Rapid-sequence induction of anesthesia and tracheal intubation (RSII): Effects of alfentanil on intubation conditions, release of stress hormones, and hemodynamic responses.

Thesis for the degree of Philosophiae Doctor (PhD)

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إهداء

إلى والدي رحمه الله وإلى والدتي الحنونه

لكم الفضل كله بعد الله سبحانه و تعالى

This work is dedicated to my father and mother, the credit goes to them in everything I achieve

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2. List of Papers

I Abou-Arab MH, Heier T, Caldwell JE. Dose of alfentanil needed to obtain optimal intubation conditions during rapid-sequence induction of anaesthesia with thiopentone and rocuronium. Br J Anaesth. 2007 May; 98(5):604-10

II Abou-Arab MH, Feiner JR, Spigset O, Heier T. Alfentanil during rapid sequence induction with thiopental 4 mg/kg and rocuronium 0.6 mg/kg: tracheal intubation conditions. Acta Anaesthesiol Scand. 2015 Nov; 59(10):1278-86.

III Abou-Arab MH, Rostrup M, Heier T. Dose requirements of alfentanil to eliminate autonomicresponses during rapid-sequence induction with thiopental 4 mg/kg and rocuronium 0.6 mg/kg.

3. Overview

Managing and securing the airway is a fundamental aspect of anesthetic practice, and studies have shown that direct laryngoscopic tracheal intubation is a potentially lifesaving procedure. However, laryngoscopy and tracheal intubation are also very potent noxious stimuli. The response of the airway muscles may be vigorous, stress hormones are released, and the autonomic hemodynamic responses may be significant. Under certain circumstances, and in certain groups of patient, such responses may not be well tolerated. Therefore anesthesiologists have over the years constructed various drug regimes in order to contain these potentially lethal physiological responses occurring during airway manipulation. When control of the airway must be performed rapidly, i.e. during rapid-sequence induction of anesthesia, the clinical situation is particularly challenging. This is because the noxious stimulation (i.e. laryngoscopy and tracheal intubation) may take place before the optimal effect of the drugs given is achieved. In order to overcome this problem, the doses of the anesthetic and neuromuscular blocking drugs may have to be increased when compared to routine drug regimens used during elective surgery. There is limited information in the literature regarding optimal dosing of anesthetic drugs during rapid-sequence induction and tracheal intubation (RSII). This thesis focuses on the advantageous effects of alfentanil under RSII-conditions when used in conjunction with standard induction drugs. The main aim of this project is to define a drug regime that is associated with a high probability of success when both optimal tracheal intubation conditions and hemodynamic control are needed.

4. Introduction

Anesthesia is a unique medical intervention where patients under the influence of certain drugs (anesthetics) are able to tolerate painful procedures, like surgical treatment. The ultimate goals of anesthesia are amnesia (inability of learning and remembrance) and immobility during noxious stimulation[1]. If these two requirements of anesthesia are met, it is assumed that the concentrations of anesthetics in the central nervous system are sufficiently high to render the patient unconscious as well[1].

Anesthetics depress to a variable extent respiratory function, i.e. impede the ability to breathe and to maintain a patent airway [2] [3]. Also, laryngeal and pharyngeal reflexes in anesthetized patients are responding inadequately if the airway is exposed to foreign objects [3] [4]. Therefore, there are multiple reasons why artificial devices may be needed during anesthesia in order to secure the airway and optimize oxygenation at all times. An endotracheal tube is one such device which is often used during anesthesia. The tube is placed in trachea under direct vision using a laryngoscope, i.e. during the induction of anesthesia. A distally located inflatable cuff prevents gas leakage when the patient´s lungs are ventilated via the endotracheal tube. Tracheal intubation is an extremely unpleasant experience in the unanesthetized state and the procedure therefore requires high concentrations of anesthetics.

4.1 RSII: Definition

In some clinical situations anesthetized patients are at risk of regurgitation of gastric content, i.e. when the stomach is not empty prior to anesthesia induction. Because airway protective reflexes are severely weakened by most anesthetics, aspiration of gastric content to trachea is a real danger if regurgitation should occur. Under such

circumstances airway control, i.e. tracheal intubation, must be undertaken rapidly in order to minimize the time period where the airway is unprotected during anesthesia induction. The tracheal intubation procedure will in such cases contain specific elements that are introduced in an orderly manner, from the time the patient enters the operating room until the airway is secured with a cuffed endotracheal tube and artificial ventilation is established. This specialized kind of anesthesia induction, which primarily is indicated to use in situations where aspiration of gastric content to the airway is imminent when the patient becomes unconscious, is called rapid-sequence induction and tracheal intubation (RSII). RSII is in this way defined by its purpose (avoiding aspiration of gastric content to the airway) and not by specific components of the algorithm used. This is because there is no consensus on how to perform this specialized kind of anesthesia induction[5].

RSII has been an integral part of anesthesia practice since Stept and Safar in 1970 [6] introduced a 15 steps procedure in order to avoid Mandelson's syndrome, i.e. aspiration of gastric-content to the airway in parturients[7], thus outlining the classic rapid-sequence induction and tracheal intubation procedure. The main components of the classic RSII are preparedness (equipment and drugs readily available), decompression of the stomach with a large-bore nasogastric tube, positioning the patient semi-sitting, preoxygenation, cricoid pressure to collapse and obstruct esophagus, rapid injection of a predetermined dose of the fast acting hypnotic drug thiopental and the short-onset neuromuscular blocking drug suxamethonium, avoidance of mask ventilation after cessation of spontaneous breathing because insufflation of air into the stomach might provoke regurgitation, and tracheal intubation within 60 s after injection of suxamethonium.

Although regurgitation of gastric content during induction of anesthesia primarily has been a concern with emergency conditions [7-13], and in particular when patients with bowel obstruction are anesthetized, many other clinical conditions have been associated with this potentially lethal anesthesia-related complication:

Gastroesophageal reflux disease, hiatal hernia, peptic ulcer, prior esophageal surgery, obesitas, trauma, pregnancy, diabetes, renal disease, pain, and food intake during the last hours prior to surgery [14]. RSII has also become a frequently used technique in ICU-patients when emergent tracheal intubation is needed [15].

4.2. RSII: Modifications of classic technique

Over the last 40-50 years the validity of various elements of the original RSII-procedure has been debated [16]. Although most steps are generally accepted in clinical practice even today, there is limited scientific evidence for any of the RSII components to be important when it comes to prevention of aspiration of gastric content to the airway. This is to be expected as aspiration is not a frequently occurring phenomenon, making it difficult to design clinical studies in order to investigate the efficacy of each of the RSII components. Because there is no definitive evidence supporting the use of any of the RSII components, many clinicians feel comfortable altering the classic procedure outlined by Stept and Safar in 1970 [16], and the term "modified RSII" has been introduced. A recent survey on how RSII is performed in teaching hospitals in US investigated the attitudes of clinicians (residents and attending physicians) regarding the use of central elements of the classic RSII procedure (preoxygenation, use of suxamethonium vs other neuromuscular blocking drugs, cricoid pressure, and mask ventilation prior to tracheal intubation) [14]. All respondents in the survey preoxygenated the patients prior to drug administration, suxamethonium was the preferred neuromuscular blocking drug, and cricoid pressure was applied by 90%. The only identified deviation from the classic RSII was how respondents dealt with mask ventilation. The majority of the clinicians in the survey allowed mask ventilation prior to tracheal intubation, both before and after administration of the muscle relaxants. The same result was obtained in a similar survey in England [17]. The reason given for testing mask ventilation was the potential ability to "enable escape wake-up".

Suxamethonium was preferred as neuromuscular blocker because it was believed that the effect would wear off quickly enough to prevent significant hypoxemia in case mask ventilation should be difficult, despite previous studies clearly suggest that this is not true [18 19].

4.3 RSII: Timing of drug administration

The term ”rapid-sequence” implies urgency, meaning that the time period during anesthesia induction where the airway is unprotected because of failing pharyngeal and laryngeal reflexes, should be shorter than normally required in elective cases. This is an element of the RSII-procedure that is subject of significant modifications [5 20]. Stept and Safar advised tracheal intubation to be performed within 60 s after injection of suxamethonium during RSII, apparently because their experience was that acceptable intubation conditions were achieved in most patients at that time point in thiopental-anesthetized patients[6]. This assumption was later confirmed when the onset time of suxamethonium at the laryngeal muscles was determined[21]. This is probably why”60 s” is a number most anesthesiologist would associate when asked about their opinion regarding the speed with which RSII should be performed. However, available RSII-related literature is not consistent regarding interpretation of this”60 s” limit, and the results accordingly difficult to interpret. When designing an RSII-study the appropriate use of this number ”60 s” would be to ensure that the intubation attempt is performed within 60 s after commencement of any drug administration[22]. Many investigators still claim they have employed an RSII procedure even after titration of the induction agent over a time span of 45 s. However, this technique implies that tracheal intubation is rather performed approximately 120 s after commencement of drug administration[20]. Data obtained in the latter kind of RSII-studies are consequently less relevant for clinical situations where the danger of aspiration during anesthesia induction is imminent.

An important RSII-related question is: How fast after commencement of drug

administration can tracheal intubation be safely performed? Interestingly, even in leading textbooks of anesthesia this question is not really asked [5]. The answer to this question is obviously dependent on the drug combination used during anesthesia induction. Studies indicate that acceptable intubation conditions can be obtained even if laryngoscopy is initiated less than 60 s after commencement of drug administration[22].

4.4 RSII: Physiological responses

4.4.1 Airway responses

The upper airway, which includes oral and nasal cavities, pharynx and larynx, is provided with sensory receptors located in mucosa[23 24]. These receptors serve an airway-protecting function against foreign objects[25]. Receptor stimulation activates reflex arches that run mainly in the vagal and glossopharyngeal nerves. The afferent part of the reflex ends in nucleus tractus solitarius in the brain stem, the efferent part results in increased muscular activity, either in striated (sneezing, coughing, temporary glottis closure, or laryngospasm) or in smooth muscles (bronchospasm). Tracheal intubation may provoke laryngospasm or bronchospasm, both potentially lethal responses, in lightly anesthetized individuals if the endotracheal tube is touching the vocal cords or mucosa of the lower part of the airway (subglottic)[26].

In order to avoid such airway responses patients should be deeply anesthetized during laryngoscopy and tracheal intubation. However, deep anesthesia will, on the other hand, deprive the patients from the protection active reflexes provide against potentially airway-occluding gastric content that might be regurgitated to the pharyngeal area during anesthesia induction in an RSII situation[3].

4.4.2 Release of stress hormones and hemodynamic responses

Laryngoscopy and tracheal intubation represent intense noxious stimuli that via vagal and glossopharyngeal afferents result in activation of the sympathetic nerve system and the hypothalamus-hypophysis-adrenal axis [27]. Apparently, stretching of pharyngeal-laryngeal tissues and stimulation of mucosal proprioceptors during laryngoscopy is the major cause of these autonomic responses[28]. Norepinephrine is released from cervical sympathetic nerve endings[29-31], epinephrine and norepinephrine from the adrenal medulla to the blood[32]. Vasopressin may also be released from the pituitary gland [33]. The response is exaggerated by secondary activation of the renin-angiotensin-aldosterone system[27]. Clinical studies show that the pressor response to laryngoscopy and tracheal intubation is even stronger than that elicited by surgical incision and intraabdominal manipulation[34 35]. The ultimate effect of these autonomic responses to mechanical stimulation of the airway is peripheral vasoconstriction and myocardial stimulation, the end result being increased cardiac output, hypertension, and tachycardia[36-38]. Studies of laryngoscopy with and without tracheal intubation suggest that most of the increase in arterial blood pressure occurs with laryngoscopy. Tracheal intubation adds to the tachycardic [39] but probably not the hypertensive response [38]. The intense autonomic stimulation provoked by laryngoscopy may cause cardiac arrhythmias, even in normal hearts [37 40-43].

Although there is agreement in the literature that hemodynamic responses to laryngoscopy and tracheal intubation are preceded by release of stress hormones [44], the relative importance of each individual hormone is uncertain. This is especially so with regard to RSII conditions, because all studies on the release 6of stress hormone after airway manipulations has been undertaken in elective cases. Most authors find a close relationship between blood concentrations of *norepinephrine* and arterial blood pressure or heart rate post tracheal intubation[29 30 32 38 45-48]. A relationship between release of *epinephrine* and hemodynamic responses to airway manipulation is less

clear than with norepinephrine. Derbyshire [32] and Miller [47] report a significant relationship between pre induction and post intubation values, but no such relationship was found by several other investigators [29 30 45 49-52] . However, they all report a striking decrease in the blood concentrations of epinephrine measured pre intubation, an effect apparently caused by the anesthesia induction agents. *Dopamine*, a precursor of norepinephrine, is also suspected to be involved in the hemodynamic responses to laryngoscopy and tracheal intubation[44]. However, no study has shown any change in the blood concentration of this catecholamine pre vs post stimulation [30 53-56]. Although most investigations have focused on the relationship between airway manipulation and catecholamines, other stress hormones may be involved in the autonomic hemodynamic responses occurring secondary to laryngoscopy and tracheal intubation. *Renin* is released from the juxtaglomerular apparatus of the kidneys in response to activation of the sympathetic nerve system. Angiotensin II may therefore be involved in the hemodynamic responses following laryngoscopy and tracheal intubation [57 58]. *Vasopressin*, a neurohypophysial hormone, is found to be released secondary to endotracheal intubation[35], but it´s role in the hemodynamic response to airway manipulation is not clear.

4.5 RSII: Special challenges

RSII deviates in several ways from induction of anesthesia in elective cases:

1. In 1986 Chraemmer-Jørgensen et al[59] compared hemodynamic responses to laryngoscopy and tracheal intubation occurring in two groups of elective surgical patients having identical anesthetics (precurarization with Pancuronium 0.015 mg/kg, thiopental 5 mg/kg, suxamethonium 1.5 mg/kg), but administered either in a rapid-sequence fashion (rapid succession of drug administration, tracheal intubation 60 s after suxamethonium) or according to standard procedure used in elective cases (thiopental over 15 s, 60 s later suxamethonium, laryngoscopy 60 s

after the neuromuscular blocking drug). The groups differed in two ways: Patients undergoing RSII were preoxygenated, and were not mask ventilated pre intubation. Those anesthetized with standard technique were not preoxygenated, but ventilated a short period of time with O2/nitrous oxide before tracheal intubation. The RSII group had significantly higher arterial blood pressure and heart rate post intubation than the group anesthetized with standard technique. Apparently, the RSII procedure is an independent risk factor of added stress during anesthesia induction, potentially influencing outcome in patients that do not tolerate hemodynamic responses to noxious stimulation well.

2. The reported success rate of RSII (correctly placed endotracheal tube on first attempt) is > 85% in adults [60] and approximately 80% in children [61], where numbers are based on data obtained from > 12000 patients treated with this technique in an Emergency Department. The frequency of serious complications during RSII is approximately 1% [61], and mainly related to development of hypoxemia prior to successful placement of the endotracheal tube, adverse drug reactions, or the need for cricothyroidotomy [62]. Awareness of a higher risk of serious complications in situations where RSII is needed adds tension to the atmosphere in the operating room, potentially affecting negatively the ability of the caretakers to focus on important issues related to anesthesia induction, especially correct technique when laryngoscopy is performed. Additionally, because intubation conditions often may be less than optimal in an RSII-setting, i.e. due to inappropriate drug dosing or timing of drug administration, more power may be exerted during laryngoscopy than in ordinary anesthesia induction situations. As there is an association between intensity of the noxious stimulation and magnitude of the release of stress hormones, hemodynamic responses may be greater during RSII than in elective cases[63]. Also, chances of laryngeal injury may be increased [64]. Accordingly, there are good reasons to believe that the emotional status of the anesthesia personnel may influence the outcome of RSII, but apparently no formal investigation has been conducted to study this specific issue.

3. In an RSII situation, where regurgitation is to be expected when the patient is anesthetized, it is even more important than in elective cases to check thoroughly the patient´s airway anatomy, and consider awake fiberoptic intubation in case the patient has an unfavorable Mallampati class airway[5 65]. This is a very difficult decision to make, and an experienced anesthesiologist should therefore always be present during the induction of anesthesia when RSII is needed.

4. Selecting the drugs to be used during RSII is demanding. First, the induction agent must be selected with care, and especially must the patient´s hemodynamic status be taken into consideration[5]. If the hemodynamic stability is questionable, then dosing of the induction agent may also be challenging. Second, a controversy exists regarding which neuromuscular blocking drug to use during RSII. The majority of anesthesiologist still prefer suxamethonium for muscle relaxation, despite several reports that rocuronium in conjunction with a sedative (thiopental or propofol) in many cases provides similar intubation conditions as with suxamethonium, especially if higher doses than standard are administered [66 67]. Some clinicians may also choose suxamethonium because of its short duration of action, assuming that the patient´s ability to breathe will recover before significant hypoxemia occurs in case tracheal intubation or mask ventilation should be impossible. Unfortunately there is no reason to believe that the effect of suxamethonium will wear off quickly enough [18 19]. In case a can´t ventilate – can´t intubation situation should occur, the patient would probably be better off being paralyzed with rocuronium, because the reversal agent sugammadex can terminate the effect of rocuronium completely within 2 min, irrespective of the time gap between administration of the blocker and the reversal agent[68]. Another argument against the use of suxamethonium in many RSII situations is the fact that hypoxemia occurs much earlier than after a nondepolarizing neuromuscular blocking drug, probably because of higher oxygen expenditure [69]. The main argument in favor of suxamethonium is that the onset time is significantly shorter than for any other available neuromuscular blocking drug[21]. This means that

acceptable intubation conditions will be achieved earlier than with other blockers, which may be important in situations where the time period between drug administration and tracheal intubation should be as short as possible.

5. In certain RSII situations there is a combined need of optimal intubation conditions and minimal hemodynamic perturbations. Relevant clinical scenarios would be to provide anesthesia to patients with myocardial insufficiency, patients who need urgent surgery for open eye injury, ruptured abdominal or cerebral aneurisms, intracranial hypertension, or C-section where serious preeclampsia is present [44] [70]. In such cases an adjuvant drug will be needed together with the hypnotic and neuromuscular blocking drug. An opioid is the most frequently administered adjuvant drug when attenuation of hemodynamic responses to airway manipulation is needed. However, the doses needed are not clearly defined[71], especially if it is preferable to complete tracheal intubation within a shorter time frame than 90 s.

4.6 RSII: Drug selection

Inhaled anesthetics may be called complete anesthetics because the basic goals of anesthesia, i.e. render the patients unconscious, amnesic and immobile, can be achieved with reasonable blood concentrations[1]. RSII has been performed with the inhaled anesthetic sevoflurane, applying the vital capacity single-breath technique [20]. In that study the success rate of tracheal intubation 60 s after the administration of the neuromuscular blocking drug was equal compared to a technique using iv propofol. Also, the induction time (time to achieve unconsciousness) was equal, approximately 40 s when a titration technique was used to induce unconsciousness. However, a significant disadvantage using an inhaled anesthetic is that the patient must be cooperative and able to maintain deep inspiration for sufficient amount of time.

