L/min reduces dead space, creates a positive airway pressure correlating with the rate of flow that possibly increases the FRC and provides wash out of the upper airways. The same effect cannot be expected with an oxygen flow of 5-15 L/min that is dry and of room temperature. The results from this thesis are therefore valid for clinical situations when a high-flow concept with an oxygen flow of 30-70 L/min is used. A high flow and positive airway pressure may furthermore have unwanted side effects in the form of gastric insufflation. In Study IV no signs of gastric regurgitation were detected but since the occurrence of regurgitation is rare and the number of patients included in the study was limited this was an expected finding. Gastric insufflation of gas and thereby an increased risk of regurgitation has been a concern when using THRIVE and therefore an assessment of its occurrence would be of value.

Study IV evaluating THRIVE for RSI induction was as a first step in assessing whether the method should be implemented for routine clinical use. Prediction of the difficult airway is unreliable with the methods we have at hand and therefore the majority of cases presenting intubation difficulty are unanticipated. Moreover, the THRIVE method is probably of limited value as a rescue maneuver when desaturation is already present but needs to be initiated before anesthesia induction. Since we cannot reliably identify patients with an increased risk of a prolonged intubation procedure followed by hypoxia it seems reasonable that if THRIVE is implemented for RSI induction it should be used for all patients.

5.1 Methodological considerations

Studies in this thesis have strengths and limitations that might interfere with results and interpretation of findings.

In Study I the oxygen sensing chemoreflex was examined with HVR. There are different techniques for testing the HVR. The two dominating techniques today are the progressive (ramp) and the step technique. The techniques differ in how quickly the hypoxic level is reached, the depth and duration of hypoxia and how isocapnia is maintained. Ramp hypoxic tests can be achieved by rebreathing from a circuit/bag causing hypoxia to develop progressively for 5 up to 15 minutes controlling CO\textsubscript{2} with an absorber. In step hypoxic tests the inhaled fraction of O\textsubscript{2} is lowered instantly to induce a change of the end-tidal gas concentration either with computer-controlled dynamic end-tidal forcing or manually. CO\textsubscript{2} is added to maintain isocapnia as ventilation increases. We used a step hypoxic test and manually controlled the inhaled fraction of gases.

Airway obstruction and apnea occurred during dexmedetomidine and propofol sedation in Study I. The apnea periods occurred during induction of sedation when administering the bolus dose and are, therefore, less likely to have affected the measurements during the ventilatory tests. However, data from one participant sedated with dexmedetomidine was excluded from analysis due to repetitive upper airway obstruction and irregular breathing during the hypoxic ventilatory test.
In Study II the number of participants included may have been insufficient to rule out a difference in upper airway collapsibility during sedation with propofol and dexmedetomidine. The fact that some participants had an airway highly resistant to collapse regardless of sedative level or drug and the difference in sedation level between groups contributed to difficulty of interpreting the results. The study can consequently be regarded as descriptive and be used to design a future study to further clarify pharyngeal collapsibility with dexmedetomidine at various sedation levels and in different phenotypes. However, if equal sedative levels were to be achieved using BIS as a target an infusion rate higher than recommended for sedation would be necessary.

Recruitment of participants to Study II was challenging as it required examinations on two different days and invasive monitoring which will present a challenge also in future studies.

A larger number of test subjects combined with genioglossus EMG recordings during dexmedetomidine sedation would be of additional value to relate the level of sedation to its effect on pharyngeal neuromuscular activity and collapsibility and could provide further insight into underlying mechanisms causing airway collapsibility.

In Study III only ASA class 1-2 non-obese patients (BMI< 30) were included. Conclusions on applicability in other patient groups such as those with more pronounced illnesses and obesity may therefore not be drawn and should ideally be examined separately. In line with this, Study IV contained non-pregnant, non-obese patients without dependency of non-invasive ventilation. An evaluation of high-flow nasal oxygenation in the obese, the pregnant and other categories of patients would be of interest to evaluate if it is of benefit for all.

Furthermore, study IV compared the lowest SpO\textsubscript{2} during intubation, which might be of limited value since the data will almost certainly be skewed. We also compared the number and degree of desaturation/hypoxia which might be more interesting when comparing traditional facemask preoxygenation and THRIVE. The predefined desaturation limit we chose was 93% but it could have been defined as <90% which previously has been a more common approach. If we would have defined desaturation as <90% we would have found 10% of patients desaturating in the facemask group instead of the 12.5% reported in our study. Finally, study IV was performed during regular daytime and weekdays, with staff designated to run the study present at all times. The results may be influenced by the fact that patients presenting during daytime may differ from patients appearing at on-call hours. During on-call hours the number and skill of staff are more varied and this may also affect the outcome.

5.2 Clinical implications

In this thesis, dexmedetomidine and a high-flow nasal oxygenation device were investigated in order to elucidate their effects on respiration and airway physiology with the overall goal of improving airway safety. The findings are relevant for daily clinical work, both
perioperatively and in the intensive care. Because of the risk of serious injury associated with anesthetic airway complications continued efforts for a further reduction in their incidence is of utmost importance.

