Monitoring anesthesia: Optimizing monitoring strategies to reduce adverse effects of anesthetic drugs on ventilation

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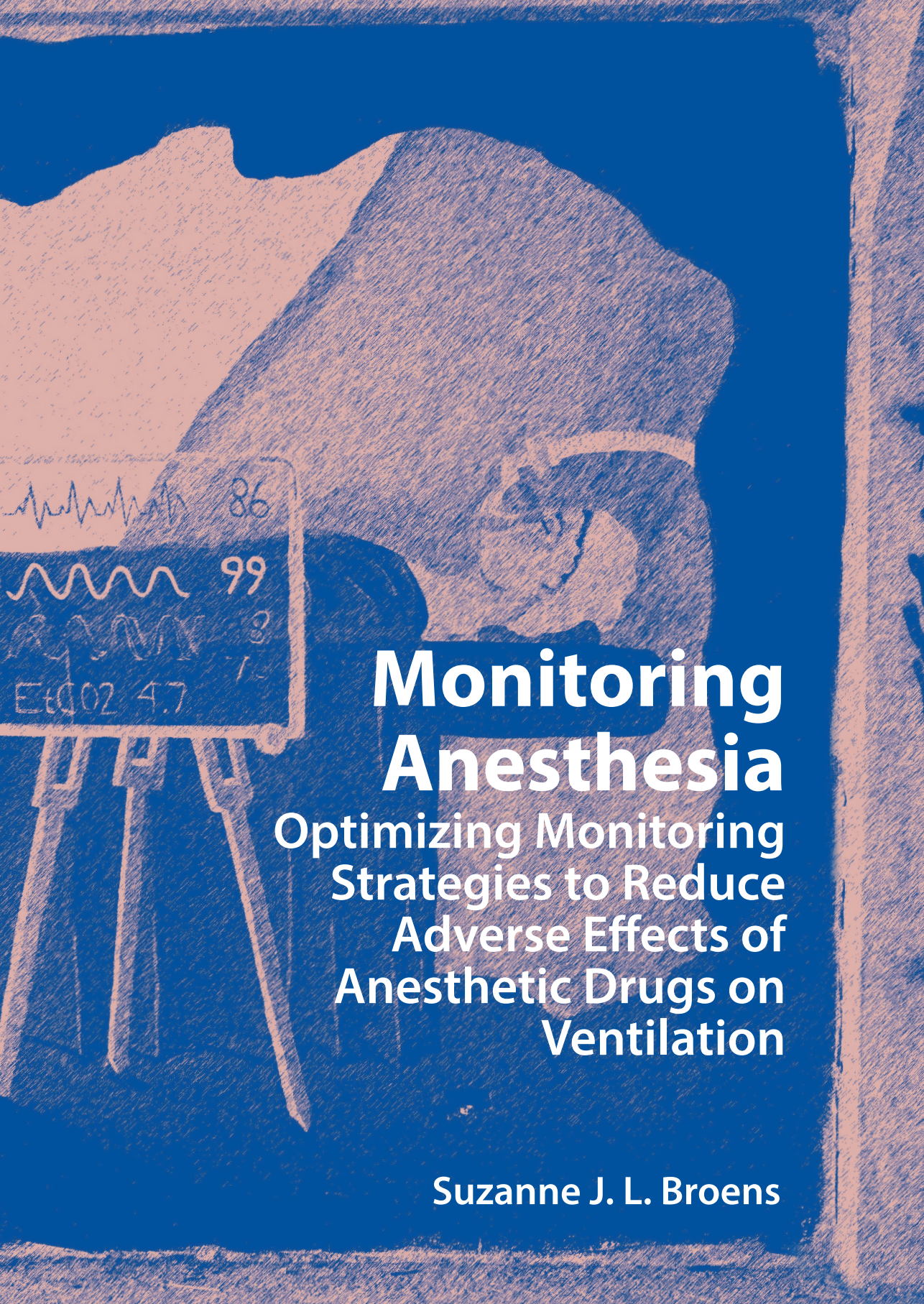

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Suzanne J. L. Broens

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CHAPTER 1

Introduction and Thesis Outline

A short history of anesthetic monitoring

The first documented anesthetic death was the death of a healthy 15-year-old girl named Hannah Greener, in 1848, after she received chloroform anesthesia for the removal of a toenail. An account of her death was published in the Edinburgh Medical and Surgical Journal(1):

'I seated her in a chair, and put a teaspoon of chloroform into a tablecloth, and held it to her nose. After she had drawn her breath twice, she pulled my hand down. I told her to draw her breath naturally, which she did, and in about a half a minute I observed muscles of the arm become rigid, and her breathing a little quickened, but not stertorous. I had my hand on her pulse, which was natural, until the muscles became rigid. It then appeared somewhat weaker—not altered in frequency. I then told Mr. Lloyd, my assistant, to begin the operation, which he did, and took the nail off. When the semicircular incision was made, she gave a struggle or jerk, which I thought was from the chloroform not having taken sufficient effect. I did not apply anymore. Her eyes were closed, and I opened them, and they remained open. Her mouth was open, and her lips and face blanched. When I opened her eyes, they were congested. I called for water when I saw her face blanched, and I dashed some of it in her face. It had no effect. I then gave her some brandy, a little of which she swallowed with difficulty. I then laid her on the floor and attempted to bleed her in the arm and jugular vein, but only obtained about a spoonful. She was dead, I believe, at the time I attempted to bleed her. The last time I felt her pulse was immediately previously to the blanched appearance coming on, and when she gave a jerk. The time would not have been more than 3 min from her first inhaling the chloroform till her death.'

The cause of her death was much debated at the time, and still is, as evidenced by an analysis of the case published in Anesthesiology as recently as 2002(2). The possible causes include an arrhythmia, possibly triggered by a 'light' anesthetic, pulmonary aspiration with asphyxia or overdosing of chloroform, which would lead to the cessation of respiration. Whatever the cause, it seems highly likely that a more sophisticated form of monitoring than we see described here could have prevented her death.