However, in an emergency situation where RSII is needed, normal clinical practice is to use iv drugs to ensure that sufficient blood concentrations of the anesthetic are

attained rapidly [5 72]. Standard practice is to administer, in rapid succession, a sedative to make the patient unconscious and a neuromuscular blocking drug to attenuate muscular responses when manipulating the airway during laryngoscopy and tracheal intubation. Adjuvant drugs may also be indicated, in order to completely suppress responses of the airway in case high doses of the neuromuscular blocking drug must be avoided, or if hemodynamic stability must be ensured at all times during anesthesia induction [24]. Therefore, frequently three different types of drugs will be administered when RSII is performed: A sedative, a neuromuscular blocking drug, and an adjuvant. There are reasons to believe that use of an adjuvant drug is associated with better patient outcome. In a survey including 100 000 patients the relative odds of dying within 7 days of surgery was approximately 3 times as great with one or two anesthetics when compared to employment of three or more drugs[73].

4.6.1 Pharmacokinetic and pharmacodynamic aspects

Appropriate bolus dosing of drugs in an RSII setting requires knowledge regarding pharmacokinetics (PK) and pharmacodynamics (PD) of the individual drugs used. PK and PD are mostly described using mathematically based compartment models[74]. PK variables determine the plasma concentration after drug administration, while PD strictly describes the physiologic response to a given effect compartment drug concentration (i.e. drug sensitivity). Some PK/PD variables are of special interest when drugs are administered as boluses: **1. Central volume of distribution (central compartment).** This is the fluid volume into which the injected drug mass mixes instantaneously (within 30-45 s) to reach a maximum initial plasma concentration. Drug delivery to the effect compartment increases with increasing drug concentration in the central compartment due to larger concentration difference between blood/plasma and effect site. Therefore, a small initial volume of distribution will enhance drug effect. **2**. **Effect hysteresis**. After drug administration there will be a delay (hysteresis) between attainment of blood/plasma drug concentration and detectable drug effect, because some time always is needed for the drug to reach it´s

effect compartment. This delay will vary between drugs, dependent on blood flow to the organ where the effect site is located and physiochemical factors (for example lipid solubility). The equilibration process between blood/plasma and effect compartment is mathematically represented by a rate constant called Keo[75]. Keo can be determined by an iterative procedure that collapses the drug concentration-hysteresis loop. A large Keo, as opposed to a low value, concur a more rapid equilibration and a relatively larger amount of delivered drug to the effect compartment per unit time because the equilibration process takes place while plasma concentration is still high[76]. **3. Drug elimination from blood/plasma**. The speed with which the drug is leaving blood/plasma is determined by drug clearance (elimination of drug out of the body) and rate constants of equilibration processes between blood/plasma and peripheral compartments. A rapid decline in plasma concentration after bolus administration is associated with rapid attainment of maximum drug concentration in the effect compartment[77]. **4**. **Pseudoequilibrium**. At some time point after drug bolus administration the concentrations in blood/plasma and in effect compartment are equal. This time point is called pseudoequilibrium and represents the time point after bolus administrations where the effect compartment concentration is at it s maximum[78]. Prior to pseudoequilibrium the blood/plasma concentration is higher than in the effect compartment, after pseudoequilibrium it is lower. The time point of maximum effect after a drug bolus is determined by the relative influence of factor 2 and 3 combined. The pseudoequilibrium concentration can be calculated after any drug dose when the drug´s Keo and distribution kinetics are known. Further, it is possible to estimate a drug´s distribution volume at pseudoequilibrium and therefore, if the effect compartment concentration that is associated with an intended drug effect is known, then the optimal bolus dose to be administered can easily be calculated (drug concentration x pseudoequilibrium volume = drug dose). **5. Drug sensitivity and drug potency.** Drug sensitivity is strictly the number of drug molecules that must be present at the effect site in order to obtain a certain drug effect. Because this number cannot be determined, by

convenience, drug sensitivity is defined as the blood/plasma concentration at steady state conditions (no net movement of drug in or out of effect compartment) that is associated with 50% of maximum drug effect (Css50)[74]. Css50 represents the drug´s potency, a variable useful when the effect of different agents within the same class of drugs is to be compared. However, the importance of Css50 in a clinical sense has limitations. First, it can only be determined if the drug effect can be recorded on an interval scale. If the effect function is binary (for example: ability to blunt physiological responses to tracheal intubation), then Css50 cannot be determined individually and must be approximated by estimation of a concentration associated with effect/no effect in 50 % of individuals[79]. Second, in order to determine Css50, it must be possible to determine 0 and 100% effect of the function measured. Third, in clinical practice an anesthesiologist operate with drug dose and not drug concentration, because the latter will not be available at the time induction of anesthesia is to take place. Drug potency based on dose rather than blood concentration would therefore be preferable clinically. Dose-effect relationships after bolus administration involve both PK and PD, but could potentially be modeled using simulations if initial volume of distribution, Keo, and Css50 are all known[80]. Unfortunately, limited information on this issue is available in the literature. Fourth, Css50 is not directly time dependent, i.e. time point of maximum drug concentration at the effect site after bolus dosing varies between drugs due to variability of Keo. Potency differences observed between drugs may therefore just be apparent, simply because the stimulus eliciting the physiologic response that the drugs are supposed to suppress is applied at a time point very different from a drug's pseudoequilibrium. Fifth, sometimes, when a response to a stimulus (for example: sympathetic responses to tracheal intubation) cannot be tolerated by the patient, it would be more clinically relevant to determine Css95 than Css50. Unfortunately, values of Css95 is normally not given in the literature. Also, because the shapes of the drug concentration-effect curves may differ between drugs, even if they have similar physiological effects, potency ratios between drugs obtained at Css50 and Css95 may differ significantly.

The above discussion shows that designing of PK/PD studies in order to define clinically useful dosing regimens for RSII is challenging, and appropriate comparison between available drugs, even with similar physiological effects, is a very complex matter. Although not ideal, this fact may cause investigators to employ rather empirically-based study designs, i.e. learning by experience. One such approach, especially relevant when binary response variables are involved, is to search the PK/PD literature to identify agents with appropriate effect profiles, and then study the probability of success with drugs based on success rates of obtaining an intended effect within a wide range of administered drug doses[81 82].

In the following, relevant drugs for use during RSII (sedatives, neuromuscular blocking drugs, adjuvants) will be discussed, with focus on the effects on tracheal intubation conditions, release of stress hormones, and hemodynamic response.

4.7 Sedative drugs

There are four sedative drugs that are regularly used during rapid-sequence induction and tracheal intubation: Thiopental, propofol, etomidate, and ketamine. The drug description will focus on issues relevant for RSII.

Drug description

4.7.1 Thiopental

Pharmacological effects. Thiopental enhances the action of GABA, which is the principal inhibitory neurotransmitter in CNS. The action opens chloride ion channels causing hyperpolarization and increased threshold of excitability of postsynaptic membranes[83]. At high drug doses thiopental may act as an agonist itself [84]. It is unclear if the hypnotic effect is also caused by inhibition of excitatory neurotransmitters (glutamate and acetylcholine)[85].

Thiopental produces dose-related central respiratory depression with apnea[86], but the duration is short (< 30 s after a 3.5 mg/kg bolus when given as a sole drug[87].

Thiopental decreases CMRO2 and CBF in a parallel manner, an effect that is related to EEG-slowing. The energy-sparing effect with increasing doses of thiopental stops when EEG becomes isoelectric[88 89].

Cardiovascular depression is caused by combined central and peripheral effects (direct vascular and myocardial). The primary hemodynamic effect is vasodilation on the venous side causing a reduction in preload [90]. Decreased cardiac contractility is caused by reduced availability of calcium to the myofibrils[91]. Compensatory tachycardia occurs via baroreceptor-reflexes[92]. It is speculated if tachycardia secondary to thiopental may be harmful in patients with coronary artery disease[93]. A significant reduction in cardiac output is seen in hypovolemic patients after administration of thiopental [94].

Pharmacokinetics and pharmacodynamics. Thiopental, being a weak acid, is highly lipid soluble, and approximately 60% of the free fraction of the drug exists in its unionized form at physiologic pH. Both factors contribute to rapid drug transportation across the blood-brain barrier[95]. However, the drug is also highly protein-bound (approximately 85%), which counteracts the speed of onset by lowering the free fraction in plasma[96]. Thiopental´s physiochemical characteristics explain why the drug has a high blood-brain equilibration rate constant ($t_{1/2}$ Keo approximately 1.2 min when using EEG measures as an index of pharmacodynamic effect [97], and consequently a very rapid onset of action. Maximum effect site concentration after a bolus appears to be achieved after 45 s in experiments where jugular venous concentrations were measured intraoperatively after rapid intravenous bolus doses of thiopental[98 99], making the drug very suitable for rapid-sequence induction of anesthesia. Due to it´s high pK-value (7.6) the free unionized fraction of thiopental increases with decreasing pH in the blood stream. Consequently,

the concentration gradient increases between the diffusible fraction of drug in the blood stream and that in the effect site, the result being that less drug is needed to obtain a certain hypnotic effect in the acidotic patient[100]. There is a significant inter-individual difference in the response to thiopental [101 102], but 4 mg/kg given over 5-15 s will anesthetize sufficiently most individuals[102]. Speed of injection may critically influence drug effect[103], high speed of injection implies that less total dose is needed to obtain a certain effect. Css_{50} (a measure of drug sensitivity) for thiopental, i.e. the plasma concentration at steady state associated with 50% of maximum effect (EEG-measures used as an index of drug effect) is approximately 15 mg/ml [97]. Drug sensitivity does not seem to change with age, but central volume of distribution may decrease[104]. This implies that bolus doses should be reduced in the elderly.

Thiopental is metabolized in the liver. Clearance is low (approximately 3.5 ml/kg/min), being enzyme capacity-limited [74]. However, despite the low hepatic extraction, plasma concentration of thiopental falls rapidly after a single bolus (even in liver failure patients). This is because distribution kinetics is a major determinant of drug concentration the first minutes after drug administration[104].

4.7.2 Propofol

Pharmacological effects. The drug´s hypnotic effect is believed to be caused mainly by stimulating effects of GABA-receptors in CNS [105], especially in hippocampus and prefrontal cortex [106]. Propofol also inhibits the action of NMDA-receptors [107], and the alfa-2 adrenoreceptor system may also be indirectly involved in the hypnotic effect of propofol [108].

Apnea occurs regularly after administration of a standard dose given over 30-60 s, but apnea duration (normally approximately 30 s duration) will depend on speed of administration and type of premedication [109]. Propofol depresses the ventilatory response to hypoxemia and inhibit vagal-induced bronchoconstriction [110].

Propofol has a significant depressive effect on the cardiovascular system. Independent of the presence of cardiovascular disease the arterial blood pressure is normally significantly reduced after a standard bolus dose, coinciding with a reduction in cardiac output, stroke volume, systemic vascular resistance, and preload[111-113]. These effects appears to be concentration and dose-dependent [114]. Vasodilation is probably caused by reduced sympathetic activity [115] and a direct effect on smooth muscle calcium mobilization [116]. Heart rate does not change significantly after a bolus dose, possibly because propofol inhibits the normal response to decreased arterial blood pressure [117]. The hypotensive effect of propofol boluses is augmented by prior administration of an opioid [118]. It is suggested that slower speed of administration will reduced the adverse circulatory effects of propofol [119].

Propofol cause pain on injection, especially when administered in a small vein. The pain is less than after etomidate [120]. Reducing the speed and adding lidocaine to the propofol solution may reduce the pain [121].

Pharmacokinetics and pharmacodynamics. Propofol is a very lipid soluble weak acid, almost entirely unionized at physiologic pH. However, high protein binding (albumin) limits the free fraction to 2% [122]. The resultant concentration gradient between plasma and effect site will therefore be low, which increases the time of onset of action. $t_{1/2}$ Keo of propofol is estimated to 2.9 min (based on EEG-measures as an index of dynamic effect), and because the drug disappears rapidly from plasma the time to maximum effect site concentration after a bolus will be approximately 2-2,5 min [123-125]. Css_{50} of propofol is estimated to 2.3 mg/ml. This implies a potency ratio between thiopental and propofol, when based on EEG-measures to estimate the pharmacodynamic effect, of approximately 6.7. However, this number says more about relative infusion rates of the two drugs needed to obtain a certain pharmacologic effect than about bolus dosing during induction of anesthesia. The propofol: thiopental equipotency is estimated to 1: 2 with regard to hypnotic effect after bolus injections [126]. Normal bolus dose in adults is 2 mg/kg, in small children rather 3 mg/kg due to increased volume of distribution and clearance [127]

Propofol is metabolized in the liver, and has a very high clearance. After a bolus plasma concentration falls rapidly, partly because of the high clearance, but also because of tissue uptake in well-perfused organs (for ex in the lungs) [74] [122]. Clearance of propofol appears to be faster in females and decrease with age [128].

4.7.3 Etomidate

Pharmacological effects. The reason for etomidates hypnotic effect is not well understood, but it is likely related to the GABA-adrenergic system since it´s action may be antagonized by GABA antagonists [129]. The mechanism of action appears to be similar to that of propofol [130].
Etomidate has minimal influence on ventilation, although the ventilatory response to increased carbon dioxide tension is somewhat depressed [131].

Etomidate appears to have minimal effect on the cardiovascular system, probably due to lack of effect on both the sympathetic nerve system and baroreceptors [115].

CMRO2 and CBF decrease after a bolus of etomidate[132]. These effects are associated with a decrease in ICP in patients with intracranial hypertension[133].

Etomidate reversibly inhibits 11beta-hydroxilase, an enzyme involved in the synthesis of cortisol in the adrenal gland [134]. The synthesis of mineralocorticoids may also be affected[135]. Even a single bolus may have an effect on cortisol production[136], and use of etomidate has been linked to increased mortality in ICU patients [137]. The safety of etomidate has not been studied in large, prospective studies, but a single induction dose appears to be safe even in patients undergoing high-stress surgery [138].

Etomidate has been associated with high frequency of nausea and vomiting, accentuated by the addition of an opioid[139]. Pain on injection is frequently occurring, but may be alleviated by injecting lidocaine prior to etomidate [140]. Hiccups and

myoclonus occur frequently, possibly dependent on the speed with which the drug is injected [141].

Etomidate is associated with shorter onset time of neuromuscular block when compared with thiopental and propofol[142]. It is assumed that this effect is due to reduced cardiac depression caused by the two latter drugs.

Pharmacokinetics and pharmacodynamics. Etomidate is an organic base with pH 4.2 and has a high free unionized fraction at physiologic pH. However, the drug is 75% protein bound (albumin), which lowers the diffusible fraction. The plasma-effect site equilibration (based on EEG-measures for dynamic effect) occurs a little slower than with thiopental ($t_{½}$ Keo 1.6 min), and maximum effect site concentration should occur after approximately 90 s [143]. Css50 (plasma concentration at steady-state associated with 50% of maximum effect) is approximately 300 ng/ml. Standard bolus dose for induction of anesthesia is 0.3 mg/kg. Etomidate is dependent on liver function for it´s metabolism, but even liver failure will not affect the short duration of effect after a bolus because the decline in plasma concentration is mainly dependent on distribution[74].

4.7.4 Ketamine

Ketamine exists as two optical enantiomers, (R and S-form), and is normally administered as a racemic mixture of the two enantiomers. The S-form has greater affinity for the NMDA-receptor than the R-form [144].

Pharmacological effects. The effect of ketamine is characterized by amnesia, analgesia, and to a variable degree, unconsciousness. Ketamine induces a dose-dependent depression of CNS via blockade of NMDA-receptors, receptors that facilitate neural transmission when activated by the natural transmitters' glutamate and glycine. The hypnotic effect of ketamine is antagonized by anticholinesterase agents, and may therefore in part be caused by interaction with muscarinic receptors

[145]. Ketamine anesthesia is called dissociative because the patient appears to be in a cataleptic state (eyes open, maintained breathing, muscle tension, and reflex activity). Associated with this clinical state is variable EEG-patterns in different parts of the brain, delta waves in thalamus and cortex (depression) and teta-waves in hippocampus and amygdala (stimulation) [144].

Activation of NMDA-receptors in hippocampus, which initiates long-term potentiation of postsynaptic cells, is essential for learning and memory. It is believed that ketamine acts, in a dose-dependent manner, on these neurons to impair memory building [144 146]. The analgesic effect of ketamine is apparently mainly caused by inhibition of NMDA-receptors at spinal and supraspinal sites [144 146]. However, ketamine also interact with opioid receptors (mu, delta, kappa), the S-form 2-3 times more potent than the R-form [147 148]. The interaction with opioid receptors is complex, antagonism of the mu-receptor and agonistic action on kappa-receptors has been described [147]. Local anesthetic effects of ketamine have also been observed [149].

Ketamine has minimal effect on ventilation, and the response to increased carbon dioxide tension is unaltered [150]. The drug is an effective bronchodilator [151].

Ketamine stimulates the sympathetic nerve system and induces catecholamine release, thereby maintaining or increasing arterial blood pressure and heart rate [152 153]. The cardiac work load and oxygen consumption increase[154]. The drug may increase vascular resistance in the pulmonary artery **[155]**. Some evidence indicates that ketamine attenuates the function of baroreceptors by an NMDA-associated effect in tractus solitarius[156]. The sympathomimetic effect is often an advantage in trauma victims or other hypovolemic patients where the activity of the sympathetic nerve system must be maintained in order to avoid significant reductions in arterial blood pressure during anesthesia induction. However, the drug is also a direct myocardial depressant, and in patients with depleted catecholamine stores, ketamine may have significant hypotensive effects [65 157 158].

Ketamine increases cerebral metabolism and CBF[159], and excitatory effects appear in EEG (teta-activity and seizure-like activity in hippocampus)[160]. Ketamine is a potent cerebral vasodilator that increases cerebral blood flow, CMRO2 and potentially ICP [161]. However, these effects may be diminished by simultaneous administration of other sedatives or opioids, and controlling pCO2 and the plasma volume [162].

Ketamine has significant psychotomimetic effects upon emergence, like excitement, euphoria, fear, and hallucinations[163]. In part, these undesirable effects can be counteracted by use of propofol, thiopental, or benzodiazepines[164].

Ketamine is associated with salivation, especially in children, which may cause laryngospasm and be so severe that the airway may be obstructed. Anticholinergic drugs may alleviate the problem[119]. Ketamine is associated with shorter onset time of neuromuscular block when compared with thiopental and propofol [165]. It is assumed that this effect is caused by augmentation of cardiac output.