Increased knowledge on the pharmacodynamic profile of dexmedetomidine, regarding both breathing and upper airway integrity, will potentially improve airway safety by highlighting the need for close surveillance during sedation when patients rely on spontaneous breathing. Even if resting ventilation is preserved and oxygen usually administered during sedation both airway obstruction and apnea put the patients at risk of hypoxia. With diminished hypoxic and hypercapnic chemoreflexes, hypoxia can be seriously aggravated. Notably, dexmedetomidine is rarely given as a single drug. Additive effects of other drugs when combined with dexmedetomidine, such as opioids, will further increase the likelihood of airway complications during sedation but also in the postoperative period.

There is a general trend of increased outpatient surgery, and accompanying increase of anesthesia and sedation for these patients. Sedation can also be administered by caregivers other than anesthesiologists, not as trained in managing the airway and detecting hypoventilation or used to administer anesthetic drugs. These two facts might increase the risk of respiratory complications and reduce safety during sedation and anesthesia. Especially if we are under the perception that dexmedetomidine does not compromise the airway or interfere with regulation of breathing. A more elaborate pharmacodynamic profile gives a better opportunity to adjust sedation and monitoring and maintain an adequate level of patient safety.

In line with prior advancements in airway management, the novel technique of high-flow nasal oxygenation presents potential benefit with extended safe apnea time and prevention of desaturation during intubation in that way opening for an opportunity to improve airway safety.

Before introducing THRIVE for clinical use on a regular basis there is an obligation to also examine its capacity to maintain oxygen saturation in other types of patients than the ones examined so far, in particular patients at high risk for desaturation such as the obese, the pregnant and the critically ill presenting for surgery. There is also a need to evaluate its generalizability when it is spread for use by many anesthesiologists in various patients. The fact that the airway has to be patent at all times for the technique to work has to be kept in mind in order to avoid drawbacks when using high-flow nasal oxygenation, as airway obstruction will impede apneic oxygenation. Events of airway obstruction and desaturation have been reported upon introduction of apneic oxygenation and therefore this needs to be emphasized when introducing the technique for all users. Finally, it should be pointed out that apneic oxygenation using THRIVE is not a replacement for good airway management.
6 CONCLUSIONS

Based on this thesis the conclusions are that:

- Both hypoxic and hypercapnic regulation of breathing is reduced during sedation with dexmedetomidine and to a similar extent as sedation with propofol.

- A difference in upper airway collapsibility could not be demonstrated between dexmedetomidine and propofol sedation. Furthermore, episodes of clinically significant apneas during sedation with both drugs were displayed.

- Apneic oxygenation using THRIVE during laryngeal surgery is able to keep patients with mild systemic disease and a BMI<30 well oxygenated and with a pH at or above 7.13 for a period of 30 minutes. Thereby THRIVE makes it possible to extend the apneic window.

- Providing continuous oxygenation THRIVE has the potential to maintain oxygen saturation better than traditional facemask preoxygenation shown as a lower number of patients desaturating below 93%.
7 FUTURE PERSPECTIVES

This thesis presents new data on how regulation of breathing and airway collapsibility is affected by sedation with dexmedetomidine. However, dexmedetomidine still is of interest for sedation in various situations. Yet, one limiting factor for its use is its long-lasting effect compared to propofol. The effect of dexmedetomidine can be reversed using the α2-adrenoceptor antagonist atipamezole that currently is used in veterinary medicine but not yet approved for use in humans. In general, reversing any effect of drugs used to produce anesthesia would be ideal. To some extent, this is possible with naloxone for opioids and sugammadex for neuromuscular block. The addition of atipamezole, reversing the sedative effect and subsequent negative effects on the respiratory system could potentially reduce the time to recover postoperatively and possibly also reduce the risk of confusion and complications in the elderly, a steadily growing part of the surgical patient population. Finally, though known for its centrally mediated side effects, ketamine is another drug of interest that might preserve airway patency.

High-flow nasal oxygenation during apnea using THRIVE might actually entail a shift of paradigm regarding preoxygenation by conversion to continuous oxygenation during airway management. It has been shown to reduce desaturation and may add to safety of airway management in many situations in the emergency department, perioperatively and in the intensive care. As a first step towards implementation, a randomized controlled multicenter study using THRIVE in RSI anesthesia would be of great interest to evaluate the generalizability of the technique when it is spread for use by a large community of anesthesiologists providing anesthesia for emergency surgery. Studies including various categories of patients are required to establish if it is a method of preoxygenation that is of benefit to all.

The risk of oxygen-induced lung atelectasis and counteracting effect by positive airway pressure induced by high oxygen flows need further considerations. An increase in lung impedance has been demonstrated in spontaneously breathing individuals indicating an increased end-expiratory lung volume. However, when using THRIVE in apneic patients 100% oxygen is administered and absorption atelectasis is a possible consequence. The positive airway pressure generated by THRIVE may counteract this effect but the overall effect measuring atelectasis formation would be of interest. Another matter of concern dependent on the positive airway pressure when using THRIVE has been the possibility of gastric insufflation with an increased risk of regurgitation. In Study III we found no signs of gastric regurgitation but this finding cannot rule out possible gastric insufflation of gas. Examining gastric insufflation in a larger patient population during THRIVE would be of value to address patient safety issues especially if it is to be used in RSI of anesthesia in non-fasting patients.
Continuous improvement in airway management is an endless quest with the final goal of no patient coming to harm due to an inability of securing the airway during anesthesia. We firmly believe that an increased level of knowledge and research regarding mechanisms protecting the airway can contribute to reaching that goal.
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