The case of Hannah Greener sparked a debate that led to increased awareness of the importance of monitoring vital signs and depth of anesthesia. Around the time of Hannah's death, dr. John Snow, anesthetist to Queen Victoria, published a case series(3) of 80 patients anesthetized by ether, in which he describes the five stages of anesthesia that later formed the basis for Arthur Ernest Guedell's more commonly known classification (which was published in 1937(4)). In his work, dr. Snow mentions the monitoring of respiration depth and frequency, pulse, muscle movement and skin color as a way to assess the degree of etherization of the patient. In the century that followed, technological

advances permitted more advanced monitoring, including the indirect measurement of blood pressure described by Korotkoff in 1905 and the first use of the electrocardiogram in theatre in 1922. However, it would take more than another fifty years before the next significant improvement in the field of anesthetic monitoring.

From the 1960's onwards, outcome studies repeatedly identified adverse respiratory events as a leading cause of anesthetic morbidity and mortality. This is clearly illustrated by the first ASA closed claims analysis, published in 1990, which structurally evaluated adverse anesthetic outcomes obtained from closed claims primarily occurring from 1975 to 1985(5).They concluded that respiratory events constituted the single largest source of adverse outcome and that better monitoring would have prevented the adverse outcome in 72% of the cases. Increasing awareness of the respiratory origin of anesthetic complications led to the widespread adoption of capnography and pulse oximetry in the operating room and ultimately to the adoption of minimal monitoring standards by the American Society of Anesthesiologists in 1986(6). From this date, continuous monitoring of the oxygenation, ventilation, circulation and temperature of the anesthetized patient became mandatory, as did the presence of qualified personnel throughout the conduct of all general and regional anesthetics. Nowadays, an anesthesia-related death like Hanna Greeners has thankfully become a rare event. Rates of perioperative mortality where anesthesia is the sole contributor have declined from approximately 1 death in a 1000 anesthesia procedures in the 1940s, to 1 in 3000 anesthesia procedures in the 1970s and 1 in 30,000 at the start of the 21st century(7-10).

Although there have never been prospective, randomized, clinical studies evaluating the relationship between basic monitoring and anesthetic outcome, it is so widely accepted that the introduction of these standards has been instrumental to the reduction in perioperative and anesthesia-related mortality that was seen around that time, that to perform such trials now would be regarded as highly unethical(11-13).

Unfortunately, with the increasing complexity of surgical procedures performed in an ageing population with an escalating number of comorbidities, perioperative mortality rate remains much higher than anesthetic mortality rate. In developed countries, the perioperative mortality rate (varyingly defined as 30-day mortality or mortality until discharge) ranges from 0.8 to 1.5%(9, 14). These patients generally do not die on the operating table. Rather, they deteriorate in the days following surgery, when the stress response elicited by the surgical intervention results in a metabolic demand that their organs, chronically diseased at baseline, cannot meet(15). Although intended to decrease this stress response, anesthetic agents, including opioids, used per- and postoperatively put

patients at additional risk by their residual effects, especially on the respiratory system(16).

As has been the case in the past, technological advancements have made available new monitoring technologies that are aimed at further reducing the harm that can occur during or following anesthesia and surgery. Some are aimed at optimizing and individualizing the intraoperative administration of anesthetic agents, such as depth-of-anesthesia monitors or monitors of nociception. Others have been developed to function as algorithm-based alarms in the postoperative period, or even mobile applications that monitor the patient after discharge(17).

Thesis Outline

The aim of the current thesis is to evaluate the use of a variety of monitoring modalities in various stages of validation and implementation, that have been developed to reduce the risk of potential harm associated with the use of anesthetic agents, in particular the risk of respiratory depression associated with the use of opioids and neuromuscular blocking drugs.

In the following paragraphs, a brief introduction of the monitoring modalities of each section of this thesis will be provided.

Section 1: Monitoring of Nociception

Noxious stimuli, such as occur during surgical procedures, are processed by the body through a neural process referred to as nociception. Nociception elicits a surgical stress response when insufficiently suppressed by anesthetics. The resulting activation of neuroendocrine pathways negatively influences wound healing, immune function and metabolic response(15). It is also thought to affect cancer progression(18). At present, the amount of opioids administered to patients during surgery to suppress nociceptive pathways and thus surgical stress is determined by measurement of heart rate and (intermittent) blood pressure. As these are neither very sensitive or very specific measures of nociception, under- and overdosing of opioids frequently occurs(19). Where underdosing is associated with the aforementioned neuroendocrine response as well as the development of acute and chronic pain, overdosing is associated with prolonged emergence, the development of hyperalgesia and increased risk of postoperative respiratory depression. Opioids may also affect the immune system and oncogenetic factors such as angiogenesis, apoptosis, and invasion in a deleterious manner(20).

Several monitors have been developed that aim to enable more optimal titration of perioperative opioids in search of the nociception/antinociception balance that is

associated with the most favorable postoperative outcome. Most of these monitors rely on detection of a single or multiple parameters that reflect autonomic activity, such as heart rate variability, pulse wave amplitude or skin conductance. Other monitors use spinal reflexes (such as the withdrawal reflex or the ciliospinal reflex) to more directly measure the activation or suppression of nociceptive pathways. A third monitoring modality uses EEG derived variables as a measure of nociception.

Current research efforts attempt to either evaluate the ability of new monitors to differentiate between nociceptive and non-nociceptive events or to evaluate the intraoperative use of existing monitors and their effects on clinical outcomes in randomized trials(19, 21). A recent review of the literature suggest that intra-operative opioid consumption may be less with nociception monitoring, with no difference in postoperative pain and opioid consumption(22). Data in these studies have been insufficient to demonstrate an effect on intra-operative hemodynamics or adverse events.

Section 1 of this thesis presents two monitoring devices that rely on different parameters that reflect activation of the sympathetic nervous system to provide a measure of nociception. Their ability to differentiate between states of nociception and non-nociception is assessed.

Chapter 2 introduces a new method for detection of nociceptive events by quantifying skin blood flow dynamics using a miniaturized dynamic light scattering (mDLS) sensor. The ability of the mDLS sensor to detect a physiological response to noxious stimulation is tested in healthy volunteers.

In ***Chapter 3*** a new multidimensional index of nociception, derived from a composite of parameters that reflect autonomous activity, is used to assess nociception in surgical patients during propofol-remifentanil anesthesia. Its ability to detect noxious from non-noxious stimuli is compared to heart rate and mean arterial blood pressure.