Pharmacokinetics and pharmacodynamics. Ketamine is highly lipophilic, which facilitates entry into CNS. With a pKa of 7.5 it is partly ionized at physiologic pH, and ionization is enhanced by it´s normal formulation in an acidic solution[74]. However, the degree of protein binding is low, which increases the free fraction of diffusible unionized drug. The mean Css50 of racemic ketamine, based on median EEG-frequency as measure of drug effect, has been estimated to approximately 2 mg/ml [166]. Unfortunately, specific data on the drug´s onset characteristics (plasma-effect site equilibration rate and simulation of time to peak effect site concentration after bolus administration) are lacking. However, clinical experience suggests that the anesthetic effect is attained within 1-2 min after a standard iv dose of 2 mg/kg[119].

Ketamine is mainly eliminated by the liver, the clearance being close to liver blood flow (i.e. liver blood flow-limited elimination). Blood concentration falls rapidly after a

bolus, caused by both elimination and distribution, and is normally below therapeutic range approximately 10 min after a standard bolus[119]

4.7.5 Effects on intubation conditions

Thiopental

Thiopental was introduced into clinical practice in 1934. Slow speed of administration was encouraged to avoid respiratory depression, but with low blood concentrations hyper reactivity of laryngeal reflexes was seen [167]. With high drug plasma concentrations it is possible to perform tracheal intubation without provoking preventive muscular actions from the patient, even when using thiopental as the sole agent. In studies where thiopental was infused using TCI (target control infusion) it has been determined that steady-state plasma concentration of approximately 80 mg/ml is needed[168]. The bolus dose needed to obtain such high plasma concentration in sufficient length of time in order to allow tracheal intubation, has not been determined. However, early studies on thiopental suggest that > 10 mg/kg would be needed[169]. Based on studies and clinical experience with thiopental over a period of 75 years, normal anesthesia practice is to administer a neuromuscular blocking drug together with thiopental before laryngoscopy and tracheal intubation.

Propofol

Propofol significantly attenuates pharyngeal and laryngeal reflexes[170]. 120 s after propofol 2.5 mg/kg laryngoscopy was successful in 90%, and the vocal cords were abducted in 30% of the patients[171]. It has been reported that propofol, given as the sole induction agent in premedicated patients (opioid or benzodiazepine), provides acceptable intubation conditions in 35-70% of the patients. This wide range of success may be due to differences in assessment protocol used, and because of variable times between drug administration and airway stimulation (90-150 s) [172-174]. Propofol does not possess any neuromuscular blocking effect and does not potentiate neuromuscular

blocking drugs with clinical doses[175]. The relaxation of muscles in the upper airway caused by propofol may rather be related to it´s ability to reduce spinal motor neuron excitability [176-179].

Etomidate and ketamine

Ketamine and etomidate do not have significant depressive action on airway reflexes, and therefore there are no reports available regarding intubation conditions after administration of these drugs when given without neuromuscular blocking drugs or adjuvants.

4.7.6 Comparison between sedative drugs

Comparisons between sedative agents have been made in two ways. First, intubation conditions after thiopental, propofol, and etomidate have been compared when administered in conjunction with an adjuvant (an opioid), but in the absence of a neuromuscular blocking drug. The results vary. If doses are given that are considered equivalent with respect to sedative effect [126 180-182] (thiopental 5 mg/kg vs propofol 2.5 mg/kg vs etomidate 0.3 mg/kg) and approximately 120 s is allowed before intubation is completed, then propofol is the favorable induction agent with high probability of acceptable intubation conditions (> 80%) [181 183 184]. However, the efficacy difference between thiopental and propofol disappears when intubation is performed approximately 60 s after drug administration. Actually, intubation conditions may under these circumstances be scored better for thiopental [185]. This is an expected finding when taking into consideration that the two drugs differ significantly with respect to onset times of maximum effect site concentration after a bolus. The success rate of acceptable intubation conditions drops accordingly when waiting time before laryngoscopy is reduced to 60 s (< 40%). Second, studies have investigated the efficacy of sedative drugs in order to improve intubation conditions 60 s after a standard dose of rocuronium. Again, results are apparently conflicting. In one study

intubation conditions were favorable with propofol compared to thiopental, even if laryngoscopy was initiated as early as 30 s after rocuronium. However, propofol was probably administered approximately 90 s prior to the neuromuscular blocking drug. [186]. When patients were intubated after 45 s the intubation conditions were similar with thiopental and propofol[22]. Apparently, intubation conditions are better with propofol than etomidate when tracheal intubation is completed within 60 s after rocuronium [187]. Intubation conditions 60 s after rocuronium 0.6 mg/kg was found to be better with ketamine than thiopental [188 189]. However, the difference in efficacy (100% vs 50% of acceptable intubation conditions for ketamine and thiopental, respectively) can be explained by the time elapsed between administration of the induction agent and airway stimulation (180 s).

4.7.7 Effects on release of stress hormones and hemodynamic responses

Thiopental

The release of stress hormones and hemodynamic responses secondary to tracheal intubation have been recorded several times in premedicated (opioid or benzodiazepine) patients anesthetized with thiopental as the sole anesthetic drug [30 32 45 46 48 49 190-201]. In most studies 4-6 mg/kg has been administered. There have not performed dose-response studies, but it is not unreasonable to believe that the autonomic response is dose-dependent. Increases in post intubation concentrations of catecholamines compared to pre intubation values vary between 30 and 150 % (norepinephrine) and between 0 and 200 % (epinephrine). The concomitant increases in hemodynamic variables vary between 15 and 60% (arterial blood pressure) and between 5 and 35% (heart rate). All studies agree: Thiopental, irrespective of dose within a clinical range (4-6 mg/kg) does not significantly protect against increases in arterial blood pressure and heart rate after tracheal intubation. It appears that magnitude of the responses are smaller if airway stimulation occurs at 60 s. [198] than 120 s after administration of thiopental [30 191]. This may not be unexpected when taking

into account that maximum effect site concentration of thiopental probably is achieved approximately 60 s after a bolus.

Propofol

The magnitude of the pressor responses to tracheal intubation (arterial blood pressure and heart rate) appears to be similar to that seen after thiopental [46 48 172 173 187 196 201-203]. However, because arterial blood pressure after propofol drops significantly the increase after airway stimulation may not even bring the pressure back to baseline level [196]. The release pattern of catecholamines post intubation follows the same pattern as after thiopental.

Etomidate

Hemodynamic variables increase significantly after tracheal intubation when patients are anesthetized with etomidate (0.3 mg/kg) as the sole anesthetic [187 204], approximately 40% (arterial blood pressure) and 25% (heart rate). The magnitudes of responses were significantly greater with etomidate than that of propofol [187]. Catecholamine release post intubation has apparently not been reported with etomidate.

Ketamine

Arterial blood pressure may increase as much as 50% post intubation when patients receive ketamine as the sole anesthetic[205]. Heart rate increases almost to the same extent. Midazolam reduces the pressor effect, but increasing the dose of midazolam from 0.2 to 0.4 mg/kg does not attenuate the pressor response any further [206]. The release pattern of catecholamines post intubation associated with ketamine is not presented in the literature.

4.8 Neuromuscular blocking drugs

Aspiration of gastric content to the airway has been a concern for anesthesiologists during the entire history of modern anesthesia [7] [194]. After the introduction of neuromuscular blocking drugs this issue was even accentuated because normal doses of this drug type completely eliminate protective reflexes of pharynx and larynx, which facilitates aspiration to the airway [207]. Therefore a rapid-sequence technique of anesthesia induction was developed where focus was on securing the airway rapidly with a cuffed endotracheal tube [207]. In order to achieve this goal a rapid-acting neuromuscular blocking drug was needed. Until suxamethonium was introduced into clinical practice in 1952[208-211] a slow-onset nondepolarizing neuromuscular blocking drug was used to induce full muscle paralysis [207]. From 1970 suxamethonium has been the preferred neuromuscular blocking drug during RSII due to it´s rapid onset characteristics [6]. Today four nondepolarizing neuromuscular blocking drugs are available on the Norwegian market: Vecuronium, mivacurium, cisatracurium, and rocuronium. The onset times of blockade at the laryngeal muscles of the former three agents are too slow (onset times 150-180 s) to make these drugs attractive alternatives to suxamethonium when rapid muscle relaxation is needed [212-216]. The only alternative to suxamethonium in an RSII-setting is rocuronium, a nondepolarizing neuromuscular blocking drug that was introduced into clinical practice in 1994[217].

4.8.1 Drug description

All neuromuscular blocking drugs are structurally related to acetylcholine, the transmitter substance active at the neuromuscular junction. The positive charges at the quaternary ammonium sites of these drugs mimic the quaternary nitrogen atom of acetylcholine, which is the reason why these molecules are attracted to cholinergic nicotinic receptors, located both presynaptically on the nerve endings and at the end plate region of the muscle fiber[218].

4.8.2 Pharmacological effects

Normal neuromuscular function involves binding of acetylcholine to both alfa-units of the cholinergic nicotinic receptor. The binding causes a conformational change of the receptor into an ion channel, allowing short-lived fluxes of sodium, potassium, and calcium through the cell membrane of the muscle fiber [219]. The sudden influx of calcium is needed in order to activate the contractile elements of the muscle cell. If 5-30% of the receptors on the end plate are activated simultaneously the change in the electric potential of the membrane will reach the threshold for a muscle contraction to occur [220] [221]. The acetylcholinesterase, also located in the end plate region hydrolyzes acetylcholine within 1/1000 of a second[222]. Degradation of acetylcholine brings the receptor back to the resting state and the ion channel closes. Ion channel closure is associated with restoration of the resting potential of the end plate, making the receptors ready to respond to a new nerve impulse [223].

Suxamethonium (MW approximately 300) [211] consists of two acetylcholine molecules linked through an acetate methyl group. The ED95 (the dose needed to suppress the adductor pollicis twitch tension 95%) is approximately 0.3 mg/kg[224] [225]. The drug stimulates the nicotinic receptor at the neuromuscular junction in a similar way as acetylcholine, but because it is not hydrolyzed by the cholinesterase at the end plate it blocks the receptor by desensitization[226] Because suxamethonium is an agonist at the nicotinic receptor, it is believed that approximately 30% of the receptors must be occupied by the drug in order to induce blockade of muscle function[227] [228]. Suxamethonium is metabolized by butyrylcholinesterase in the blood[229], and in most individuals the plasma concentration is rapidly declining after a bolus administration. The drug at the neuromuscular junction leaks back into the blood stream due to the concentration difference that occurs, and the block eventually subsides[72].

Rocuronium is an aminosteroid with rigid structure, and has a molecular weight of

approximately 600 [224]. An allyl group attached to one of the quaternary nitrogen atoms makes it 6-10 times less potent than it´s predecessors vecuronium and pancuronium[230], and the ED95 is approximately 0.3 mg/kg [224] [231]. Rocuronium is a nondepolarizing drug, i.e. it blocks normal neuromuscular function by inhibiting acetylcholine´s ability to open the ion channel. One single molecule of rocuronium is sufficient to block the function of one receptor. However, due to the safety margin at the neuromuscular junction, in many muscle fibers > 90% of the receptors must be blocked in order to induce blockade of the muscle function[221].

4.8.3 Pharmacokinetics and pharmacodynamics relevant for RSII

The onset time (time to maximum effect) of neuromuscular blocking drugs is governed primarily by two pharmacokinetic factors. First the speed of drug equilibration between the blood stream and effect site (i.e. the neuromuscular junction) characterized by Keo, the equilibration rate constant [75]. This factor is mostly relevant for nondepolarizing drugs. Second, the speed with which the plasma concentration is declining after a bolus administration. This factor is mostly relevant for suxamethonium [77].

There is an inverse relationship between Keo and onset time of the drug[232]. Rocuronium has the greatest Keo among nondepolarizing drugs, i.e. 0.16/min at the adductor pollics and 0.26/min at the laryngeal muscles[233]. It is believed that the low potency (greater number of molecules needed in order to obtain a certain effect) of rocuronium compared to other nondepolarizing drugs is a significant factor determining it´s rapid onset [232] [234] [235]. Suxamethonium, the drug with the fastest onset time at the laryngeal muscles[21], which is also a low-potency drug [235] with ED95 similar to rocuronium, has a Keo value of only 0.06/min[77]. Obviously, Keo is not the factor determining the onset time of suxamethonium. However, with normal function of the butyrylcholinesterase in plasma the degradation of suxamethonium occurs very rapidly[236]. This means that the maximum effect site concentration occurs early after

drug administration, because the plasma concentration rapidly falls below that of the effect site [77] [232]. This explanation for suxamethonium rapid onset is consistent with findings that time to maximum effect site concentration of this drug is significantly prolonged in individuals with reduced activity of the butyrylcholinesterase[237] [238]. Suxamethonium rapid onset may in part be caused by it´s agonistic actions i.e. that only approximately 30% of the receptors must be blocked in order to paralyze a muscle fiber[227] [228].

After a standard bolus dose of suxamethonium (1 mg/kg)[239] average lag time and onset time (time to maximum effect) at the laryngeal muscles are 25 s and 35 s, respectively. The equivalent times for high-dose rocuronium (1-1.2 mg/kg), are approximately 30 and 60 s [21]. Further, after a bolus dose of suxamethonium (1 mg/kg) the success rate of completely paralyzing the laryngeal muscles within 60 s is close to 100%. This is not the case for rocuronium where significant number individuals need another 30 s to obtain this effect [21]. However, one factor is normally not taken into account when the effects of suxamethonium and rocuronium are compared, namely that a significantly greater number of molecules normally are given with the former drug. Suxamethonium is about half the size of rocuronium, i.e. when suxamethonium 1 mg/kg is compared with rocuronium 1-1.2 mg/kg twice as many molecules are administered with the former drug. It would therefore be fair to compare suxamethonium 1 mg/kg with rocuronium 2 mg/kg. Although a high probability of excellent intubation conditions is obtained with this dose of rocuronium, the long recovery time (approximately 3 hrs.) makes this an unattractive option clinically [82].

4.8.4 Side effects relevant for RSII

4.8.5 Suxamethonium. Suxamethonium acts as an agonist on nicotinic cholinergic receptors located in autonomic ganglia and on muscarinic cholinergic receptors in various locations (especially the sinus node). The effects may cause various kinds of

dysrhythmias, and both bradycardia and tachycardia are described [240]. Bradycardia is prominent in children because of their increased vagal tone [241]. Bradycardia is effectively counteracted by thiopental or atropine[242] [243].

Under normal circumstances serum-K+ increases approximately 0.5 mmol/l after suxamethonium administration due to stimulation of the cholinergic receptors at the end plate and prolonged opening times of the ion channels[72]. Potentially lethal concentrations of potassium have been reported with a variety of clinical conditions: Abdominal infections, closed head injury, burns, ICU-stay, immobility, neurologic and muscle diseases[244–246]. Pathological hyperkalemia is associated with upregulation of the fetal type of acetylcholine receptors, which are more sensitive to the effect of suxamethonium than nondepolarizing neuromuscular blocking drug[247].

Suxamethonium causes increased intraocular pressure, an effect that may be counteracted by precurarization or opioid administration[248]. Suxamethonium has been associated with increased intracranial pressure, probably related to fasciculation and increased pCO2 [249].

Suxamethonium causes increased intragastric pressure [250]. However, the clinical relevance is uncertain because the tone of the gastroesophageal sphincter is increased as well. Increased probability of aspiration is likely when suxamethonium is used in patients with incompetence of the lower esophageal sphincter.

All neuromuscular blocking drugs have the potential of causing allergic reactions. This is because these molecules have the ability of bridging, i.e. that each molecule can bind two antibodies simultaneously, which is needed for mast cells to degranulate [251] [252]. In a Norwegian registry suxamethonium clearly causes more side effects than other neuromuscular blocking drugs [252] [253].

4.8.6 Rocuronium. Rocuronium, in clinical doses, has no vagolytic effect or effects on autonomic ganglia, and does not release histamine[72].

Anaphylactic reactions have been reported with rocuronium, but there is no reason to believe that it occurs more frequently than with other nondepolarizing neuromuscular blocking drugs [253].

4.8.7 Intubation conditions during RSII

There is a general agreement in the literature that suxamethonium is the number one neuromuscular blocking drug to use when rapid-sequence induction and tracheal intubation is indicated [72]. This is because acceptable intubation conditions can be obtained in most unpremedicated patients 40-60 s after administration of a standard recommended dose (1 mg/kg) [239] when used in conjunction with a rapid bolus of a sedative, either thiopental 4-6 mg/kg or propofol 2-2,5 mg/kg (tracheal intubation completed within 70-90 s after commencement of drug administration)[22 254 255]. There are two reasons why this is an expected finding: First, the laryngeal muscles are paralyzed in most patients 60 s after suxamethonium [232], and second, the sedative is contributing to optimize the intubation conditions in those individuals not completely paralyzed by the neuromuscular blocking drug [171]. This simple, attractive method (using a sedative + suxamethonium) therefore has become a gold standard with which alternative induction regimens must be compared.

It has been suggested that suxamethonium can be replaced with rocuronium under many RSII-situations [256-259]. This assumption is based on results from several studies where intubation conditions 60 s after rocuronium or suxamethonium have been compared and judged similar [67 260-268]. Common for these studies is that in one or several ways the study designs deviated from traditional RSII, i.e. use of premedication, use of supplemental doses or greater doses of sedatives than normal during RSII, use of opioids or inhaled anesthetics, or not completing tracheal intubation within 70-90 s after commencement of drug administration. One large study, designed according to traditional RSII-settings (sedative + neuromuscular

blocking drug, tracheal intubation completed within 90 s after commencement of drug administration), concluded that rocuronium 1 mg/kg potentially may replace suxamethonium 1 mg/kg if propofol 2.5 mg/kg is used as the sedative agent, and if 5-10% poor intubation conditions can be accepted [66]. This is in line with a Cochrane report concluding that rocuronium probably cannot replace suxamethonium [269].

In a clinical sense, previous studies show that intubation conditions after rocuronium cannot easily replace suxamethonium when used in an RSII-setting. However, if the clinical circumstances allow modification of the drug induction regimen, i.e. either using high doses of the sedative or adding an opioid, then rocuronium might be an attractive alternative to suxamethonium [22]. At this time there is insufficient information available in the literature regarding the optimal drug combination to be used together with rocuronium during RSII.

4.8.8 Effects on release of stress hormones and hemodynamic responses

Suxamethonium. Suxamethonium increases plasma concentrations of norepinephrine in unstimulated patients, an effect that is independent of administration of a sedative drug [270]. The source of norepinephrine is likely nerve endings in the autonomic nerve system. The effect of suxamethonium on norepinephrine plasma concentration appears not to be associated with any increase in blood pressure in unstimulated patients anesthetized with thiopental [271]. However, the catecholamine and arterial blood pressure responses to tracheal intubation is exaggerated when compared to that observed in patients having a nondepolarizing drug for muscle relaxation [32]. Epinephrine concentrations decreases before airway stimulation, but increases significantly post intubation. This observation suggests that release of catecholamines from the adrenal gland is involved in the pressor response to laryngoscopy and tracheal intubation when suxamethonium is used. The catecholamine response to tracheal intubation appears to subside within five min after conclusion of airway manipulation [32 271].