Section 2: Monitoring of Neuromuscular Block

The introduction of neuromuscular blocking drugs revolutionized anesthetic practice by allowing for longer and more complex surgical procedures. More recently, several studies have demonstrated the potential of a deep neuromuscular block to improve surgical conditions in laparoscopic surgery(23-25). However, use of neuromuscular blocking agents is not without risk. Return to normal neuromuscular function is an absolute prerequisite for the safe emergence from anesthesia. Monitoring the depth of neuromuscular block is usually done with devices that measure the muscle response to peripheral nerve stimulation via acceleromyography. The resulting Train-of-Four (TOF) ratio determines the level of neuromuscular block and consequently the reversal strategy. When neuromuscular

blocking drugs are not, or incompletely, reversed, partial paralysis may continue into the early postoperative period. This is likely why the use of neuromuscular blocking drugs is associated with postoperative respiratory complications(26). Even small degrees of residual neuromuscular block (at TOF ratio's >0.6 and <0.9) have been shown to affect lung volumes, swallowing and upper airway patency in volunteers(27). The routine use of objective neuromuscular monitoring has therefore been advocated by experts in order to improve postoperative outcome. However, adherence to this recommendation in clinical practice is low and the incidence of postoperative residual neuromuscular block remains substantial (as high as 65%)(28, 29). Current research focuses on strategies to prevent postoperative respiratory complications by the appropriate use of reversal agents and routine use of neuromuscular monitors(30). In this context, the use of sugammadex, a relatively new reversal agent introduced in Europe in 2008, is increasingly advocated to prevent postoperative respiratory complications, as is an increasingly high TOF ratio as a threshold for extubation(28). Despite the attention given to the adverse effects of neuromuscular blocking drugs on respiratory mechanics via their effect on the neuromuscular junction, their effect on the ventilatory response to hypoxia mediated by the carotid bodies(31) is consistently overlooked.

Section 2 of this thesis is concerned with the respiratory effect of neuromuscular blocking agents mediated by the carotid bodies and the consequences of this effect for reversal strategies and monitoring practices.

Chapter 4 describes the effect of a modern neuromuscular blocking agent on the hypoxic ventilatory response (HVR) in healthy volunteers. The effect of several reversal strategies on HVR is evaluated with the use of a neuromuscular function monitoring device.

Section 3: Postoperative Respiratory Monitoring

No universal definition for postoperative adverse respiratory events has been established and as a result the incidence reported in the literature varies from as low as 0.3% to as high as 17%(32). Adequate oxygenation and ventilation can be compromised postoperatively as a result of a variety of surgical, anesthetic and patient-related factors. Surgical incision site and pain can lead to altered respiratory mechanics and atelectasis. The residual effect of anesthetics and neuromuscular blocking agents as well as the use of sedatives and opioids blunt the physiologic response to the resulting hypoxia and hypercarbia. Certain co-morbid conditions, such as the presence of sleep disordered breathing, which causes an increased sensitivity to the central and peripheral effects of opioids, place patients at risk even further(33). When the presence of hypoxia or respiratory depression is not identified, this can lead to cardiorespiratory arrest, brain injury and death(34).

Many of these risk factors cannot be modified. Currently available risk prediction tools based on the presence of these risk factors do not predict serious adverse respiratory events reliably(35). Therefore, research efforts have focused on monitoring strategies to identify patients experiencing respiratory events and institute timely interventions to prevent further deterioration.

A systematic review and meta-analysis published in 2017(36) compared the effectiveness of either continuous pulse oximetry or continuous capnography to routine nursing care. The analysis showed that both pulse oximetry and capnography outperformed routine nursing care in recognizing desaturation or opioid-induced respiratory depression, respectively. At the same time, both methods have their drawbacks. Hypoxemia is a late sign of respiratory depression in the presence of supplemental O2. Capnography is more sensitive for the detection of opioid-induced respiratory depression than pulse oximetry, because it measures ventilation rather than oxygenation. However, when it is measured non-invasively, it can generate a significant amount of false positive alarms when the sensor is malpositioned, or when airflow is inadequate for detection of ETCO2 (such as occurs with mouth breathing or snoring)(37, 38). Monitoring devices using smart algorithms that rely on multiple physiological parameters aim to increase sensitivity and reduce the number of false positive alarms(39).

In **Section 3**, two respiratory monitors are introduced and used to assess the incidence of adverse respiratory events in the postoperative period. Additionally, the effect of the use of a smart respiratory monitor on the incidence of and response to adverse respiratory events is evaluated.

In ***Chapter 5***, the Respir8 monitor, a monitor for the continuous measurement of respiratory rate, is used in a population of postoperative patients aged sixty years or older in the first 6 hours following surgery to quantify the incidence of adverse respiratory events and identify risk factors.

In ***Chapter 6***, the Integrated Pulmonary Index (IPI), an index derived from a smart algorithm based on multiple physiological parameters, is used in a population of surgical patients on the first postoperative night in the post anesthesia care unit (PACU) to assess the feasibility of clinical use of the monitor, as well as to quantify incidence of respiratory events.

Chapter 7 describes a randomized controlled trial in which the use of the IPI monitor is compared to routine PACU care, consisting of continuous monitoring of respiratory rate and pulse oximetry. The effect on the incidence of and response to adverse respiratory events is assessed.