It has been shown in dogs that suxamethonium lowers the threshold for catecholamine-induced ventricular dysrhythmias [272]. Therefore, during RSII prevention of hypoxia, hypercarbia, and acidosis is important, factors known to increase plasma levels of catecholamines [270 273]. Further, the simultaneous increase in release of potassium may increase the probability of ventricular dysrhythmias [72].

Rocuronium. Rocuronium has a low potential for cardiovascular effects, even when 4 times the ED95 is administered [72 274]. Occasionally, minor vagolytic effect has been reported in non-elderly humans after rocuronium 0.6 mg/kg [275]. No cardiovascular effects or changes in plasma concentrations of catecholamines were observed in a study in elderly patients anesthetized with thiopental, fentanyl and nitrous oxide [276].

However, partial paralysis may have an effect on the hemodynamic response to tracheal intubation. Sparr et al compared the hemodynamic response to tracheal intubation in patients either 100% or 65% paralyzed at the adductor pollicis muscle, or found that the arterial blood pressure increased significantly more in the partially paralyzed group [197]. In this study vecuronium was used for muscle relaxation, but similar responses should be expected after rocuronium, which is similar to vecuronium in most pharmacologic aspects [72].

4.9 Adjuvant drugs (Opioids)

A variety of adjuvant drugs have been tested during induction of anesthesia in order to facilitate tracheal intubation or blunt hemodynamic responses to airway manipulation. In particular, opioids and local anesthetics may be used during RSII.

Opioids

4.9.1 Drug description

There are four opioids in regular use during anesthesia practice with potential for employment during RSII: Fentanyl, sufentanil, alfentanil, and remifentanil. Morphine was an integral part of anesthesia for many years, but is now replaced by fentanyl or it´s congeners.

4.9.2 Pharmacological effects. Opioids inhibit release of acetylcholine in prefrontal cortex of the brain and thereby affect the level of consciousness [277]. In vitro studies also suggest that opioids inhibit the activity of NMDA-receptors [278]. However, opioids are not considered complete anesthetics because even very high doses may not induce unconsciousness [79 279 280].

The well-known respiratory depressant action of opioids is primarily caused by it´s mu-receptor activation in the caudal medulla raphe region [281 282], a dose-dependent effect.

Fentanyl, sufentanil, and alfentanil rather increase than decrease cardiac contractility [283]. Remifentanil caused cardio depression in dogs [284], but cardiac function was unaffected in conscious human volunteers during low-dose infusion (< 0.1 μg/kg/min) [285]. None of the fentanyl congeners cause significant histamine release [286]. Opioids cause vasodilation by a combined central and peripheral effect [287 288]. Hypotension appears to be more common with remifentanil than other fentanyl congeners [79 289] and may be seen at clinical doses (> 0.25 μg/kg/min) [290]. The accentuated tendency to hypotension by remifentanil may be related to Ca2-channel inhibition in arteries [291]. Bolus doses of remifentanil are associated with bradycardia[292]. Higher likelihood of significant hypotension, bradycardia, and muscle rigidity makes it advisable to administer remifentanil by constant-rate infusion, and not by rapid boluses [293].

Opioids normally reduce cerebral metabolic rate and cerebral blood flow [294], and do not normally affect ICP, even in patients with serious head injury [295].

Although opioids do not influence the degree of neuromuscular block when used together with a neuromuscular blocking agent [296], they still affect tracheal intubation conditions during induction of anesthesia in a favorable way. Opioids effectively desensitize the responses of the respiratory tract and the glottis to the presence of foreign objects. The main mechanism of this effect seems to be an attenuation of the cough reflex that is mediated from the central nervous system [297] [298].

Both sympathetic and parasympathetic nerve fibers located in the upper airway, traveling in the glossopharyngeal and vagal nerves are activated by laryngoscopy and tracheal intubation. The responses may be hypertension, tachycardia or bradycardia. Opioids are believed to attenuate these responses by deepening the level of anesthesia and thereby reducing the activity of the autonomic nerve system [76] [201] [299]. It appears that specific effects on brain stem nuclei known to be involved in cardiovascular homeostasis (nucleus solitarius, dorsal vagal nucleus, ventrolateral periaqueductal gray matter), and on the hypothalamic-pituitary-adrenal axis are involved [300]. An agonistic effect on alfa2-adrenergic receptors has also been observed [301].

Rapid boluses of opioids may cause muscle rigidity, possibly related to activation of mu-receptors on GABA interneurons. The muscle rigidity occurs in laryngeal muscles, chest wall or extremities [293]. Mask ventilation problems appear to be related to closure of the vocal cords [302]. This phenomenon is described with fentanyl > 25 μg/kg and alfentanil > 80 μg/kg [79] [303]. Muscle rigidity is more frequently occurring with remifentanil, but has not been described if doses < 2 μg/kg has been administered for 60 s or more. However, muscle rigidity is easily relieved by simultaneous use of neuromuscular blocking drugs [304].

4.9.3 Pharmacokinetics and pharmacodynamics. The four different opioids frequently used during anesthesia induction (fentanyl and it´s three congeners alfentanil, sufentanil, and remifentanil) have very different pharmacokinetic and pharmacodynamic profiles. Fentanyl and sufentanil have much higher lipid solubility, potency, and distribution volumes when compared to alfentanil and remifentanil, while remifentanil has much higher clearance from the blood stream than the other three opioids [305-310]. At steady state conditions the relative potencies have been estimated to be approximately 1:10-12:20-30:1000 for sufentanil: fentanyl: remifentanil: alfentanil, respectively [309 311]. The four opioids have approximately the same molecular mass (350 g/moll), which means that in order to obtain similar effects, the number of molecules that must be present in blood/plasma at steady state of each opioid will be equivalent to their respective potency ratio. When it comes to bolus dosing, remifentanil and alfentanil appear to be much more potent in comparison to fentanyl and sufentanil than what should be expected from steady state blood/plasma concentrations. This is due to smaller initial volume of distribution, higher free, diffusible fractions in plasma, higher Keo values, and more rapid decline in blood/plasma concentration after boluses when the two former drugs are given [76 309 310]. Investigations using various measures to record drug effect (EEG-slowing, algometry, loss of consciousness, ventilatory depression) suggest bolus dose-based potency ratios to be 1:10 for fentanyl vs alfentanil, and 1:20-40 for remifentanil vs alfentanil [79 306 307 311-314]. It is not known if similar potency ratios exist with regard to attenuation of responses to laryngoscopy and tracheal intubation.

Time to maximum effect site concentration after bolus administration is 4-6 min for fentanyl and sufentanil [76 308] and 60-90 s for remifentanil and alfentanil [309], when Keo determinations are based on EEG changes [306] or algometry [312]. The relatively slow onset of effect of fentanyl and sufentanil makes these drugs less relevant to use in an RSII setting. However, Keo for functions like attenuation of responses to tracheal intubation has not been determined.

The central volume of distribution of alfentanil appears to decrease with increasing body weight, and to increase in females compared to males when normalized by body weight [315]. Assuming greater average body weight in males than females, the sum of these pharmacokinetic effects suggests that higher maximum blood concentrations of alfentanil are achieved in males when the drug is administered on mg/kg basis. However, it is not known if this effect causes a higher likelihood of perfect intubation conditions and hemodynamic response control in males.

4.9.4 Effects on intubation conditions

The beneficial effect of opioids on airway responses secondary to laryngoscopy and tracheal intubation has been demonstrated clinically with fentanyl, alfentanil, and remifentanil, both in the presence and absence of a neuromuscular blocking drug. [316–320], and is also present when inhaled anesthetics are used as induction agent [321 322]. Much focus has been on anesthesia induction regimens based on a combination of an opioid and a sedative drug, thereby omitting use of neuromuscular blocking drugs. However, this approach to anesthesia induction has been challenged because the frequency of adverse effects associated with the use of neuromuscular blocking drugs is considered acceptable [323]. Also, avoiding full paralysis during tracheal intubation is associated with less than optimal intubation conditions [324] and may cause laryngeal injuries [64].

Unfortunately, the designs of the investigations studying the effect of opioid drugs on tracheal intubation conditions vary to a great extent. This fact makes data interpretation a complex matter when it comes to a decision regarding the optimal opioid to use during anesthesia induction, and especially if rapid-sequence should be performed in the absence of a neuromuscular blocking drug. There are especially five study-related issues concerning the selection of the appropriate opioid: First, in many studies comparing the efficacies of different opioids, equipotent doses have clearly not been used and author's conclusions may therefore be misleading. Second, timing of

drug administration before laryngoscopy varies to a great extent (between approximately 80 and 200 s), and may not even be described. This variable is potentially a significant confounder when judging drug effect, especially if the efficacy of two drugs with dissimilar blood-brain equilibration rate constants is to be compared in the same study, or if a drug´s efficacy determined in two different studies is compared. Third, dosing of the hypnotic agent varies to a large extent in the literature, especially with respect to propofol where bolus doses from 2 to 4 mg/kg have been administrated. In some studies dosing even varied between individuals participating in the same investigation because the drug was infused until lack of the eyelid reflex indicated loss of consciousness. It is well known that the dose of the induction agent has a significant impact on tracheal intubation conditions [171] [186]. Therefore, it is reasonable to believe that differences in dosing regimens of the induction agent in part explains why studies report different needs for opioids in order to obtain acceptable intubation conditions. Fourth, the scoring systems used when judging intubation condition vary between studies, which may represent a confounding factor when different studies are compared. Fifth, the effect of premedication on intubation conditions may be underestimated. For example, benzodiazepines may influence the intubation conditions in a favorable way [325].

4.9.5 Fentanyl. The beneficial effect of fentanyl on tracheal intubation conditions has been demonstrated [204] [326], but the efficacy of standard dosing (bolus < 3 μg/kg) has been questioned. In patients anesthetized with thiopental 5-7 mg/kg and fentanyl 2.5 μg/kg 180 s prior to laryngoscopy 7% of the patients had unacceptable intubation conditions despite being 65% paralyzed with vecuronium [197]. In a study involving children 3-7 years of age 20% of the patients had unacceptable intubation conditions approximately 90 s after propofol 3.5 mg/kg when preceded by 3 μg /kg fentanyl 5 min before anesthesia induction [327]. Further, in a study on propofol-anesthetized patients where laryngoscopy, preceded by topical application of lidocaine, was initiated approximately 150 s after either fentanyl 2 μg /kg or alfentanil 20 μg /kg, 40% of the patients in the fentanyl group and 5% in the

alfentanil group had unacceptable intubation conditions [328]. The interpretation of the result from these three studies is that fentanyl probably is less suitable than alfentanil for RSII, especially in the absence of a neuromuscular blocking drug. In patients anesthetized with thiopental, and in the presence of a slow-onset neuromuscular blocking drug like vecuronium, rapid administration of large doses of fentanyl might overcome the disadvantages of it´s slow onset-kinetics, but long recovery times from fentanyl´s drug effects makes this solution clinically unattractive and has not been tested.

4.9.6 Alfentanil. The effect of alfentanil on tracheal intubation conditions has been investigated several times, and in all studies a beneficial effect was found. The study designs differ widely. The efficacy of alfentanil has been studied in the absence of a neuromuscular blocking drug when given as an adjunct to propofol [172 173 316 329-332], as an adjunct to propofol in comparison with a technique using a neuromuscular blocking drug [198 317 329 333 334], and as an adjunct drug to improve intubation conditions obtained with an induction regimen involving the use of a neuromuscular blocking drug [22 335]. It appears that alfentanil 30-60 μg /kg, as an adjunct to propofol in the absence of a neuromuscular blocking drug, is needed to obtain comparable intubation condition with an induction technique using suxamethonium when trachea is intubated 90 -120 s after commencement of drug administration. The wide dose range observed in different studies is probably caused by design-related factors: Variable doses of propofol (2-4 mg/kg), variable use of premedication, and use of different methods for assessment of tracheal intubation condition. The beneficial effect of alfentanil during rapid-sequence induction has also been demonstrated in two investigations with vecuronium (0.1 mg/kg) [335] and rocuronium (0.6 mg/kg) [22] where tracheal intubation was completed within 90 s after commencement of drug administration. In both studies the addition of alfentanil 20-30 μg /kg to thiopental 5 mg/kg or propofol 2.5 mg/kg, effectively improved the intubation conditions, i.e. the frequency of unacceptable conditions was reduced from 30% to approximately 5%. Available literature therefore suggests that acceptable intubation conditions can be obtained with high probability within a 90 s

time frame if a moderate dose of alfentanil is given together with a sedative during RSII in the absence of a neuromuscular blocking drug. When used in conjunction with a neuromuscular blocking drug the needed dose is probably much lower. However, the dose needed has not been determined

4.9.7 Remifentanil. The efficacy of remifentanil during tracheal intubation using propofol as the sedative and in the absence of a neuromuscular blocking drug has been studied several times [320 336-341]. The results are reasonable consistent, showing that remifentanil 4 μg /kg with propofol 2-3 mg/kg provides > 90% acceptable intubation conditions 120-180 s after commencement of drug administration. Alfentanil and remifentanil have also been compared in adult patients anesthetized with propofol 2-4 mg/kg in the absence of neuromuscular block [318 342-344]. Remifentanil 4 μg /kg provided better intubation conditions than alfentanil 40 μg /kg (acceptable conditions 80-95% and 45%, respectively). The superiority of remifentanil observed in these studies is not unexpected because the potency difference between the drugs was not taken into account when designing the dose regimens (remifentanil assumed to be approximately 20-40 times more potent than alfentanil [311]. This fact was demonstrated in another study where alfentanil 50 μg /kg was compared with remifentanil 2 μg /kg in patients anesthetized with propofol 2 mg/kg in the absence of a neuromuscular blocking drug [337]. Acceptable intubation conditions 150 s after commencement of drug administration was found in 90 and 35% of patients having alfentanil and remifentanil, respectively. However, in that study only propofol 2 mg/kg with suxamethonium 1 mg/kg provided acceptable conditions in all study subjects.

Remifentanil has not been studied under RSII conditions (tracheal intubation completed within 90 s after commencement of drug administration), neither with nor without the use of a neuromuscular blocking drug. This is because of the potential side effects (muscle rigidity and hypotension) associated with rapid administration of the drug. Since most anesthesiologist probably prefer not to administer high doses of remifentanil as rapid boluses, remifentanil must be considered less attractive than

alfentanil if an opioid is to be used in a clinical setting where RSII is needed.

4.9.8 Opioids plus a neuromuscular blocking drug during RSII.

Although both sedative drugs and opioids significantly reduce the responses to laryngoscopy and tracheal intubation, it appears that a neuromuscular blocking drug must be part of the anesthesia induction regime if rapid-sequence tracheal intubation is to be successfully completed (acceptable intubation conditions) in most patients within 70-90 s. We know this goal is achievable when using suxamethonium together with a sedative drug like thiopental or propofol, even in the absence of an opioid [22]. Because the onset time of rocuronium is longer than for suxamethonium the success rate with this drug is lower if an opioid is not used [66]. A few studies in existing literature indicate that the slower onset of rocuronium can be compensated for by adding an opioid to the rapid-sequence induction regime, i.e. allowing tracheal intubation to be performed before maximum effect of the neuromuscular blocking drug is attained. In 1996 Sparr et al [22] studied the intubation conditions in four groups of non-premedicated patients (25 individuals each) anesthetized with thiopental 5 mg/kg (2 groups) or propofol 2.5 mg/kg (2 groups) in conjunction with rocuronium 0.6 mg/kg. Endotracheal intubation was completed within 90 s after commencement of drug administration. Alfentanil 20 μg /kg were added to the drug regimen in one thiopental and one propofol group. The results were compared to those obtained in a control group of fifty patients receiving thiopental 5 mg/kg and suxamethonium 1 mg/kg. They found that the probability of acceptable intubation conditions in those who received rocuronium and suxamethonium was comparable only if alfentanil was given. Choice of induction agent, thiopental or propofol, did not influence the success rate of acceptable intubation conditions. In 2005 Larsen et al [263] studied 222 patients scheduled for emergency abdominal or gynecological surgical procedures premedicated with intramuscular morphine 2, 5–10 mg 30 min before anesthesia. The patients received alfentanil 10-20 μg/kg at the attending anesthesiologist´s discretion, propofol 2–2.5 mg/kg, and either rocuronium 0.6 mg/kg or suxamethonium 1 mg/kg over a period of 30 s. The endotracheal intubation was completed within 90 s after

commencement of drug administration. Unfortunately, the study did not include a control group where alfentanil was not administered. However, they concluded that the intubation conditions were comparable in patients receiving rocuronium and suxamethonium if alfentanil was added to the drug regimen. In 1988 Helbo-Hansen [335] studied 100 patients premedicated with diazepam 10-20 mg orally, and anesthetized with thiopental 5 mg/kg + vecuronium according to a priming principle (0.01 + 0.1 mg/kg). Groups given alfentanil 15 and 30µg /kg were compared with separate control groups without alfentanil. Endotracheal intubation was completed within 90 s of commencement of drug administration. If a recommended system for scoring of intubation conditions [345] is applied on the data obtained in this study, the results suggest that the rate of unacceptable intubation conditions was < 10% in the alfentanil 30µg /kg dose group. As vecuronium is a drug with slower onset that rocuronium, the results clearly demonstrate the beneficial effect of alfentanil on the tracheal intubation conditions. In 1997 Groener [254] compared two induction regimes, propofol 2.5 mg/kg + vecuronium 0.1 mg/kg vs thiopental 5 mg/kg + suxamethonium 1 mg/kg. Endotracheal intubation was performed within 90 s after administration of the induction agent and 60 s after the neuromuscular blocking drug. Patients in the propofol-vecuronium group had alfentanil 20 µg /kg 120 s prior to tracheal intubation. They found excellent intubation condition in approximately 75% of the patients in both study groups, unacceptable conditions in 10%. In this study, the combination of propofol and alfentanil 20 µg/kg apparently compensated for the difference in onset times between suxamethonium and vecuronium. Even if the effect of alfentanil on intubation conditions during RSII has not been the main aim of previous studies, it is not unreasonable that an expert opinion recommends administration of alfentanil 20 µg/kg in order to increase the probability of acceptable intubation conditions when rapid airway control is needed [71].