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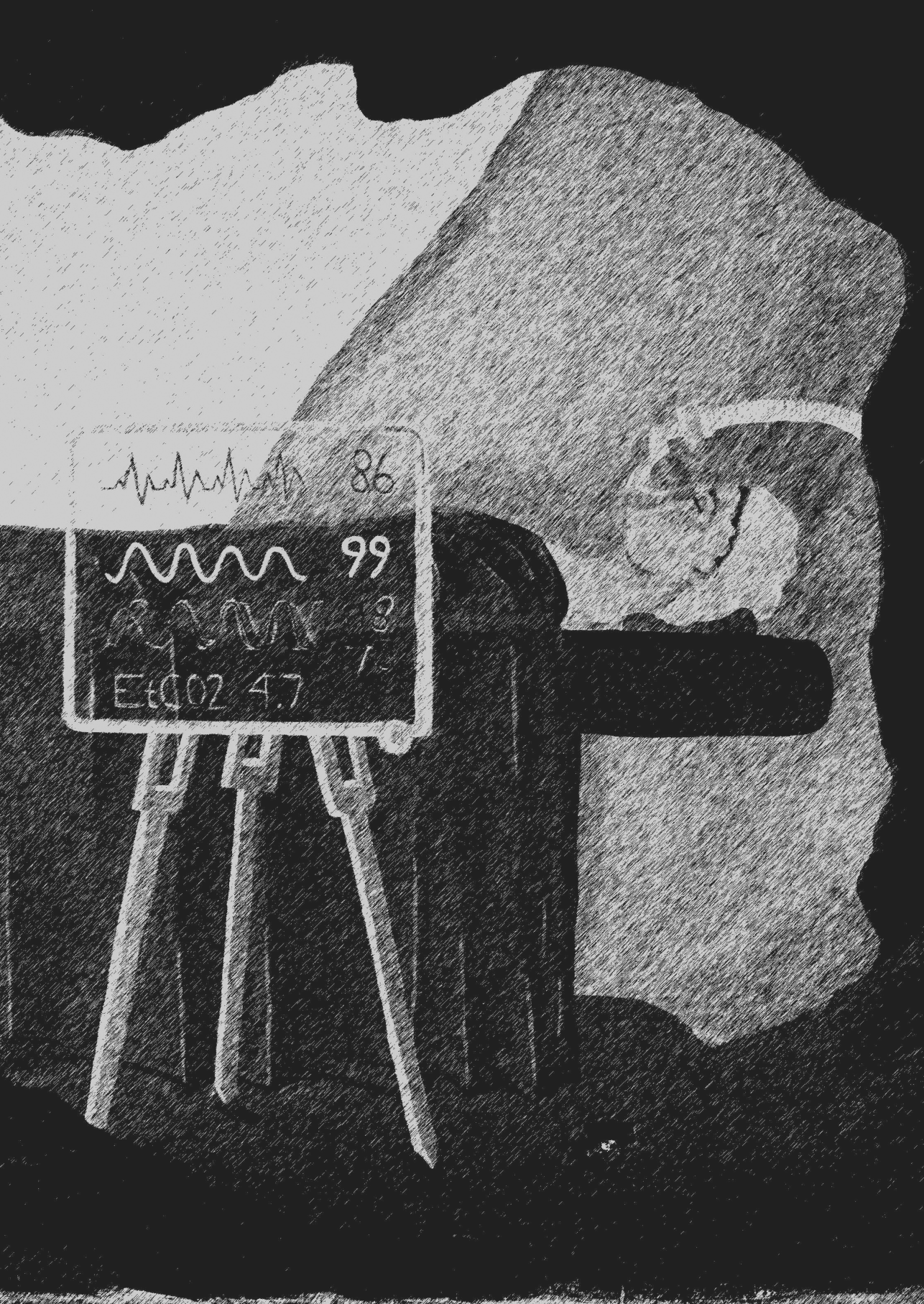
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Section 1

Monitoring of Nociception

CHAPTER 2

2

Use of dynamic light scattering for assessing acute pain

Suzanne Broens, Adi Schejter Bar-Noam, Ilya Fine, Louis Shenkman, Monique van Velzen, Marieke Niesters, Albert Dahan

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Introduction

During the state of drug-induced unconsciousness (for example anesthesia or deep sedation), detection of nociceptive stimuli, such as (surgical) stimuli that actually or potentially cause tissue damage, relies commonly on the measurement of blood pressure or heart rate (HR)(1). These measurements, however, may not detect all events or detect events with some delay. Recently, new non-invasive technologies have been developed to detect nociceptive events in awake and anesthetized individuals that rely on signals of the autonomic nervous system such as heart rate variability, pulse pressure, pupil diameter, peripheral vasoconstriction, skin galvanic response, or on a combination of these signals (1-5). Most studies indicate that nociceptive indices based on these autonomic signals outperform BP and HR in the detection of nociceptive events. Changes in blood flow could offer an additional option for detecting noxious responses during anesthesia, as is demonstrated with the SPI(6). The SPI method relies on heart rate variability (HRV) and total blood perfusion in the fingertip extracted from the plethysmographic signal.

We propose a new method for detection of nociceptive events by quantifying skin blood flow dynamics using a miniaturized dynamic light scattering (mDLS) sensor(8-9). This sensor enables extraction of multiple hemodynamic parameters that can indicate changes in the autonomic nervous system.

Theoretical background

The sensor technology used in the following experiments relies on a phenomenon known as dynamic light scattering.(7) The laser beam from a miniaturized DLS probe is projected into the skin, and the light scattered from the flowing RBCs in the blood vessels creates a speckle pattern on the mDLS detector. The overall measured dynamic light scattering pattern is originated by the interaction between the coherent light that is scattered by the moving red blood cells. The relative movement of the particles is responsible for the speckle dynamics. This relative movement is characterized by the velocity shear rate. Therefore, for laminar flow, the signal measured by the mDLS sensor is correlated with the gradient of the velocity in the blood stream, also known as the shear rate γ(7).

In a very simplified case, for the vessel of radius *R*, axis symmetric velocity profiles *v(r,t)* can be described in cylindrical coordinates by this empirical relationship:

$$v(r,t) = v(0)\left[1-\left(\frac{r}{R}^{\xi}\right)\right]f(t) \quad -R \le r \le R\,; \tag{1}$$

Where $v(0)$ - is maximum velocity at r=0 and R is the radius of the vessel, $f(t)$ is a periodic function of heart beat frequency, and ξ represents the degree of blunting. The velocity shear rate can be determined by:

$$\gamma = \frac{\partial v(r,t)}{\partial r} = \xi \cdot v(o,t) \cdot \frac{r^{\xi-1}}{R\xi}, \; v(o,t) = \frac{\xi+2}{\xi} < v(t) \tag{2}$$

For each sub-ensemble s , the autocorrelation function decay g(s,τ) is given by:

$$g(s,i) = \alpha * exp\left[-\Gamma(s)\, t^2\right], \; \Gamma(s) = (\gamma(s)\, d^* q)^2 \tag{3}$$

where $q = 2 \cdot k \cdot \sin(\theta/2)$, θ - is scattering angle, k is wavelength number and d^* is the effective distance across the scattering volume in the direction of the velocity gradient. Since the skin is characterized by a variate of different vessels with different shear rates the overall autocorrelation function of the measured signal can be represented as a sum of n weighted (w) contributions from different sub-ensembles of RBC's, corresponding to their shear rate:

$$G(\tau) = \sum_{s=1}^{n} w(s) g(s,\tau) \tag{4}$$

The power spectrum representation of this expression will be given by Fourier transform of

$$P(\omega) = w(i) \sum_{s=1}^{n} \int_{-\infty}^{\infty} g(s,\tau)\, exp(i\omega\tau) d\tau \tag{5}$$

Therefore, the total power spectrum can be represented as a sum of different bandpass, where each bandpass corresponds to the different shear rate RBCs. Thus, it is possible to extract multiple physiological parameters from this signal by analyzing the power spectrum of the signal, P(ω,*t*), over time(8). We defined the hemodynamic index (HI), which corresponds to a certain range of shear rates determined by the frequencies $\omega 1$ and $\omega 2$:

$$HI[\omega_1, \omega_2] = \int_{f1}^{f2} P(\omega,t) d\omega \tag{6}$$

Each HI represents a subtype of blood vessel or different regions in the vessels, according to the blood flow shear rate(9). It is possible to distinguish between large vessels such as arteries and arterioles and small vessels such as capillaries or venules, for instance, by observing a pulsatile pattern resembling the blood pressure wave in HIs that are associated with pulsatile blood vessels(8) see also Figure 1.

HI is an absolute parameter that may vary between trials due to slight changes in sensor location or proximity to the skin. The relative HI (relHI) is a normalized parameter defined as(8):

$$relHI([f1, f2],t) = \frac{HI\,[f_1, f_2\,]}{HI\,[0, f\,samp]} \tag{7}$$

Where fsamp is the sampling frequency of the measured signal. The variations in relHI following physiological events can be compared between different measurements.

An additional parameter that is extracted from the mDLS signal is the relative blood flow velocity. This parameter is equivalent to the value measured by laser Doppler flowmetry(14), which is used in various applications of hemodynamic research, including quantification of acute noxious stimuli(12). In Doppler flowmetry, the measured Doppler-evoked frequency shift is proportional to the particles' velocity and thus the statistical representation of the skin blood velocity can be derived. Formally, the equivalent skin blood velocity parameter can be defined as the normalized first moment of the power spectrum of the mDLS sensor signal. We term this parameter the relative blood velocity (RBV).

$$RBV = (\int \omega\, P(\omega,t)d\omega \Big/ \int P(\omega,t)d\omega \tag{8}$$

Our goal was to determine the significance of the various hemodynamic parameters in relation to noxious stimulation. To this end, we tested the responses of two hemodynamic parameters derived from the optical signal of the mDLS sensor: relHI and RBV. These hemodynamic parameters are directly related to autonomic nervous system activity(10), and could potentially be used for detecting (and quantifying) the autonomic response to nociceptive events.

Materials and Methods

Measurement system

Two mDLS sensors (Elfi-Tech Ltd., Rehovot, Israel), each of which contain a probe and a three-axis accelerometer (Fig. 1), are positioned on the skin and gently fixated with adhesive tape. One sensor is placed on the palmar aspect of the left index finger, the other on the palmar aspect of the right index finger. The probes are made up of 850 nm vertical cavity surface emitting laser operating in CW mode and two detectors. The mDLS sensor placed on the skin projects a laser beam at blood vessels in the dermis. Light scattered from passing red blood cells (RBCs) in superficial blood vessels is collected by the photo detectors (Fig. 1A). The inputs of the accelerometers are utilized for identifying

and removing motion artifacts. The sensors are connected to an electronic control unit (Elfor-1, Elfi-Tech Ltd.) that collects the data at 48 kHz using a computer interface program.

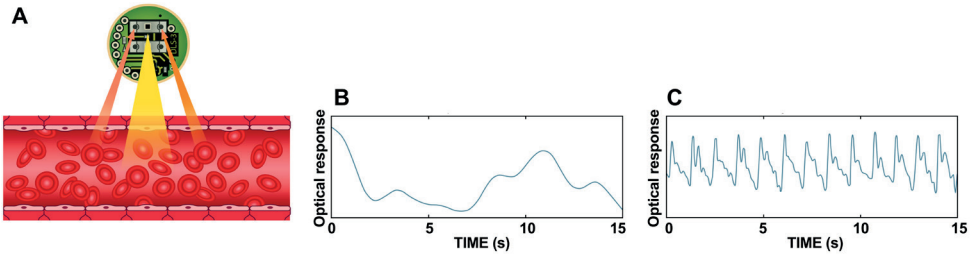

Figure 1. Schematic overview of the miniature dynamic light scattering (mDLS) technique used in this study. The small (diameter 1 cm) mDLS sensor radiates laser light through the skin. The light reflected from flowing red blood cells is collected via two optical sensors (**A**) and further analyzed. Non-pulsatile (**B**) and pulsatile (**C**) signal are derived from the fluctuations in intensity of the reflected optical signal through power spectrum analysis.

Subjects

The protocol, with reference code P15.156, was performed after obtaining approval from the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands) and was registered at www.trialregister.nl under number 5454. All subjects gave oral and written informed consent before enrolment into the study, which was performed from February until November 2016. Protocol P15.156 includes additional studies on the effect of nociceptive stimuli and analgesic medication on mDLS measurements and other hemodynamic measurement devices; here we report on data obtained from the mDLS sensor without administration of any medication.

The study was conducted on seventeen healthy volunteers (7 males, 10 females). Exclusion criteria included a body mass index of 30 kg/m^2 or greater, the presence or history of any medical, neurological or psychiatric disorders, a history of illicit drug use or alcoholism. Additionally, individuals with acute or chronic pain conditions or who used any medication were excluded. The data from the 17 subjects (10 women/7 men; age 23.5 ± 3.4 years, range: 19-31 years; body mass index 22.5 ± 1.8 kg/m^2, range 19.0-26.3 kg/m^2) are presented in this study.

Stimulation protocol

Subjects were first trained in scoring pain intensity on an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable) with just integers allowed for scoring. Next, subjects underwent electrical and heat pain tests. According to previous protocols, we first determined the thresholds to pain detection (pain detection threshold,

Pth) and to pain tolerance (Ptol) for both tests; Pth was defined as NRS = 1, Ptol as NRS = 10.