4.9.9 Effects on release of stress hormones and hemodynamic responses

Interpretation of results from different investigations studying effects of opioids on

the autonomic responses to laryngoscopy and tracheal intubation becomes a complex matter of several reasons. First, opioids are not anesthetics [346] and are just administered as adjuvant drugs, i.e. in addition to a sedative/induction agent. The specific effect of opioids can therefore not be distinguished from that caused by the induction agent. Second, the effect on release of stress hormones and hemodynamic responses vary between induction agents [34 46 48 347-349], and will likely be significantly influenced by the doses given. Third, timing of drug administration (time allowed between commencement of anesthesia induction and laryngoscopy/tracheal intubation) is crucial because drug effects obtained after a bolus is largely determined by the rate constant (Keo) for the equilibration process between blood and the effect site in the central nervous system. Keo varies to a great extent, both for induction agents and opioids, and must be taken into account whenever the goal is to achieve optimal drug effect after bolus administrations. Fourth, the potential effects of premedication must also be taken into consideration when the effect of opioids is estimated. Fifth, in most studies arterial blood pressure was measured noninvasively with one min intervals. Experience with this kind of monitoring equipment is that it is not always possible to get a reading every minute, especially if the blood pressure is changing. Because opioids influence the hemodynamic variables, we have to question the accuracy of such recordings. It is not unlikely that it may take two min to obtain a reliable noninvasive blood pressure reading if the blood pressure is dropping significantly after drug administration. Maximum and minimum arterial blood pressure after stimulation (i.e. laryngoscopy and tracheal intubation) may therefore easily be missed when monitoring hemodynamic variables noninvasively.

Fentanyl. Several studies have shown the attenuating effect of fentanyl on the release of stress hormones and the associated hemodynamic variables (arterial blood pressure and heart rate) during anesthesia induction [50 196 197 199 202 350-354]. When plasma concentrations of catecholamines are changing, then the magnitude of hemodynamic variables are following in the same direction[197 199 355]. Arterial blood pressure and heart rate decrease after fentanyl, but less so when administered together with thiopental or

etomidate than after propofol [196]. The optimal fentanyl dose in order to abolish all autonomic responses to laryngoscopy and tracheal intubation is dependent on choice of induction agent, timing of drug administration, and use of premedication. Fentanyl 5-6 μg /kg is apparently needed when administered 2-4 min before tracheal intubation in premedicated (opioid or benzodiazepine) patients anesthetized with thiopental 5mg/kg or etomidate 0.3 mg/kg[196 199 351 355]. In case propofol is used (2.5 mg/kg) as induction agent under similar anesthesia induction conditions the fentanyl dose may be reduced 25-50%.

Experimental studies have shown that the equilibration between blood and effect site is a slow process for fentanyl [76 306]. In order to obtain optimal effect of a fentanyl bolus, noxious stimuli (i.e. laryngoscopy and tracheal intubation) should be applied approximately 5 min after it´s administration. This assumption was confirmed in a clinical study by Ko et al[354] where 2 μg/kg fentanyl was administered at several time points (1 to 10 min) prior to laryngoscopy. The hemodynamic responses were optimally diminished if fentanyl was administered 5 min prior to laryngoscopy.

Sufentanil. The effect of sufentanil on responses to tracheal intubation has been studied a few times [200 202 203 352 356-360]. In 10 morphine-premedicated cardiac patients 7 μg/kg sufentanil, in the absence of induction agent, was given as a rapid bolus followed by suxamethonium 1.5 mg/kg. Tracheal intubation was initiated approximately 90 s after commencement of sufentanil administration. Arterial blood pressure decreased 25% on average pre intubation, but increased back to control level 1 min post intubation. Catecholamine levels pre induction and post intubation were similar, however with great standard deviations [356]. In a study with 30 unpremedicated patients anesthetized with thiopental 4 mg/kg and sufentanil 1 μ/kg completely abolished increases in arterial blood pressure when administered 180 s before initiation laryngoscopy and tracheal intubation [200]. In a study on children sufentanil 0.3 μg /kg was given 6 min before tracheal intubation. Arterial blood pressure and heart rate decreased on average 20% pre intubation, and increased

back to baseline 1 min post intubation [203].

Sufentanil is a slow-onset drug, but these studies show how that disadvantage can be compensated for by matching the drugs onset characteristics to the time interval between drug administration and laryngoscopy. The documentation is sparse, but available literature suggest that sufentanil 1 µg /kg is close to optimal in order to prevent hemodynamic changes post intubation when given approximately 3 min before laryngoscopy in adult patients anesthetized with standard doses of thiopental. However, the drug´s slow onset makes it less attractive in an RSII-setting.

Alfentanil. All available literature suggests that alfentanil effectively attenuates the autonomic responses to laryngoscopy and tracheal intubation. This has been shown in both single [45, 173, 317, 319, 342, 359, 361-364] and multiple dose studies [47, 49, 172, 191-193, 329, 331, 358, 365-368]. The release of stress hormones and hemodynamic responses change in parallel when alfentanil drug doses are altered [47]. There are also clear indications in the literature with regard to the average dose of alfentanil that is needed in order to obtain complete control of autonomic responses post intubation under non-RSII conditions. This is because an almost uniform study design has been used in previous investigations studying this issue: Equipotent doses of propofol and thiopental used for (2-2.5 mg/kg and 4-5 mg/kg, respectively), timing between start of induction and laryngoscopy within a tight range (2-3 min), and premedication (either an opioid or a benzodiazepine). It appears that 30-40 µg /kg of alfentanil given 2-3 min before laryngoscopy is sufficient in premedicated patients when the goal is to prevent arterial blood pressure and heart rate post intubation from increasing above baseline level. When pre (immediately prior to initiation of laryngoscopy) and post intubation values are compared a small increase in arterial blood pressure and heart is normally observed, which frequently coincides with a small increase in noradrenaline levels [47].The price to pay for this lack of significant response to airway stimulation is a 20-30% reduction in arterial blood pressure pre

intubation, and 3-5 min post intubation.

Alfentanil is a fast-onset drug, maximum effect site concentration apparently occurring approximately after one min of a bolus administration. Therefore, it should be appropriate to apply noxious stimulation earlier than two minutes after it is injected. However, the alfentanil dose needed to prevent autonomic responses if laryngoscopy is applied < 60 s after commencement of drug administration has not yet been determined.

Remifentanil. The effect of remifentanil on hemodynamic responses to laryngoscopy and tracheal intubation has been studied in healthy patients [195, 336, 338, 342, 353, 357, 358-360, 367, 369-372], and rather extensively in preeclamptic parturients undergoing C-section[35, 373-374]. The pattern is the same with remifentanil as with the other opioids. Dose-response studies show that magnitude of release of stress hormones and hemodynamic changes that occur secondary to laryngoscopy and tracheal intubation vary in parallel with drug dose [190 195 336 338 373 374], and plasma catecholamine levels do not increase unless a simultaneous increases in arterial blood pressure occur. The results in healthy patients are fairly consistent between studies, and most authors find adequate control of hemodynamic responses post intubation with 1 μg/kg of remifentanil when laryngoscopy is initiated 2-3 min after ending a slow bolus administration [336 369-371]. It seems that this pattern is independent of choice of induction agent (thiopental 4-5 mg/kg or propofol 2-2, 5 mg/kg). Only in one study did arterial blood pressure increase > 20% when pre and post intubation values were compared [338]. However, all authors find remifentanil, even if administered as a short infusion over 30 s, to be very potent hemodynamically. Reductions in arterial blood pressure between pre induction and pre intubation of approximately 10 to 45% have been reported. Several authors also recommend preemptive use of anticholinergic in order to avoid bradycardia.

Remifentanil has been tested in an RSII fashion (laryngoscopy initiated 90 s after commencement of administration of remifentanil 1 μg/kg over 10 s) [373] in

preeclamptic patients undergoing C-section, anesthetized with thiopental 5 mg/kg and suxamethonium 1.5 mg/kg. Arterial blood pressure, invasively recorded, dropped approximately 25% pre intubation and increased marginally (5%) one min post intubation. Norepinephrine concentrations did not change significantly between baseline and post intubation, while epinephrine concentrations decreased 25% prior to laryngoscopy. However, all patients had hydralazine and magnesiumphospate prior to anesthesia induction.

Available literature suggests that remifentanil 1 μg/kg provides acceptable intubation conditions in most patients when administered 2-3 min before airway stimulation. In one study on regular surgical patients even 4 μg /kg was given without any significant adverse reactions [336]. However, the tendency to hypotension and bradycardia reported with remifentanil makes caution necessary when using the drug in an RSII setting.

4.9.10 Opioids and autonomic responses: Drug comparison. It appears that abolition of autonomic responses to laryngoscopy and tracheal intubation is obtainable with all opioids used in anesthesia today, it is just a matter of dose. However, there is a price to pay with increasing doses: The frequency of side effects will increase, primarily hypotension and bradycardia during the time interval between drug administration and initiation of laryngoscopy, and again sometime after tracheal intubation is completed. Opioids may differ in this respect. In a study comparing equipotent bolus dose of fentanyl (5 μg /kg) and alfentanil (30 μg /kg) the average reduction in systolic arterial pressure from baseline to pre intubation was 5% and 15%, respectively [351]. Unfortunately, only 10 + 10 individuals were included in the comparison, and the difference was not statistically significant. When fentanyl and sufentanil in reasonable equipotent doses were compared, no differences between the drugs were observed [202] [352]. The potential for hypotension and bradycardia associated with the use of remifentanil is well known [311], and normal practice is therefore to avoid bolus administration of this drug. Unfortunately, there is no clinical study available comparing the hemodynamic effect of equipotent doses of alfentanil and remifentanil,

but in an experimental study in healthy volunteers' remifentanil reduced arterial blood pressure and heart rate significantly more than alfentanil [79]. Therefore, taking into account onset time and potential for hypotension and bradycardia after bolus administration, alfentanil appears to be the logical first option opioid to use during RSII. However, information regarding doses needed in order to abolish autonomic responses under such clinical circumstances is essentially lacking.

4.10 Other adjuvants: Lidocaine

4.10.1 Drug description

Lidocaine may be administered orally, topically, or intravenously. During RSII, where patients may be uncooperative and the time factor is essential, the intravenous route appears to be most appropriate to use.

4.10.2 Pharmacological effects. Lidocaine is a class IB antiarrhythmic agent with local anesthetic properties. It exerts analgesic and sedative actions [375], probably due to the inhibition of G protein-coupled [376] and NMDA receptors [377]. The effect on anesthesia depth was demonstrated in a clinical study reporting reduced need for inhaled anesthetics when lidocaine was administered simultaneously [378]. Lidocaine suppresses the cough response to foreign objects in the airway, either by a central effect in the brainstem or by blocking peripheral receptors in tracheal mucosa [379 380].

Toxic effect (tinnitus, dizziness, circumpolar paresthesia) may be experienced with lidocaine 2 mg/kg if the drug is administered over less than 30 s [330 381].

4.10.3 Pharmacokinetics and pharmacodynamics. Lidocaine is eliminated by the liver, flow‐dependently. Wide variability in disposition of lidocaine has been reported [382]. Because plasma concentrations after bolus administration vary significantly, even

in healthy individuals, precise dosing regimens are difficult to design. Clinical studies, using the cough response to tracheal intubation as a measure of pharmacodynamics effect, suggest that the optimal time interval between drug administration and airway manipulation is 3-4 min [381 383].

4.10.4 Effects on intubation conditions

A beneficial effect of lidocaine on intubation conditions was reported already in the early 1960s[57]. However, later investigations show inconsistent results, either positive [316 330 340 369 381], or no significant effect [183 384]. This apparent discrepancy between different investigations may be explained by a shorter than optimal time interval between drug administration and laryngoscopy (< 2 min) in the studies showing no effect. However, there is agreement in the literature that opioids have a superior and more consistent positive effect on tracheal intubation conditions [316 340 369].

4.10.5 Effects on release of stress hormones and hemodynamic responses

Early studies showed that intravenous lidocaine attenuated the cardiovascular response to laryngoscopy and tracheal intubation [385 386]. Later studies, however, show variable effect of lidocaine. Tam et al found lidocaine to be better than placebo [387 388], and Wilson et al observed beneficial effect on arterial blood pressure and no effect on heart rate response to laryngoscopy and tracheal intubation [383]. Other studies conclude that no significant effect of lidocaine on hemodynamic responses to airway manipulation exists [59 192 361 363 380 389-397]. In part, the discrepancy may be explained by shorter time interval between drug administration and tracheal intubation than optimal in the studies showing no effect. However, Miller et al did not observe a beneficial effect of lidocaine when it was administered 3 min before airway stimulation [390]. In only one investigation studying the effect of lidocaine on responses to tracheal intubation has the release of stress hormones simultaneously been measured [383]. The results were inconclusive due to small number of study subjects.

4.11 Other adjuvants: Nonanesthetic drugs

The use of nonanesthetic adjuvant to modify cardiovascular responses to laryngoscopy and tracheal intubation has a long tradition. In 1960 De Vault et al. [398] found that pretreatment with phentolamine, 5 mg i.v prevented the hypertensive and tachycardic response to intubation during a light barbiturate- suxamethonium anesthesia. In later years many different vasoactive drugs have been introduced in clinical practice [399], and some may potentially be used in an RSII setting [400] .

4.11.1 Hydralazine

Hydralazine has been the antihypertensive of choice for many years in pregnant women with severe hypertension [401] [402]. It relaxes the tone of vascular smooth muscle, with a greater effect on arterioles than veins. The recommended bolus dose of hydralazine is 2.5 to 10 mg IV, with onset time described to be 10 to 15 min. Few studies have been conducted to evaluate the efficacy of hydralazine in attenuation of cardiovascular changes after laryngoscopy and tracheal intubation. Hodgkinson et al.[403] and Safavi et al. [404] reported that hydralazine does not adequately control the brief but sudden episode of hypertension that occurs during laryngoscopy and tracheal intubation in preeclampsia patients, while Davies et al.[405] found hydralazine 0.4 mg/kg IV given 10 minutes prior to induction effective in attenuating the arterial blood pressure, but not heart rate response in nonpregnant patients undergoing intracranial surgery. Inconsistent result, long onset time, and compensatory tachycardia, makes hydralazine an unattractive drug to use during RSII.

4.11.2 Nitroprusside

Nitroprusside is a direct-acting vasodilator that reduces peripheral vascular resistance on both the arterial and venous sides. Sudden decreases in preload and afterload of the heart may change cardiac output and arterial blood pressure

significantly after bolus administration [406], but the effect is short-lived. Stoelting [407] reported that nitroprusside i.v bolus dose of 1μg /kg and 2 μg/kg given 15 seconds prior to laryngoscopy effectively blunt the BP response to laryngoscopy and tracheal intubation. However, unpredictable effect, reflex tachycardia, dilation of cerebral vessels, and that the drug must be protected against light, makes the nitroprusside an unattractive drug to use during RSII.

4.11.3 Nitroglycerin

Nitroglycerin is an organic nitrate that is primarily used to counteract angina pectoris. It dilates venous capacitance vessels and large coronary arteries, producing peripheral venous pooling and decreased myocardial wall tension [408 409]. The drug can be administered sublingually or intravenously. It has a rapid onset and offset and is therefore normally given as a continuous intravenous infusion [406]. Mikawa et al. [410] reported that intravenous boluses of nitroglycerin 1.5 μg /kg or 2.5 μg /kg, administered at initiation of laryngoscopy, was a safe and protective method against secondary increases in arterial blood pressure, but not tachycardia. Similar effect was obtained when nitroglycerine was given as a continuous intravenous infusion during laryngoscopy and tracheal intubation [411]. Unpredictable effects (hypotension)[406] and reflex tachycardia makes nitroglycerine an unattractive drug to use in RSII situations.

4.11.4 Magnesium Sulfate

Magnesium is primarily used for prophylaxis and treatment of convulsions in preeclamptic parturients [412] , but has also vasodilator and antiarrhythmic effects [413]. Pretreatment with magnesium sulfate prior to airway stimulation reduces catecholamine release from adrenal medulla and sympathetic nerve endings[345 414 415] and consistently attenuates arterial blood pressure responses [363 415]. The tachycardic response to laryngoscopy and tracheal intubation is less well contained with

magnesium sulfate [363] . A favorable effect of magnesium sulfate on hemodynamic responses to airway stimulation has been observed when magnesium sulfate is given together with small doses of alfentanil [416].

Magnesium sulfate potentiates the effect of nondepolarizing neuromuscular blocking [417-420], and prolonged duration of muscle paralysis may be expected when both magnesium sulfate and rocuronium are used during the RSII procedure.[418-420].

4.11.5 Calcium Channel Blockers

Nicardipine, diltiazem and verapamil are calcium channel blockers that dilate peripheral and coronary arterial vessels, and are used primarily to treat hypertension, angina, vasospasm, and supraventricular arrhythmias [421-431]. Nicardipine, diltiazem, and verapamil can be administered intravenously. Nicardipine (15-30 μg/kg), diltiazem (0.2 mg/kg), or verapamil 0.1 mg/kg given 1 min prior to initiation of laryngoscopy attenuate the arterial blood pressure response, but not the reflex tachycardia [426 427]. Lack of effect on the tachycardic response to airway stimulation makes this class of drug unattractive to use in an RSII setting.

4.11.6 Beta-Blockers

Beta-blockers are normally used to treat hypertension and angina pectoris. Selective beta1-blockers attenuate the effect of sympathetic nerve impulses on the heart. Heart rate and contractility of cardiac muscle cells are reduced, which improves the balance between oxygen supply and demand. Prophylactic beta-adrenergic receptor blockade was shown to prevent hypertensive crises during laryngoscopy and tracheal intubation in treated and untreated hypertensive patients already in 1973 [432]. Later, various beta-blockers have been tested: Practolol [432] , acebutolol [433] , propranolol, atenolol [434], metoprolol [435] , labetalol [355 436-438] and esmolol[439 440]. Although they effectively attenuate hemodynamic stress responses to laryngoscopy and tracheal

intubation, serious side effects (bronchospasm, bradycardia, hypotension, heart failure, and cardiac dysrhythmias) have been a concern with some of the old nonselective beta-blockers [355 432]. Typically, higher plasma concentrations of catecholamines are measured post tracheal intubation in beta-blocker-treated patients compared to controls, despite the attenuating effect on hemodynamic responses. It is speculated if beta-blockers slow the clearance of catecholamines [441]. In an RSII setting it is always preferable to use drugs with rapid onset times, which simultaneously may be administered as rapid boluses (≤ 15 s). Only esmolol fulfills these criteria of available beta-blockers [442 443]. Labetalol has been shown to attenuate sympathetic stress reactions during airway manipulation, but the drug has slow onset and must be titrated to obtain a targeted response before application of a stressful stimulus [355]. Therefore, labetalol is not an attractive drug to use during RSII. Esmolol 1-2 mg/kg given 1-2 min prior to airway stimulation significantly attenuates the ensuing hemodynamic responses, although the effect is more pronounced on heart rate than arterial blood pressure [191 368 380 438 441 444–447]. The magnitude of effect is also dependent on the anesthetics simultaneously administered, the effect of esmolol being greater in the presence of an opioid [438]. In a Canadian multicenter study including > 500 patients, placebo was compared with groups having either esmolol 100 mg or 200 mg [447]. In patients having opioids simultaneously with esmolol a significantly higher number of individuals experienced hypotension when 200 mg was given, despite equal effect on arterial blood pressure responses to tracheal intubation were observed in both esmolol groups.

Available literature suggests that esmolol may be a valuable adjunct in order to reduce the requirements of opioids during RSII, but the appropriate dose in situations where patients do not tolerate increases in arterial blood pressure is not determined.

4.11.7 Various vasoactive agents

Several other agents with hemodynamic effects have been tested in order to attenuate increases in arterial blood pressure and heart rate post intubation: Angiotensin-converting enzyme inhibitors [448] [449], clonidine [450] [451], prostaglandin E [426] [452] and adenosine triphosphate [453]. The efficacy of these drugs when used during induction of anesthesia is not thoroughly studied, and their place in an RSII setting is therefore unsettled.

4.12 Summary of introduction

Rapid-sequence induction and intubation (RSII) is a stressful anesthesia induction technique that was introduced in 1970 as a measure to prevent aspiration of gastric content to the airway in patients at risk of regurgitation. The basic concept, that the airway in some patients must be secured with a cuffed endotracheal tube rapidly during anesthesia induction, is well established in anesthesia practice. However, recent surveys show that most clinicians modify the original technique. Specifically, pre anesthesia aspiration of gastric content is less frequently practiced, many clinicians allow mask ventilation before tracheal intubation, and the relevance of cricoid pressure has been challenged. Over the years, many new drugs relevant for RSII have been introduced into clinical practice. Therefore, thiopental has in many instances been replaced with other induction agents, and rocuronium is often preferred as the neuromuscular blocking drug instead of suxamethonium. In addition, opioids are frequently used during RSII because they have beneficial effect on intubation conditions and attenuate hemodynamic responses to laryngoscopy and tracheal intubation.

Despite that all aspects of RSII have been extensively investigated; there are still issues that are inadequately addressed:

4.12.1 Acceptable vs perfect intubation conditions

In an emergency anesthesia induction situation, where securing the airway is the

main issue, clinicians may accept less than ideal intubation conditions. The term ”acceptable intubation conditions” is frequently used in the literature, implying

that, although the intubation conditions are not perfect, no significant harm to laryngeal structures will ensue if tube insertion into the trachea is attempted. This is probably a major reason why most previous RSII studies have focused on successful intubation rather than optimal intubation conditions. Therefore, literature regarding optimal drug regimens to use when perfect intubation conditions are needed in an RSII setting is essentially lacking.

4.12.2 Timing of drug administration

Timing of drug administration, i.e. the time frame from commencement of drug administration until tracheal intubation is completed, is an important aspect of RSII. If hypoxemia or aspiration of gastric content is imminent it would be preferable with tracheal intubation as fast as the drug action allow. Most previous clinical investigations have aimed at completing tracheal intubation within 90 s, but experimental studies in humans suggest that laryngoscopy safely can be initiated < 60 s after commencement of drug administration if suxamethonium is used for muscle relaxation (i.e. 40 s after administration of suxamethonium). High probability of obtaining acceptable intubation conditions 40 s after rocuronium can only be expected if administered together with an adjuvant drug (i.e. rapid-acting opioid). However, information on dose requirements of the opioid in this situation is scarce, especially if perfect intubation conditions are needed. It is likely that dose requirements when high probability of perfect intubation conditions is needed are significantly greater than recommended in existing literature to be used during RSII (i.e. alfentanil 20-30 μg/kg).

4.12.3 Hemodynamic responses

Opioids are used in conjunction with a sedative and a neuromuscular blocking drug

when hemodynamic responses must be attenuated. In an emergency situation a rapid-acting drug, like alfentanil, is frequently used. However, information regarding dose requirements when the noxious stimulation (laryngoscopy) is applied < 60 s after commencement of drug administration is scarse, especially if a simultaneous need for perfect intubation conditions and minimal hemodynamic response exist.

4.12.4 Covariates

Demographic variables, like sex, body weight, and age, influence the effect of anesthetic drugs. It is therefore not unlikely that such covariates also may influence the physiologic responses to laryngoscopy and tracheal intubation, as well. There is no available information in the literature regarding this issue.

5.0 Specific study aims addressed in this thesis

1. Define the dose of alfentanil that is needed during RSII (tracheal intubation completed within 70 s) to obtain high probability of perfect intubation conditions when given in conjunction with thiopental 4 mg/kg and, a: Standard dose of rocuronium (0.6 mg/kg), and b: High dose rocuronium (1 mg/kg).
2. Define the dose of alfentanil that is needed during RSII (tracheal intubation completed within 70 s) to prevent significant increases in stress hormones (epinephrine, norepinephrine, vasopressin) post intubation in most patients, when administered in conjunction with thiopental 4 mg/kg and rocuronium 0.6 mg/kg.
3. Define the dose of alfentanil, when given in conjunction with thiopental 4 mg/kg and rocuronium 0.6 mg/kg during RSII (tracheal intubation completed within 70 s) that is needed, to obtain with high probability, simultaneous achievement of perfect intubation conditions and minimal hemodynamic responses to

laryngoscopy and tracheal intubation.

4. Determine if demographic variables, i.e. sex, body weight or age, influence dose requirements of alfentanil during RSII.

6.0 Methods

6.1 RSII technique used

The original RSII procedure outlined by Stept & Safar in 1970 consists of fifteen steps [6]. In the following these steps are listed, and our modifications described:

Step 1. Intravenous access was established with a venflon on the dorsum of the hand, through which lactated Ringer´s solution was rapidly running. All drugs were administered via that iv line.

Step 2. Equipment check

Equipment check was made before anesthesia induction. Specifically, a stylet was used with the endotracheal tube.

Step 3. Stomach emptying

This step involves decompression of the stomach with a large-bore nasogastric tube. As our patients were undergoing elective surgery and were fasting over-night, aspiration of gastric content was not performed.

Step 4. Removal of foreign objects in the mouth

Removal of dentures

Step 5: Preoxygenation

Preoxygenation (flow 10 L/min) with a tight-fitting mask for 3 minutes.

Step 6. Body position

As regurgitation was not a concern with any of the study subject included, patients were lying flat, not with the upper body elevated 30^0 as recommended by Stept & Safar. Sniffing position of the head was secured with a specially designed pillow.

Step 7. Monitoring of vital organ functions

Surveillance equipment used in order to monitor cardiac and respiratory function was: Precordial ECG, continuous monitoring of arterial blood pressure using an indwelling catheter in the radial artery, peripheral oxygen saturation using a finger probe, and BIS (bispectral index).

Step 8. Precurarization

Stept & Safar recommended precurarization. As suxamethonium was not used in our studies, a precurarization drug was not part of the anesthesia drug induction regimen.

Step 9. Drug administration

A small dose of thiopental was recommended by Stept & Safar (150 mg/70 kg body weight). We used thiopental 4 mg/kg, which is a recommended dose in most comprehensive anesthesia textbooks (Millers Anesthesia). Thiopental was preceded by a predetermined, but variable, dose of alfentanil, and followed by rocuronium, either 1 mg/kg (paper 1) or 0.6 mg/kg (paper 2 and 3). All drugs were injected rapidly, i.e. 15 s total administration time.

Step 10. Cricoid pressure

Cricoid pressure, which was recommended by Stept & Safar, was not applied.

Step 11. Administration of suxamethonium

Not applicable

Step 12. Omission of mask ventilation and nerve stimulation

Mask ventilation, was not performed after occurrence of apnea in our study subjects (in accordance with recommendation of Stept & Safar). Stept & Safar recommended use of peripheral nerve stimulation in order to detect onset and degree of muscle relaxation after administration of the neuromuscular blocking drug. We did not use nerve stimulation during the procedure because recent studies have shown that responses of the adductor pollicis to nerve stimulation do not reflect the status of the neuromuscular function at the laryngeal muscles during RSII [82].

Step 13. Timing of tracheal intubation

Stept & Safar recommended inserting the endotracheal tube 30-60 s after injection of suxamethonium. In our studies laryngoscopy was initiated 40 s after injection of rocuronium. The timing of neuromuscular blocking drug administration and tube insertion was therefore similar to that outlined by Stept & Safar. Tracheal intubation was completed when the cuff was inflated, i.e. within 15 s after initiation of laryngoscopy.

Step 14. Release of cricoid pressure

Not applicable in our studies.

Step15. Stomach emptying post intubation

Not applicable in our studies.

6.2 Inclusion of study subjects

Following approval from the local institutional review board, written informed consent was obtained from all patients.

We studied two series of ASA physical status I patients. 60 patients were included in series #1 (paper 1), 84 patients were included in series #2 (paper 2+3). All patients were admitted for elective surgical procedures. Patients aged more than 55 or less than

18 yrs, having gastro-esophageal reflux, BMI > 28, suffering from neuromuscular disease, or undergoing treatment with drugs known to interfere with neuromuscular transmission, were excluded. All patients enrolled had a Mallampati class 1 or 2 airway anatomy and no anticipated difficulty with mask ventilation or tracheal intubation.

We included 24 more study subjects in the second series of patients compared to series #1, because the results from the first investigation (paper 1) revealed that more than 5 different dose groups of alfentanil might be needed in order to make the logistic regression analysis work properly.

6.3 Study conduct

Premedication (midazolam 0.03 mg/kg IV 15 min prior to anesthesia induction) was offered to patients in series #1 (paper 1). In series 2 (paper 2 and 3) no premedication was provided.

The patients were randomly allocated using random-number table to receive one of five (series #1) and one of seven (series #2) different doses of alfentanil (Series #1: 0,15, 30, 45, or 60 μg/kg. Series #2: 0, 10, 20, 30, 40, 50, or 60 μg/kg). The allocation sequence was concealed from the researchers by using numbered, opaque and sealed envelopes containing information on the dose of alfentanil to be used. A nurse anesthetist not involved in the study picked the envelope that would be assigned to the study subjects, and prepared the drug amount to be administered. The allocation process consequently produced study groups with 12 subjects each.

Anaesthesia was induced in rapid-sequence fashion after 3 min of preoxygenation, i.e. the aim being to have a cuffed endotracheal tube in place within 70 s after commencement of drug administration. Three drugs were administered in rapid succession, a blinded dose of alfentanil (first), thiopental 4 mg/kg (second), and rocuronium 1 mg/kg (series #1) or 0.6 mg/kg (series #2)(third). Drugs were injected

into an IV catheter at the dorsum of the hand, through which NaCl 0.9% was running rapidly. Laryngoscopy was initiated 40 s after administration of rocuronium, i.e. 55 s after commencement of anesthesia induction.

Tracheal intubation was performed by only one of the researchers, the same researcher in both series of patients. He was blinded to the dose of alfentanil administered and scored intubation conditions in accordance with a recommended assessment scale [345]. If the score was excellent in all categories (ease of laryngoscopy, vocal cord position, reaction to tracheal tube insertion) the procedure was assessed as a success (i.e. perfect intubation conditions). If the score was different from excellent in any assessment category the procedure was considered as a failure.

Ephedrine 0.2 $mg \cdot kg^{-1}$ was administered if systolic ABP decreased below 70 mm Hg. If systolic ABP post intubation increased > 50% of pre induction values either thiopental 1 $mg \cdot kg^{-1}$ or alfentanil 10 $\mu g \cdot kg^{-1}$ was allowed. A BIS sensor was attached to the forehead of the patient. Thiopental 1–2 $mg \cdot kg^{-1}$ was allowed if the BIS value increased above 60 during the first five min post intubation. Five min post intubation the patient received additional anesthesia-related drugs at the attending anesthesiologist´s discretion.

6.4 Data acquisition

6.4.1 Intubation conditions

The fraction of patients with perfect intubation conditions within each alfentanil dose group was recorded and later used in logistic regression analyses.

At laryngoscopy an arterial plasma sample was collected and the concentration of alfentanil measured. Alfentanil assay: Blood samples were centrifuged immediately and plasma stored at -70 °C. Specimens were analyzed with liquid chromatography

mass spectrometry (LC-MS) after liquid-liquid extraction. Flurazepam was used as the internal standard. The analyses were performed on an Agilent LC-MSD 1100 system (Agilent Technologies, Palo Alto, CA, USA), with a Zorbax SB-C18, 150 mm x 4.6 mm, 5 µm particle size, as analytical column. The mass transitions were *m/z* 417.2>268.2>197.1>165.1 for alfentanil and *m/z* 388.1 for flurazepam. The limit of quantification was 1.5 ng·ml^{-1} and the method was linear at least up to 500 ng ml^{-1}. Between-day coefficients of variation were assessed at three different concentrations (low, medium and high), and were < 5% at all concentration levels.

6.4.2 Stress hormones (epinephrine, norepinephrine and vasopressin)

Concentrations of stress hormones were measured at baseline (before drug administration), pre intubation, and post intubation (at 0.5, 1, 2, 3, and 5 min post intubation for epinephrine and norepinephrine, at 1 min for vasopressin). Concentration differences between baseline and pre intubation (base-pre), baseline and post intubation (base-post), and pre and post intubation (pre-post) were calculated. In response categories involving post intubation concentrations (base-post and pre-post) the maximum value recorded during the blood sampling period was used in the calculations.
The time point of maximum increase post intubation in each response variable was recorded.

Catecholamine assay: Arterial blood samples of 5 ml were mixed with EGTA and reduced glutathione, placed on ice, and centrifuged to separate plasma from blood cells. Plasma was stored at -80 ^{0}C. Epinephrine and norepinephrine concentrations were analyzed using a single isotope radioenzymatic assay [454]. The assay is sensitive to 1 pg (20 pg/ml of plasma) and linear between 3 and 3000 pg. The coefficient of variation varied between 0.8 and 3% (dose range 1 - 1000 pg.).
Vasopressin assay*:* Arterial blood samples (2.25 ml) were collected on chilled EDTA tubes, mixed thoroughly, placed on ice, and centrifuged within 30 min. Plasma was

stored at- 80 ^{0}C. Concentrations of vasopressin were determined by competitive radioimmunoassay, RIA (Buehlmann Laboratories AG, Schoenenbuch, Switzerland). The assay is sensitive to 0.6 pmol/l and linear in the range 0.6 – 75 pmol/l with coefficient of variation < 10%.

6.4.3 Hemodynamic variables: Arterial blood pressure (ABP) and heart rate (HR)

ABP and HR were continuously monitored via the indwelling catheter inserted in the radial artery. Values were recorded at baseline, pre and post intubation. Differences between baseline and pre intubation (base-pre), baseline and post intubation (base-post), and pre and post intubation (pre-post) were calculated. The lowest value measured pre intubation and the highest value post intubation (during 5 min period following tracheal intubation) was used in these calculations.

The time point of maximum ABP and HR during a 5 min period post intubation was recorded. The success rate of preventing a post intubation increase in hemodynamic variables > 10% of baseline was recorded within each alfentanil dose group and used later in logistic regression analyses.

6.5 Outcome measures

6.5.1 Primary:

Determine alfentanil doses associated with 50, 90, and 95% probability of perfect intubation conditions (paper 1 and 2)
Determine relationships between alfentanil dose and magnitude of stress hormone release post intubation (paper 3).
Determine alfentanil doses associated with 50, 90, and 95% probability of preventing increases post intubation > 10% compared to baseline values in hemodynamic

variables (paper 3).
Determine the influence of covariates (sex, body weight, age) on primary outcomes (paper 2 and 3).

6.5.2 Secondary:

Determine if plasma concentration of alfentanil at laryngoscopy is a better predictor of perfect intubation conditions than alfentanil dose (paper 2).

Influence of alfentanil dose on stress hormone release and hemodynamic responses pre intubation (paper 3).

7.0 Statistics

7.1 Sample size determination

Power analysis, in order to estimate a relevant number of patients to include in a study, is normally required by scientific journals before a paper is accepted for publication. This prerequisite is appropriate in investigations were study results are based on pairwise group-comparisons. A major goal of the present thesis is to define doses of alfentanil that, with high probability, reliably secure optimal intubation conditions and prevent significant hemodynamic changes after completed tracheal intubation. A pairwise group-comparison technique is not suitable to answer this research question. Rather, logistic regression should be used when data analysis is based on binary variables, in this case either success or failure in order to obtain perfect intubation conditions or minimal changes in hemodynamic variables. Because all data were analyzed simultaneously in the same process, no formal power analysis was performed. Logistic regression has been used successfully in previous studies where data have

been analyzed with a probability-based approach [81 82], and the number of study subjects were therefore estimated based on the experience obtained in these studies.

7.2 Logistic regression analyses

Logistic regression [455] was used to analyze the success rates of obtaining perfect intubation conditions (paper 1 and 2) and minimal hemodynamic responses, i.e. arterial blood pressure and heart rate (paper 3). The equation used for the logistic regression was:

Fraction of success = m3 + (1 - m3) (A/ (A + 1))

Where A is EXP (m1 + m2 (dose)). m 1 and m2 are the inbuilt parameters of the logistic regression program, and m3 is an additional parameter which allows for the proportion of patients who would have perfect intubation conditions/minimal hemodynamic responses when no alfentanil is used. The doses of alfentanil which gave a 50, 90 and 95% probability of success (D50, D90 and D95, respectively) were calculated from these dose-response curves.

In order to estimate confidence intervals for the D50, D90 and D95 variables, Monte Carlo simulations were run[456], and the bootstrap technique with resampling was used. The original data set is assumed to represent a very large population, and new data sets are compiled by resampling from the original set of data. This approach is taken because there are no good formula-based methods to estimate confidence limits for variables calculated from three parameters (m1, m2, and m3 in the equation), all of which vary independently. When new data sets are generated, an individual result from the original data is picked at random, and replaced in the original data set before the next random pick is made. Each new data (normally > 1000 new sets are generated) are then analyzed with logistic regression to estimate alternative D50, D90, and D95 values.

Multivariate logistic regression was used to analyze the effect of alfentanil dose, sex,

body weight, age, and alfentanil plasma concentration at laryngoscopy on the success rate of perfect intubation conditions (paper 2).

7.3 Linear regression analyses

Least-squares linear regression was used to analyze the following relationships (data recorded on an interval scale):

1. The relationship between alfentanil dose and alfentanil concentration at initiation of laryngoscopy (paper 2).

2. The relationships between alfentanil dose and:
   - Concentrations of stress hormones at baseline, pre and post intubation
   - Concentration differences of stress hormones (base–pre, base–post, pre–post)
   - Hemodynamic variables at baseline, pre and post intubation
   - Differences in hemodynamic variables (base–pre, base–post, pre–post)

   (paper 3)

To examine if a non-linear, rather than a linear relationship should be used to describe the data, a polynomial term ($dose^2$) was added and tested for statistical significance (paper 2 and 3).