Electrical pain was induced with the locally designed and manufactured computer interfaced current stimulator (CICS, Leiden University Medical Center, Leiden, The Netherlands)(13). The stimuli were applied to the skin overlying the left tibial bone, approximately 10 cm above the medial malleolus through two surface electrodes (electrode surface area 0.8 cm^2; space between the electrodes 2 cm). For detection of Pth and Ptol an escalating current (5-s trains of 200 ms pulses at 10 Hz) was given from 0 to 128 mA at a rate of 0.5 mA/s, during which the subjects indicated their Pth and Ptol by flipping a switch. This process was repeated at least 3 times to obtain an average value ± 0.5 mA for both Pth and Ptol.

Heat pain was induced through a 3-cm^2 thermode positioned on the volar side of the non-dominant forearm. The thermode was connected to the Pathway Neurosensory Analyzer (Medoc Ltd, Ramat Yishai, Israel), which controls the temperature of the thermode. To determine the temperatures that result in Pth and Ptol we randomly delivered ten to fifteen 30-s heat stimuli with fixed temperatures in the range of 40.0 to 47.9 °C. The subjects scored the NRS of each stimulus; the lowest temperature with NRS scores 1 and 10 were considered Pth and Ptol, respectively. This process was repeated until reproducible values were obtained (i.e. ± 0.5 °C).

After obtaining Pth and Ptol values for electrical and heat tests, we constructed a linear distribution of 8 interpolated currents and temperatures in between Pth and Ptol, corresponding with estimated NRS scores of 2 to 9(11,12). We then randomly applied stimuli to the subjects corresponding with NRS values 1, 4, 6 and 9 with at least 1-min intervals between stimuli. First one complete set of stimuli (heat or electrical) was applied and followed by a second set after a 30-min pause, the order of which was random. Both heat and electrical stimuli lasted 30s. The subjects were blind to the expected NRS values of the stimuli. After each stimulus, the subjects were asked to rate the stimulus using the NRS.

Data Analysis

In the current study, we used the hemodynamic information from the mDLS sensor to assess whether this new approach can detect nociceptive responses during application of a series of thermal and electrical nociceptive stimuli in awake healthy volunteers. Nociceptive stimuli were randomly applied in the range between the subject's pain threshold and pain tolerance(11,12). The analysis focused on the effect of nociceptive stimuli on autonomic dynamics in larger (*e.g.* arterioles, small arteries) and smaller skin vessels (*e.g.* capillaries, venules) following interpretation of the processed mDLS signal.

In this study, two frequency bands were selected for calculating the relHI. The first one was adjusted in order to represent the relative blood flow for very small vessels, such as capillaries or venules (spectrum band of 0-500 Hz) and the second frequency band was selected in order to represent the periodically oscillating high shear rates for greater vessels, such as arterioles (4-10 kHz); the appearance of the pulsatile component was used as a marker to ensure that the latter HI represents the blood flow of the arterioles or small arteries. From here on these HI parameters will be known as the small vessels representation (SVR) and the large vessels representation (LVR).

For data analysis, the data was divided into two main groups, electrical and heat pain stimulation. Each group was further divided into four subgroups referring to the different pain intensities applied at (expected) NRS scores of 1, 4, 6 and 9 (NRS 1, NRS 4, NRS 6 and NRS 9). The differences between the responses and baseline values were calculated for each of the mDLS derived measures (HR, RBV and relHI). Baseline refers to a 60-s period of relaxation prior to any stimulus given; the stimulus refers to the 30-s mean of the response. To get an indication of the temporal profile of the response, we additionally divided the response into three 10-s episodes (0-10 s, 10-20 s and 20-30 s) and calculated their differences with baseline values. The data was analyzed using paired-t-tests with p-values < 0.005 considered significant

Results

Evaluation of stimulation-response curve

First we validated the linearity of the pain test for both electrical and heat stimulation. The mean reported NRS ± 95% confidence interval plotted against the expected NRS shows a clear dose response relationship (figure 2), indicating that higher intensity stimuli were reported as more painful, albeit with small deviations in reported scores.

HR and RBV response to pain stimuli

Relative to baseline, no significant changes in HR were observed during stimulation in heat or electrical tests (Table 1). However, a decrease in RBV values was observed for both types of stimulation (Table 1, Figure 3).

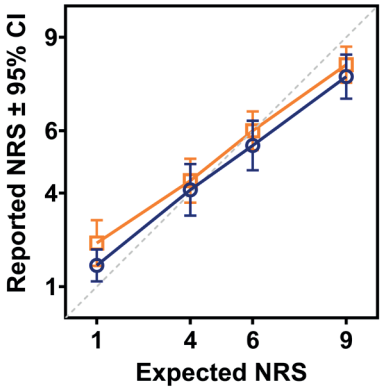

Figure 2. Expected Numerical Rating Score (NRS) *vs.* reported NRS for electrical stimuli (blue circles) and heat stimuli (orange squares). Reported values are mean ± 95% confidence interval. Dotted grey line is the line of identity. The largest deviations occurred at expected NRS values 1 and 9. At an expected NRS of 1, the reported values differed by +0.7 to +1.4 for electrical and heat stimuli, respectively. At an expected NRS of 9, the differences were -1.3 and -0.9 points for electrical and heat stimuli, respectively. At expected NRS values 4 and 6, the reported values were closer to expected values with differences ranging from -0.5 to +0.4 points.

Table 1. Effect of noxious stimulation on heart rate (HR) and Doppler equivalent (DE). ΔHR is the change in heart rate from baseline; ΔDE is the change in Doppler equivalent from baseline. The data are the mean values ± SD measured during the 30-s stimulation.

	ΔHR (BPM) (electric)			**ΔHR (BPM) (heat)**		
	0-10 s	**10-20 s**	**20-30 s**	**0-10 s**	**10-20 s**	**20-30 s**
NRS9	0.93±3.48 (P=0.3)	4.51±6.35 (P=0.01)	2.67±7.39 (P=0.2)	1.17±3.85 (P=0.2)	-0.07±4.1 (P=0.9)	0±4.87 (P=0.99)
	ΔRBV x 10^3 (Hz^{-1}) (electric)			**ΔRBV x 10^3 (Hz^{-1}) (heat)**		
	0-10 s	**10-20 s**	**20-30 s**	**0-10 s**	**10-20 s**	**20-30 s**
NRS9	-2.99±3.69 (P=0.005)	-2.54±3.5 (P=0.01)	-2.87±2.4 (P<0.0005)	-1.01±2.81 (P=0.2)	-1.56±4.36 (P=0.2)	-1.96±4.37 (P=0.1)

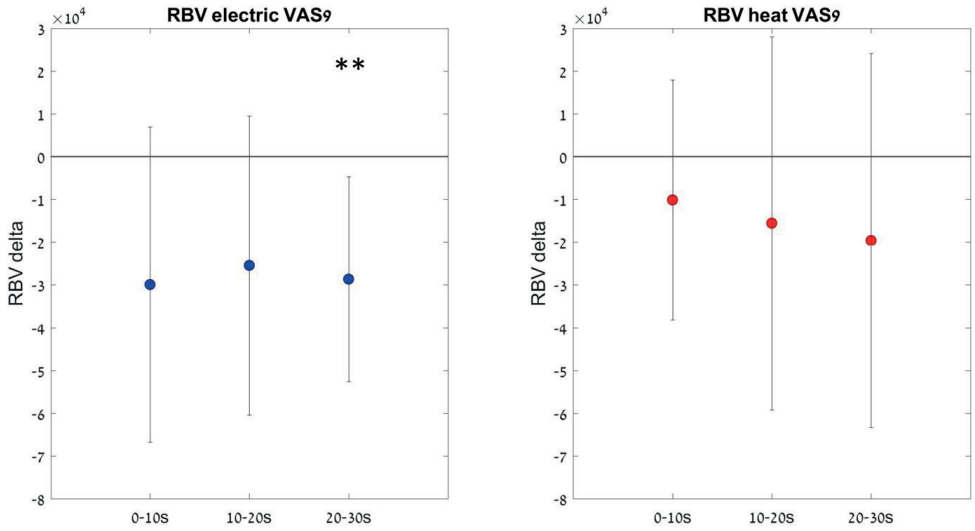

Figure 3. Temporal profile of the change in relative blood velocity (RBV) during electrical (**A**) and heat (**B**) stimulation at NRS9. The data (from the left finger) are divided into three time windows, 0-10 s, 10-20 s and 20-s, of stimulus time. Values are mean ± SD. ** $p < 0.0005$. RBV in arbitrary units.

Relative hemodynamic index response

Examples of relHI responses obtained in one subject on the left and right index fingers during electrical stimulation at NRS 9 are given in Figure 4. During stimulation, an increase in relative flow of the small non-pulsatile vessels (SVR) and a decrease in relative flow of the larger pulsatile vessels (LVR) was observed with a rapid return towards baseline values after termination of the stimulus. The responses of the left and right index fingers were highly correlated in our sample of 17 subjects with identical directions of effect in 90% for electrical stimuli and 84% for heat stimuli. This is indicative of a systemic effect of noxious stimulation on skin hemodynamics.

The effect of electrical and heat stimulation on relative blood flow in the small and large vessel representations are demonstrated in Figure 5.

At all stimulus intensities, there was an increase in the relative blood flow in the SVR and a decrease in relative blood flow in the LVR.

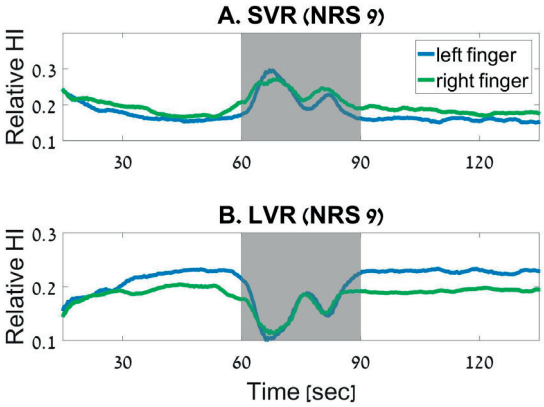

Figure 4. Example of the effect of electrical noxious stimulation at a numerical rating score (NRS) of 9 on relative hemodynamic index (HI) of the small vessel representation (SVR; **A**) and large vessel representation (LVR; **B**) of one subject. The responses of the left finger (blue lines) and right finger (orange lines) are depicted. The grey bar indicates the period of electrical stimulation. HI in arbitrary units.

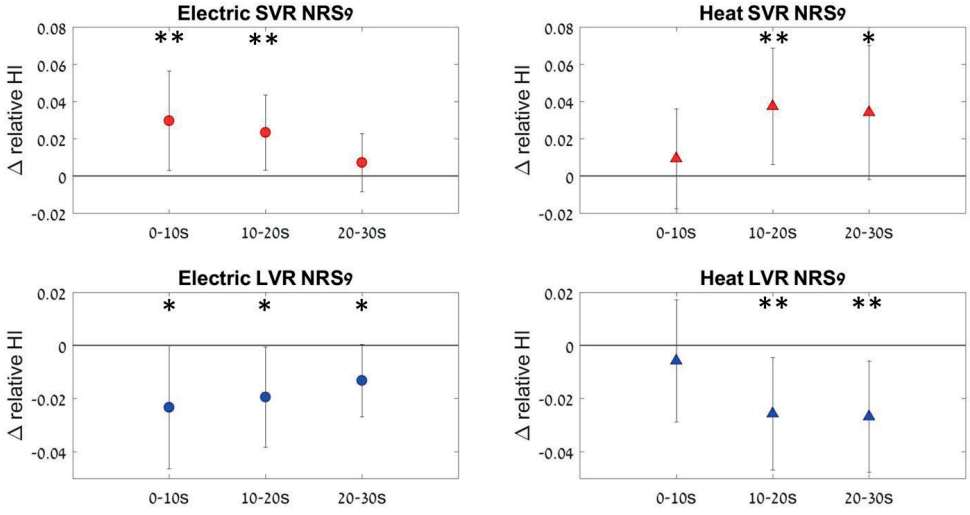

Figure 5. Temporal profile of the change in relative hemodynamic index (HI) during electrical and heat stimulation at different stimulus intensities. **A, B.** Responses for the small vessel representative (SVR). **C, D.** Responses for the large vessel representative (LVR). The data are divided into three time windows, 0-10 s, 10-20 s and 20-s, of stimulus time. Values are mean ± SD. * $p < 0.005$, ** $p < 0.0005$. HI in arbitrary units.

For electrical stimulation, the change in both SVR and LVR is immediate, occurring in the first 10-s episode, followed a by a slow decline towards baseline. The changes in relHI responses for heat pain stimuli are somewhat slower in onset and offset and less marked with a peak in response occurring in the 10-20 s episode.