Multiple linear regressions were used to determine whether sex, body weight or age affected alfentanil blood concentration at laryngoscopy (paper 2).

Multiple linear regression was used to analyze the effect of sex, body weight, age, and alfentanil plasma concentration at initiation of laryngoscopy on the relationship between alfentanil dose and the pre–post category of each response variable (epinephrine, norepinephrine, vasopressin, arterial blood pressure, and heart rate) (paper 3).

7.4 Pairwise comparisons

Demographic data were analyzed with ANOVA + Newman-Keuls (interval data) or Chi Square (categorical data) (paper 1, 2, and 3).

Paired t-test was used to analyze individual changes pre and post intervention (i.e. before and after drug administration and tracheal intubation).

Data were analyzed using JMP 10.0 (SAS Institute, Cary, NC), Stata 12.0 (StataCorp, College Station, TX), or IBM SPSS Statistics (version 22, 2013).

Differences were considered significant at $P < 0.05$.

8.0 Results

The alfentanil dose groups did not differ with respect to sex, body weight, or age (paper 1, 2, and 3). 4 patients were excluded due to technical reasons or unanticipated difficult airway. 4 patients (three in alfentanil 0 μg.kg---1, and one in alfentanil 10 μg.kg---1 groups) needed additional anesthetics post intubation due to exaggerated arterial blood pressure response. All patients were asked (immediately after surgery and on first postoperative day) if they had slept well during surgery, and none reported awareness.

8.1 Intubation conditions (paper 1 and 2)

Success rates of perfect intubation conditions increased gradually with increasing doses of alfentanil (both paper 1 and 2), and therefore it was possible to construct dose-response curves based on logistic regression. The estimated ED95 of alfentanil for perfect intubation conditions was 36 μg /kg (95% CI 33-39) with rocuronium 1 mg/kg and 56 μg/kg (95% CI 44-68) with rocuronium 0.6 mg/kg. A steeper slope was obtained with rocuronium 1 mg/kg because the success rate was 1.0 with the two upper doses of alfentanil (45 and 60 μg/kg), while ideal intubation conditions in all study subjects was found only with the 60 μg/kg dose when the lower rocuronium dose was administered. As the CIs of the two dose–response curves do not overlap it is concluded that the dose requirements of alfentanil in order to obtain perfect intubation conditions

are significantly greater with rocuronium 0.6 mg/kg than 1 mg/kg.
The average alfentanil plasma concentrations were similar in patients with and without perfect intubation conditions (table 2).

8.2 Changes in release of stress hormones (paper 3)

Plasma concentrations at baseline did not differ between alfentanil dose groups for any of the stress hormones. Maximum release of epinephrine and norepinephrine post intubation was recorded within 1 min in 50%, and at ≥ 5 min in 30% of the study subjects.

8.2.1 Changes occurring between baseline and pre intubation (base-pre)

Epinephrine: The average epinephrine concentration decreased significantly between baseline and pre intubation only in the 20 μg/kg group (P = 0.01), and the pre-base concentration difference did not change with increasing doses of alfentanil (P = 0.53).

Norepinephrine: The average norepinephrine concentration decreased significantly between baseline and preintubation in the 20, 40, and 60 μg/kg groups (P = 0.01), but the pre-base concentration difference still did not change significantly with increasing doses of alfentanil (P = 0.93).

Vasopressin: The average vasopressin concentration did not change significantly in any alfentanil dose group, and the pre-base difference did not change with increasing doses of alfentanil (P = 0.54).

8.2.2 Changes occurring between baseline and post intubation (base-post)

Epinephrine: The average epinephrine plasma concentration did not change significantly between baseline and post intubation in any alfentanil dose group. The

average post-base concentration difference still decreased with increasing doses of alfentanil ($P = 0.01$, $R^2 = 0.58$), and the linear regression, based on group-averaged data, suggests that approximately 25 μg/kg of alfentanil is needed to prevent significant increases in epinephrine plasma concentrations post intubation when compared to baseline values. A non-linear model did not improve the data fit.

Norepinephrine: Average norepinephrine plasma concentration increased between baseline and post intubation in the group where no alfentanil was given ($P = 0.01$), and decreased in the 40 μg/kg group ($P = 0.03$). The average post-base concentration difference decreased with increasing doses of alfentanil ($P = 0.001$, $R^2 = 0.69$), and the linear regression, based on group-averaged data, suggests that approximately 30 μg/kg of alfentanil is needed to prevent significant increases in norepinephrine plasma concentrations post intubation when compared to baseline values. A non-linear model did not improve the data fit.

Vasopressin: Average vasopressin plasma concentration did not change significantly between baseline and post intubation in any alfentanil dose group. The average post-base concentration difference (absolute values in ng/ml) still decreased with increasing doses of alfentanil ($P = 0.007$, $R^2 = 0.49$), and the linear regression, based on group-averaged data, suggests that approximately 40 μg/kg of alfentanil is needed to prevent significant increases in vasopressin plasma concentrations post intubation when compared to baseline values. A non-linear model did not improve the data fit.

8.2.3 Changes occurring between pre and post intubation (pre-Post)

Epinephrine: Average epinephrine concentration did not change significantly between pre and post intubation in any alfentanil dose group. The average post-pre concentration difference still decreased with increasing doses of alfentanil ($P = 0.007$, $R^2 = 0.58$), and the linear regression, based on group-averaged data, suggests that approximately 50 μg/kg of alfentanil is needed to prevent significant increases in epinephrine plasma concentration post intubation when compared to pre intubation

values. A non-linear model did not improve the data fit.

Norepinephrine: Average norepinephrine concentration increased significantly between pre and post intubation in alfentanil 0 and 20 μg/kg dose groups. The average post-pre concentration difference decreased with increasing doses of alfentanil ($P = 0.002$, $R^2 = 0.70$), and the linear regression, based on group-averaged data, suggests that approximately 50 μg/kg of alfentanil is needed to prevent significant increases in norepinephrine plasma concentration post intubation when compared to pre intubation values. A non-linear model did not improve the data fit.

Vasopressin: Average vasopressin concentration (absolute value in ng/ml) increased significantly between pre and post intubation only in the alfentanil 10 μg/kg group. The average post-pre concentration difference still decreased with increasing doses of alfentanil ($P = 0.005$, $R^2 = 0.64$), and the linear regression, based on group-averaged data, suggests that approximately 40 μg/kg of alfentanil is needed to prevent significant increases in vasopressin plasma concentrations post intubation when compared to pre intubation values. A non-linear model did not improve the data fit.

8.3 Changes in hemodynamic variables (paper 3)

Average baseline values for arterial blood pressure and heart rate were similar in all alfentanil dose groups. Maximum hemodynamic response (arterial blood pressure and heart rate) post intubation was recorded within 1 min in all study subjects. Hypotension was recorded in 22 patients having alfentanil. 20 study subjects did not require ephedrine (systolic arterial blood pressure < 90 mmHg), while two individuals experiencing arterial blood pressure < 70 received ephedrine 5-10 μg. None of the patients had heart rate < 45/min either before or after tracheal intubation.

8.3.1 Changes occurring between baseline and pre intubation (base-pre)

Arterial blood pressure: Average arterial blood pressure decreased significantly

between baseline and pre intubation in the 30, 40, and 60μg/kg g roups (P = 0.01---0.03), and the pre-base difference increased with increasing doses of alfentanil (P =0.004, R2 = 0.69).

Heart rate: Average heart rate increased significantly between baseline and pre intubation only in the 0 μg/kg groups (P = 0.003), but the pre---base difference still increased with increasing doses of alfentanil (P =0.001, R2 = 0.81).

8.3.2 Changes occurring between baseline and post intubation (base-post)

Arterial blood pressure: Average arterial blood pressure increased significantly between baseline and post intubation in the alfentanil 0, 10, and 20 μg/kg dose groups, and decreased in the 50, and 60 μg/kg dose groups. The average post-base difference decreased with increasing doses of alfentanil (P = 0.001, R^2 = 0.92), and the linear regression, based on group-averaged data, suggests that approximately 30 μg/kg of alfentanil is needed to prevent significant increases arterial blood pressure (> 10%) post intubation when compared to baseline values. A non-linear model did not improve the data fit. Logistic regression, based on success rates, suggests that alfentanil 55 μg/kg is needed in order to prevent significant increases in arterial blood pressure (> 10%) post intubation in 95% of the study subjects when compared to baseline values.

Heart rate: Average heart rate increased significantly between baseline and post intubation in the alfentanil 0, 10, 20, and 40 μg/kg dose groups.

The average post-base difference decreased with increasing doses of alfentanil (P = 0.001, R^2 = 0.81), and the linear regression, based on group-averaged data, suggests that approximately 45 μg/kg of alfentanil is needed to prevent significant increases in heart rate (> 10%) post intubation when compared to baseline values. A non-linear model did not improve the data fit. Logistic regression, based on success rates, did not provide meaningful information because failures were observed in all alfentanil dose groups.

8.3.3 Changes occurring between pre and post intubation (pre-post)

Arterial blood pressure: Average arterial blood pressure increased significantly between pre and post intubation in alfentanil 0, 10, 20, 30, and 40 μg/kg dose groups (P = 0.01). The average post-pre difference decreased with increasing doses of alfentanil (P = 0.001, R^2 = 0.92), and the linear regression, based on group-averaged data, suggests that approximately 45 μg/kg of alfentanil is needed to prevent significant increases in arterial blood pressure (> 10%) post intubation when compared to pre intubation values. A non-linear model did not improve the data fit.

Heart rate: Average heart rate increased significantly between pre and post intubation in alfentanil 0, 10, 20, and 30 μg/kg dose groups (P = 0.01-0.04). The average post-pre difference decreased with increasing doses of alfentanil (P = 0.001, R^2 = 0.56), and the linear regression, based on group-averaged data, suggests that approximately 50 μg/kg of alfentanil is needed to prevent significant increases in heart rate (> 10%) post intubation when compared to pre intubation values. A non-linear model did not improve the data fit.

Although not being a primary focus of the study, hemodynamic responses to tracheal intubation were also studied in patient series #1 (paper 1). These observations broadly parallel the findings observed in patient series #2 (paper 3). For clarity reasons, data on hemodynamics reported in paper 1 are therefore not included in the Results section of the thesis.

8.4 Influence of covariates

8.4.1 Alfentanil plasma concentration at laryngoscopy (paper 2):

A significant linear relationship was found between alfentanil dose and alfentanil concentration (Fig. 2, $P < 0.0001$). The polynomial term did not indicate that the

relationship was better described with a nonlinear function. The alfentanil plasma concentration increased with 1.7 ng·ml-1 per kg increase in body weight (*P* = 0.0084). Sex did not affect alfentanil concentration (*P* = 0.33), even when adjusting for body weight (*P* = 0.32). Age was not a statistically significant factor either alone (*P* = 0.082) or when including body weight (*P* = 0.17).

8.4.2 Intubation conditions (paper 2):

When adding both alfentanil dose and concentration to the multivariate model, only alfentanil dose (P = 0.03) was a significant predictor. Neither body weight (*P* = 0.76) nor age (*P* = 0.58) were significant predictors of perfect intubation conditions. ED95 of alfentanil was 62 μg/kg in males and 44 μg/kg in females (P = 0.15).

8.4.3 Epinephrine (paper 3):

Increasing age and body weight were associated with a significant reduction in release of epinephrine post intubation (P = 0.03), but the effect on the parameter estimates (values of epinephrine at each alfentanil dose) was small (< 10%). Neither sex (P = 0.37) nor alfentanil plasma concentration at initiation of laryngoscopy (P = 0.39) influenced the relationship between alfentanil dose and epinephrine release post intubation.

8.4.4 Norepinephrine (paper 3):

Neither of sex (P = 0.87), body weight (P = 0.49), age (P = 0.16), or alfentanil plasma concentration at initiation of laryngoscopy (P = 0.73) influenced the relationship between alfentanil dose and norepinephrine release post intubation.

8.4.5 Vasopressin (paper 3):

Neither of sex (P = 0.49), body weight (P = 0.25), age (P = 0.88), or alfentanil plasma concentration at initiation of laryngoscopy (P = 0.91) influenced the relationship between alfentanil dose and vasopressin release post intubation.

8.4.6 Arterial blood pressure (paper 3):

Neither of sex (P = 0.48), body weight (P = 0.84), age (P = 0.82), or alfentanil plasma concentration at initiation of laryngoscopy (P = 0.43) influenced the relationship between alfentanil dose and arterial blood pressure post intubation.

8.4.7 Heart rate (paper 3):

Neither of sex (P = 0.40), body weight (P = 0.95), age (P = 0.52), or alfentanil plasma concentration at initiation of laryngoscopy (P = 0.12) influenced the relationship between alfentanil dose and heart rate post intubation.

9.0 Discussion

9.1 Intubation conditions

The beneficial effects of opioids and alfentanil in particular, during induction of anesthesia are well known. Our studies show how alfentanil, in conjunction with thiopental and rocuronium, can be used in order to obtain perfect intubation conditions during RSII, even when the procedure is carried out within a short time frame (70 s) from commencement of drug administration until completion of tracheal intubation. The dose of alfentanil needed varies with the dose of rocuronium given. With high dose rocuronium, i.e. 1 mg/kg, alfentanil 36 μg/kg was

needed (paper #1) to ensure optimal intubation conditions in most healthy patients (95%), while the dose had to be increased to approximately 55 μg/kg when a standard dose of rocuronium (0.6 mg/kg) was used (paper #2). Our results suggest that suxamethonium can be replaced with rocuronium in many clinical situations where emergency anesthesia care is needed. Actually, the drug regimens we have applied provide intubation conditions in an RSII setting that are comparable, if not even better than that obtained when using the standard combination of a sedative and suxamethonium. In a multicenter study including 350 patient Andrews et al reported perfect intubation conditions in 74% of the patients when tracheal intubation was performed 50 s after the administration of suxamethonium (75 s after commencement of propofol administration) in the absence of opioids [66]. The combination of alfentanil, thiopental, and rocuronium applied in our studies therefore represents an attractive alternative when use of suxamethonium should be avoided.

The dose requirement of alfentanil decreased significantly when the rocuronium dose was increased from 0.6 to 1 mg/kg, i.e. from 55 to36 μg/kg. This finding underscores the importance of the neuromuscular blocking drug for the intubation conditions in an RSII setting. In fact, by increasing the rocuronium dose to 2.0 mg/kg the dose requirement of alfentanil is reduced to approximately 10 μg/kg in an RSII setting (tracheal intubation within 70 s) where healthy patients are anesthetized with thiopental 4 mg/kg [82]. However, such high doses of rocuronium are inconvenient to use clinically because of the very prolonged duration of neuromuscular block.
Previous and our studies suggest that increasing doses of alfentanil compensate adequately for incomplete laryngeal muscle relaxation obtained with rocuronium in RSII settings. Alfentanil 50-60 $\mu g \cdot kg^{-1}$, which is needed to obtain perfect intubation conditions in most patients if a standard dose of rocuronium is used, might be considered a relatively large dose of this drug. However, our data show that such doses can safely be administered as rapid boluses in healthy individuals, because none

of the study subjects receiving 50 or 60 $\mu g \cdot kg^{-1}$ experienced hemodynamic derangements requiring vasopressor treatment. Prolonged respiratory depression might be a concern when alfentanil 50-60 $\mu g \cdot kg^{-1}$ is administered, but alfentanil distributes rapidly [76] and therefore it´s plasma concentration should decline below the threshold for spontaneous ventilation within 30 min after a bolus dose of this magnitude[47].

The average alfentanil plasma concentrations were similar in patients with and without perfect intubation conditions. Pharmacokinetic-pharmacodynamic factors may explain this unexpected finding: An identical plasma drug concentration obtained at laryngoscopy in two different individuals after bolus administrations of alfentanil will likely be associated with dissimilar effect site concentrations due to inter-individual variability in the blood – brain equilibration rate (hysteresis), and consequently with different magnitude of airway responses to tracheal intubation. In addition, inter-individual differences in sensitivity to alfentanil will certainly also contribute to response variability, even if the effect site concentrations were similar.

9.2 Release of stress hormones

Plasma concentrations of all stress hormones varied to a large extent between study subjects (both at baseline, pre, and post intubation), and therefore all group mean values had large standard deviations. However, although values for post-base and post-pre concentration differences within each alfentanil dose group therefore not always were statistically significant, we still observed significant inverse relationships between alfentanil dose and changes in release of epinephrine, norepinephrine, and vasopressin post tracheal intubation (paper #3, table 2-4, fig 1-3). This suggests that all endogenous vasoactive substances that we studied contribute to the hemodynamic response during RSII. Our findings are in line with results from previous investigation under non-RSII conditions. Miller et al [47] observed no significant increase in the release of catecholamines post intubation (compared to

baseline values) when alfentanil ≤ 30 μg/kg was administered 2-3 min prior to tracheal intubation in elective cases. Linear regression of the data in our investigation suggests that alfentanil 30 -40 μg/kg is needed in an RSII situation. Apparently, a larger dose of alfentanil is needed to contain the release of stress hormones during RSII conditions. At least two factors may explain this observation:

First, the intensity of airway stimulation is higher during RSII than in elective cases [59]. Second, maximum alfentanil concentration after a bolus in the effect compartment involved in the airway response to tracheal intubation may be achieved closer to two than after one min post drug administration[78]. We still conclude that, even if the needed alfentanil dose is greater in an RSII-setting, adequate release control of catecholamines can be achieved with clinically relevant doses of this drug when used during emergency induction of anesthesia.

We found a similar inverse linear relationship between alfentanil dose and release of stress hormones when post-pre concentration differences were analyzed, but the required drug dose to minimize stress hormone release were greater than that estimated with post-base data. The linear regression analyses, based on post-pre data, suggest that alfentanil 50 μg/kg (epinephrine), 50 μg/kg (norepinephrine, and 40 μg/kg (vasopressin) are needed (paper #3, fig. 1-3). This finding is to be expected because a concentration difference between pre and post intubation, due to concentration reductions pre intubation, may be significant even though the post intubation value is lower than baseline. Our observations are consistent with data from previous work [49]. However, although the post-pre concentration difference indicates the alfentanil dose that is needed in order to eliminate any response to laryngoscopy and tracheal intubation, the dose estimated by post-base data is probably more relevant in a clinical perspective.

Although the result was not statistically significant, Yoo et al [35] observed a 50 % increase in plasma vasopressin concentration 1 min post intubation in

unpremedicated patients anesthetized with thiopental as sole induction agent. This finding is consistent with our results, i.e. that vasopressin concentrations increase after potent stimulation of the airway, and therefore contribute to the hemodynami responses to tracheal intubation. In another previous study, no increase in plasma concentration of this vasoactive substance was found secondary to tracheal intubation [33]. Differences in study design may explain the discrepancy. In that study the first plasma sample was obtained 2 min post intubation. Our data indicate that vasopressin release to the blood stream after laryngoscopy and tracheal intubation occurs much earlier, probably after < 1 min. Therefore, in the study by Kayhan et al the peak plasma concentration after tracheal intubation may have been missed. Also, in that study the patients were anesthetized with a high dose of thiopental in conjunction with fentanyl, potentially attenuating release of the hormone. In contrast, the study design we used, i.e. inclusion of a study group without opioid administration and collection of blood samples one min post intubation, enabled us to detect the contribution of vasopressin to the hemodynamic response secondary to laryngoscopy and tracheal intubation.

Previous studies have shown significant decreases in epinephrine release between baseline and pre intubation, apparently caused by an effect of the anesthetic drugs [29 30 45 49-52]. In our study such change in release of epinephrine was only observed in one alfentanil dose group (alfentanil 20μg/kg). However, large standard deviations in the group mean values (pre-base difference) may explain the apparent discrepancy.

Our study was not specifically designed to explore the relative contribution of each endogenous vasoactive substance to the hemodynamic responses post intubation, but the timeline of catecholamine release may indicate that norepinephrine is a more consistent contributor than epinephrine. While maximum hemodynamic response to laryngoscopy and tracheal intubation occurred within 60 s in all patients, peak arterial plasma concentrations of catecholamines post intubation were recorded within that time frame in only 50%, and at ≥ 5 min in 30%. With

respect to norepinephrine, this apparent discrepancy can be reconciled assuming that this neurotransmitter is released rapidly from sympathetic nerve endings upon airway manipulation, and then leaks slowly back into the blood stream in significant numbers of patients. Epinephrine, on the other hand, is released from the adrenal gland and therefore must appear in the blood stream before reaching its effect site. Therefore, in those patients where the peak concentration of epinephrine occurred at ≥ 5 min post intubation this hormone probably contributed to the hemodynamic response to a lesser degree than norepinephrine. This observation may explain why two previous studies, including a limited number of patients (26 and 16) report an insignificant relationship between opioid dose and epinephrine release post intubation [29 30]. Our data, based on a much larger number of individuals, suggest that the release of epinephrine to the blood stream is rapid in approximately 50% of the patients and therefore frequently contributes significantly to the hemodynamic response occurring secondary to airway manipulation.

9.3 Hemodynamic responses

We have found that both arterial blood pressure (ABP) and heart rate (HR) responses to tracheal intubation decrease significantly with increasing doses of alfentanil. Linear regression analyses based on group-averaged post-base data suggest that in order to prevent significant increases in ABP and HR compared to baseline values alfentanil 30 μg/kg (ABP) and 45 μg/kg (HR) is needed (paper #3, table 5-6). Corresponding alfentanil doses based on post-pre intubation differences were approximately 45 μg/kg (ABP) and 50 μg/kg (HR) (paper #3 fig 4-5). There are two reasons for the difference in alfentanil dose requirements between post-base and post-pre data. First, the pre-base difference increased with increasing doses of alfentanil. Second, because pre intubation values of ABP and HR decreased with increasing doses of alfentanil, a post-pre difference might be significant even though

the post intubation values was lower than baseline. The determined alfentanil dose requirements to prevent significant changes in hemodynamic variables post intubation roughly parallel those needed to contain the release of stress hormones. These results suggest that catecholamines and vasopressin are the main stress hormones involved in the hemodynamic responses to tracheal intubation, also during RSII.

Our estimates of alfentanil dose requirements based on group-averaged values may be misleading because large individual responses are not fully accounted for. Therefore we believe a more clinically relevant estimate of alfentanil dose requirements is obtained when based on success rates within in each dose group. Logistic regression suggested that alfentanil 55 $\mu g \cdot kg^{-1}$ is needed to avoid ABP increases >10% above baseline value in 95% of healthy, hemodynamically stable individuals < 55 years of age. This dose is similar to that determined for obtaining optimal intubation conditions when using the same dose of rocuronium (paper 2). Therefore, alfentanil 55 $\mu g \cdot kg^{-1}$ is to be recommended if optimal intubation conditions and adequate hemodynamic control are simultaneously needed during RSII when patients are anaesthetized with thiopental 4 mg kg^{-1} and rocuronium 0.6 mg kg^{-1}. Although less relevant clinically, a similar logistic regression analysis may be performed on post-pre intubation data. However, failures to obtain perfect intubation conditions (< 10% increase in ABP post compared to pre intubation values) were observed in all alfentanil dose groups, which precluded a meaningful dose determination. Apparently this dose would be > 60 μg/kg. Failures to obtain HR increases post intubation ≤ 10% of baseline and pre intubation were also observed in all alfentanil dose groups, which precluded determination of the alfentanil dose associated with minimal increase in HR post intubation with this probability-based statistical technique.

Arterial blood pressure and heart rate decreased between baseline and pre intubation with increasing doses of alfentanil, reflecting the effect of the induction agents on hemodynamic variables. Apparently, the changes in hemodynamic variables pre

intubation were not paralleled by similar changes in release of stress hormones (table 2-6 in paper 3), indicating that the effects of anesthetics on hemodynamics may be also be caused by other factors than via changes in release of endogenous vasoactive substances.

9.4 Influence of covariates

The alfentanil blood concentration increased 1.7 ng/ml per kg increase in body weight (paper #2), consistent with previous findings that the central volume of distribution of alfentanil decreases with increasing body weight[315]. The average male therefore acquire higher blood concentration of alfentanil than the average female when the drug is administered on mg per kg basis, simply because the body mass is greater. However, in the present study this did not translate into a higher probability of perfect intubation conditions in males. A plausible reason for this finding is that the stimulus intensity during tracheal intubation increases with increasing bodyweight as well, and because there is a relationship between the magnitude of noxious stimuli a nd the release of catecholamines[63], the effect of a greater alfentanil plasma concentration is balanced out. Our results are rather consistent with the assumption that females might need less alfentanil than males in order to obtain perfect intubation conditions (ED95 62 vs 44 µg /kg, paper 2). Although this apparent sex-related difference did not reach the significance level (P = 0.15), the reason might well be a type II error due to the relatively low number of subjects included in this study.

A significant linear relationship was found between alfentanil dose and alfentanil concentration (paper #2, fig. 2), but only dose was a significant predictor of perfect intubation conditions. There are plausible pharmacokinetic-pharmacodynamic reasons for this apparent discrepancy. First, during the initial minutes after an intravenous drug bolus a concentration hysteresis exists between blood stream and effect site, implying that the alfentanil plasma concentrations at laryngoscopy obtained in the present study did not reflect that of the central nervous system[76 309].

Second, this single, non-steady state measurement of the alfentanil plasma concentration does not take into account the individual variability in drug sensitivity, which is the ultimate pharmacodynamic factor contributing to drug effect [306]. Alfentanil dose is likely a better predictor of drug effect than non-steady state alfentanil plasma concentration because a drug´s dose–effect relationship accounts for both pharmacokinetics (i.e. drug concentration in the blood stream) and pharmacodynamics (i.e. drug sensitivity). Therefore, in a clinical perspective, measurements of plasma concentrations of alfentanil at the time of laryngoscopy, if they were available, do not appear to imply any advantage when an optimal regimen for alfentanil administration is to be decided.

Increasing age and body weight were associated with a significant reduction in release of epinephrine (P = 0.03), but not in any of the remaining response variables (norepinephrine, vasopressin, ABP, HR) post intubation. However, the effect on the parameter estimates (values of epinephrine at each alfentanil dose) was small (< 10%) and therefore of little clinical relevance. Sex and alfentanil plasma concentration at initiation of laryngoscopy did not influence the relationship between alfentanil dose and any of the five response variables post intubation.9.5

9.5 Methodology issues

9.5.1 Timing of drug administration and quality of intubation conditions

In a review paper in 2001 Lavazais and Debaene [71] stated that the major goals of RSII are: 1. Reduce the time interval between drug administration and completion of tracheal intubation. 2. Obtain excellent intubation conditions. Our review of previous

literature, claiming to be RSII studies, has revealed that in most investigations the study designs applied have not focused specifically on these aims. In some RSII studies the way drugs were administered was not been described at all[267 457]. If drug administration is described, variable time frames have been allowed for drug administration (15 s to several min) [22 66 82 254 255 261 263 264 266 268 458], implying that the duration of the period where the airway is unsecure (with respect to potential regurgitation) is varying to a large extent. Also, the results presented in previous RSII studies always include groups of study subjects where the intubation conditions were less than perfect. Therefore, previous literature does not provide information on drug combinations to be used in order to obtain perfect intubation conditions during RSII in all (i.e. > 95%) individuals. We believe this information is important, especially in clinical situations were bucking and straining during tube insertion should be avoided, i.e. certain cases in cardiac, ophthalmic or neurosurgery. In the present thesis we wanted to comply with the RSII requirements presented in the paper by Lavazais and Debaene [71], not least because the original RSII paper by Stept and Safar in 1970 [6] suggested that tracheal intubation should be attempted 30–60 s after administration of the neuromuscular blocking drug. Consequently, we decided that the time delay between administration of the neuromuscular blocking drug and initiation of laryngoscopy should be no longer than 40 s. This is in line with results from previous showing that the onset time of suxamethonium at the laryngeal muscles is within this time frame in most healthy individuals [21]. In order to minimize the time period of an unsecured airway all drugs used were administered as rapid boluses, total administration time ≤ 15 s. In this way our ultimate goal, to initiate laryngoscopy 55 s after commencement of drug administration was achieved. The second major goal of RSII stated by Lavazais and Debaene, i.e. achievement of excellent intubation conditions, is equally important as the drug administration–timing issue. This is because suboptimal intubation conditions may significantly delay placement of the endotracheal tube, and also be associated with intubation–related laryngeal injuries [64]. We used a probability approach to this issue. The study subjects were randomly assigned to different drug dose groups, and the

success rate obtained within each group was used in a logistic regression analysis [81 82]. With this technique we were able to estimated dose requirements in order to obtain a high success rate (95%) of perfect intubation conditions using a limited number of study subjects.

9.5.2 Drug selection

Sedative drugs: Four different sedatives may be relevant to use during RSII, thiopental, propofol, etomidate, and ketamine. We chose to use thiopental of four reasons. First, thiopental has a long tradition of use in RSII settings and is generally well tolerated, and only moderate decreases in arterial blood pressure or heart rate after rapid bolus administration are reported in hemodynamically stable patients [110]. This is in contrast to the experience with propofol [459]. Cardiovascular stability associated with the use of etomidate and ketamine is certainly an advantage, and may even increase the speed of onset compared with sedatives that decrease cardiac output [142]. However, the experience with etomidate is limited in Norwegian anesthesia practice, and ketamine has certain undesirable psychotomimetic actions [163]. Second, we wanted to use a drug that could be injected as a rapid bolus. We were uncomfortable with propofol in this respect, due to higher probability of hypotension and bradycardia [459]. The local pain elicited by rapid injections of propofol is also a serious disadvantage [172]. Experience with rapid injections of etomidate and ketamine is essentially lacking [188 189]. Third, maximum effect after approximately 60 s, which was preferable in the setting of our studies, has been shown with thiopental[98 99 460]while onset characteristics of etomidate and ketamine is less well known[188 189]. Propofol has a much slower onset than thiopental, and still reported to have better muscle relaxing effect [184], although questionable at 60 s after drug administration [185]. Unfortunately, the danger of significant hypotension after a rapid bolus injection precluded the use of this drug in our studies.

9.5.3 Neuromuscular blocking drugs: Many investigations, claiming to be RSII

studies, have shown that tracheal intubation can be performed without using neuromuscular blocking drugs[172 173 316 322 329 330 332]. However, no studies have shown that the airway can be secured within a time frame of 90 s unless a neuromuscular blocking drug is administered. If the use of suxamethonium is to be avoided due to all the potentially serious side effects of this drug, there is only one alternative drug available (rocuronium) with a reasonable short onset time at the laryngeal muscles [21]. However, if laryngoscopy is initiated 40 s after it´s administration, a high percentage of study subjects would experience less than perfect intubation condition unless an opioid is given simultaneously [22 66]. Because a second major goal of the present thesis was to determine the dose of alfentanil needed to simultaneously contain hemodynamic responses during RSII, an opioid had to be administered anyway, since this latter aim cannot be achieved with the combination of a sedative and a neuromuscular blocking drug (i.e. in the absence of an adjuvant drug). Therefore, the combined use of a sedative, rocuronium, and alfentanil was ideal in order to reach two primary goals of this thesis: Define a drug combination to be used when simultaneously perfect intubation conditions and minimal hemodynamic responses are needed during RSII (tracheal intubation completed 70 s after commencement of drug administration).

9.5.4 Opioid drugs: We chose to use alfentanil rather than any of the other available synthetic opioids (fentanyl, sufentanil, remifentanil) of three reasons: First, rapid onset time is important, in order to achieve maximum drug effect at a comparable time point as with the sedative and rocuronium (i.e. within approximately 60 after it´s administration). Maximum effect site concentrations after bolus doses of alfentanil and remifentanil have been reported to be 60-90 s after drug administration[300 309]. Fentanyl and sufentanil were excluded because their onset times are significantly slower[76]. Second, apparently, hypotension and bradycardia are more frequently occurring with remifentanil than alfentanil. Also, while alfentanil may increase cardiac contractility, remifentanil may have

myocardial depressive actions [79 289 290]. Third, muscle rigidity has not been reported with bolus doses of alfentanil < 80 μg/kg[79 303], well outside the dose range that was planned in our studies.

9.5.5 Cricoid pressure

The application of cricoid pressure has been considered a mandatory procedure to perform in patients at high risk of gastric regurgitation and an integral part of RSII, since it's introduction approximately 50 years ago[13 461 462], despite lack of compelling evidence to support this practice [463 464]. Studies have shown that the application of cricoid pressure may displace the esophagus laterally [465-467] instead of compressing it as described by Sellick [461], thereby reducing the efficacy of the procedure. Accidental compression of the glottis may impede mask ventilation and even obstruct the view of the laryngoscopy, therefore delaying the process of securing the airway [466 468 469]. Also, studies show that cricoid pressure is associated with a decreased tension in the lower esophageal sphincter [464 470], a significant disadvantage when it comes to prevention of regurgitation of gastric content. Many anesthesiologists therefore consider cricoid pressure a no longer evidence-based practice [471]. However, cricoid pressure is considered a safe procedure[472], and a recent survey shows that the procedure is still performed by most anesthetists during RSII[14]. In the present thesis we chose to omit using cricoid pressure, in order to secure as uniform intubation conditions as possible.

9.5.6 Monitoring of neuromuscular function

Whenever a neuromuscular blocking drug is used during anesthesia it is recommended to monitor the drug effect using peripheral nerve stimulation, i.e. at the adductor pollicis muscle of the hand[473]. Although an advantage when patients are recovering from anesthesia, in order to detect and prevent residual neuromuscular block in the recovery room, nerve stimulation does not reflect the status of the laryngeal muscles

during induction of anesthesia [82]. We therefore chose not to apply peripheral nerve stimulation while carrying out our studies.

9.5.7 Premedication

We offered premedication (small dose of midazolam intravenously prior to entering the operating room) to the study subjects in series # 1 (paper #1), while those of series # 2 (paper 2 and 3) did not receive any drug with sedative action pre anesthesia. Although inconsistent, at the time of inclusion of study subjects in series # 1 premedication was considered necessary by the Institutional Review Board. That practice has changed over the years, and in series # 2 premedication was omitted to mimic RSII conditions where patients frequently does not receive drugs that might affect consciousness or breathing ability prior to anesthesia induction. Although administration of midazolam might influence intubation conditions and autonomic responses during RSI, the fact that the blood pressure increase in our control group (paper #1) was similar to that of previous studies investigating autonomic responses in the absence of opioids, suggests that the premedication administered did not significantly influence the estimation of the optimal dose of alfentanil [474].

10.0 Clinical relevance and limitations

In the present thesis we have defined an anesthesia induction technique to be used during RSII conditions. It provides optimal conditions for tracheal intubation rapidly, which may be crucial in situations where aspiration of gastric content to the airway is imminent. The technique simultaneously provides control of stress hormone release and hemodynamic responses occurring secondary to laryngoscopy and tracheal intubation, and may be applicable in many clinical situations where the patient does not tolerate sudden increases in arterial blood pressure.

Because optimal conditions for tracheal intubation are obtained rapidly, the technique may be advantageous in clinical situations with increased probability of developing hypoxemia in the apnea period following drug administration, i.e. in patients with low FRC or where pre oxygenation is difficult or impossible. Also, the technique may show beneficial in patients where the neck must be positioned in a neutral position during anesthesia induction, making mask ventilation difficult (neck injuries) or when manipulation of the lower jaw may cause further bleeding or injury to the face. However, indication for using this technique under such circumstances must be tested in clinical efficacy studies.

The present study has one major limitation. The data obtained are only directly applicable to healthy individuals. Unfortunately, ethical considerations precluded inclusion of study subjects with significant organ dysfunction because, due to the study design, such participants might have been exposed to a potentially harmful drug regimen, i.e. either a relatively large dose of alfentanil or no alfentanil at all. Modification of the alfentanil dose requirements determined in the present thesis (preferentially reduced dosing) must likely be made whenever patients with limited cardiac reserves are anesthetized, especially if cardiac output must be assumed reduced preoperatively.

11.0 Summary of main results

1. Perfect intubation conditions are obtained in 95% of healthy, hemodynamically stable individuals 55 s after commencement of drug administration with alfentanil 36 μg/kg + thiopental 4 mg/kg, + rocuronium 1 mg/kg.

2. Perfect intubation conditions are obtained in 95% of healthy, hemodynamically stable individuals 55 s after commencement of drug administration with alfentanil 56

μg/kg + thiopental 4 mg/kg, + rocuronium 0.6 mg/kg.

3. Minimal increases in arterial blood pressure are experienced post tracheal intubation (compared to baseline) in 95% of healthy, hemodynamically stable individuals when laryngoscopy is initiated 55 s after commencement of drug administration with alfentanil 55 μg/kg + thiopental 4 mg/kg, + rocuronium 0.6 mg/kg.

4. Minimal average increases in stress hormone release (epinephrine, norepinephrine, vasopressin) and hemodynamic variables (arterial blood pressure and heart rate) are experienced post intubation (compared to baseline) when anesthesia is induced in rapid-sequence fashion with alfentanil approximately 35 μg/kg + thiopental 4 mg/kg + rocuronium 0.6 mg/kg.

5. Covariates (sex, body weight, and age) do not influence significantly the dose requirements of alfentanil in order to obtain perfect intubation condition and to contain hemodynamic responses to laryngoscopy and tracheal intubation.

6. Plasma concentration of alfentanil at laryngoscopy was inferior to alfentanil dose in order to predict perfect intubation conditions during RSII.

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