To get an indication of the stimulus intensity-ΔrelHI relationship, we plotted the reported NRS scores against ΔrelHI (obtained in the 20-30 s stimulus period) in Figure 6.

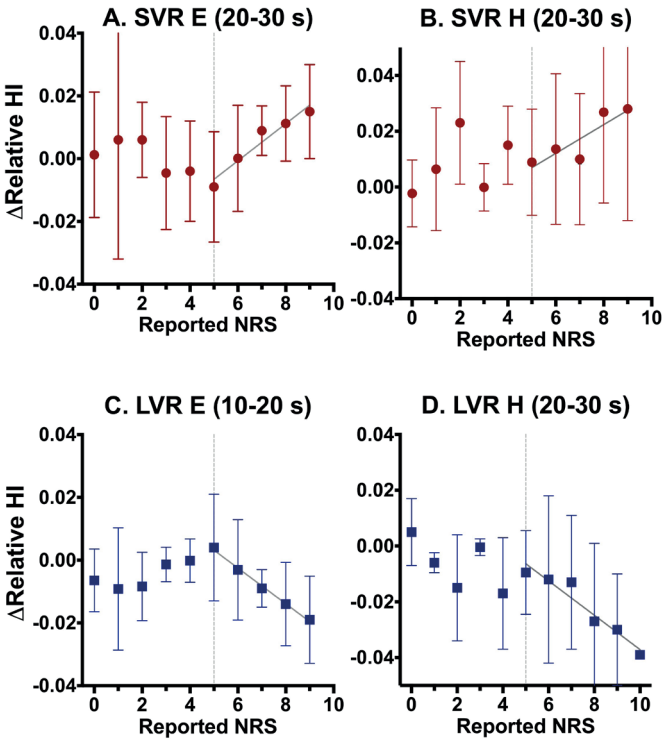

Figure 6. Effect of reported numerical rating scores (NRS) on the change in relative hemodynamic index (Δrelative HI) for the small vessel representative (SVR, panels **A** and **B**) and the large vessel representative (LVR, panels **C** and **D**) for noxious electrical (E, panels **A** and **C**) and noxious heat (H, panels **B** and **D**). A linear regression line was drawn for NRS values ≥ 5. Data are the mean Δrelative HI values ± SD obtained from the 20-30 s of the noxious stimulus. HI in arbitrary units. In panel B one subject reported an NRS of 10, his Δrelative HI was 0.15 and not included in the figure or in the linear regression analysis.

We observed a linear intensity-response relationship for NRS values ≥ 5 for both stimuli in the SVR and LVR. The dose dependency was more robust for noxious electrical pain stimuli than for noxious heat stimuli.

Discussion

In the current study, we used hemodynamic and relative hemodynamic indices, derived from scattered light intensity analysis of moving red blood cells in the vessels of the skin, to detect physiological responses to acute noxious cutaneous stimulation. Skin blood flow dynamics were measured with the mDLS sensor during the application of 30-s electrical and thermal stimuli of varying intensities in a group of young healthy volunteers. The main findings of our study are that

1) the mDLS sensor was able to detect noxious events as measured by relHI;
2) a linear dose relationship between stimulus intensity and the change in relHI relative to baseline was observed for reported NRS scores > 5;
3) heart rate was unable to detect the noxious stimuli at the intensities applied in this study;
4) there is a decrease in blood flow velocity (as quantified by the Doppler equivalent);
5) an inverse response to noxious stimulation was observed in the LVR and the SVR, with a reduction in relative flow in pulsatile vessels of the skin and an increase in relative flow in non-pulsatile vessels;
6) changes in relative hemodynamic index occurred simultaneously in left and right index fingers, independent of the site of stimulation.

In our study, two different representations of the hemodynamics of blood vessels of the skin were extracted from the scattered light intensity pattern, one which represents red blood cell flow in SVR and one which represents red blood cell flow in LVR. Similar approaches to blood flow hemodynamics are increasingly used in biomedical research. For example, in rats, this technique has been applied to quantify anastomotic healing in colorectal surgery(15). In this study, it was shown that non-pulsatile (*e.g.* capillary) anastomotic perfusion is a useful marker of anastomotic leakage in a rat colectomy model. Additionally, in a group of 19 volunteers, the effect of mental stress on the hemodynamic index was tested using the mDLS sensor showing large and consistent effects of stress on hemodynamic changes in the SVR.[9]

In the current study, apart from flow-related parameters, we extracted two "standard" hemodynamic markers, heart rate and RBV from the mDLS sensor response to nociceptive events. We observed no significant response of HR, in agreement with earlier studies(16). In contrast, flow-related parameters such as RBV and relative blood flow in the LVR and SVR, showed significant changes to nociceptive stimuli. We relate the noxious stimulation-induced reduction in skin perfusion to vasoconstriction of the larger blood vessels (LVR: arterioles, small arteries) of the skin secondary to autonomic nervous system activation(19,20). This response is most probably neurogenic, *i.e.* due to alpha-adrenergic receptor activation secondary to epinephrine and norepinephrine

release from sympathetic nerves that innervate skin arterioles and arteries. A humoral component seems unlikely, given the temporal profile of the observed response (rapid onset and offset of hemodynamic changes; Fig. 4C-D). Still, the response was generalized as it occurred in both upper extremities while noxious stimulation was either restricted to one arm (heat pain) or to one of the lower extremities (electrical pain). This suggests the central activation of the sympathetic fibers caused vasoconstriction of the pulsatile vessels (arterioles and small arteries) of the skin. Whether the vasoconstriction was restricted to the pulsatile vessels of the skin remains unknown, but we argue that the central sympathetic response also had effects at sites other than the skin.

Combining the response to noxious stimuli of flow-related indices, we postulate that there is a decrease in total flow to the LVR combined with a redistribution of blood flow between the LVR and the SVR. The analysis of absolute HI values (data not shown) indicates that the increase in flow of the SVR is relatively minor compared to the decrease in flow of the LVR. The observation that changes in the LVR and SVR exhibit similar dynamics (Fig. 4) suggests that the mechanisms of flow changes in pulsatile and non-pulsatile vessels are tightly coupled. It may be that the increase in ΔrelHI of the SVR is related to redistribution of flow. This is possibly due to a local dynamic autoregulatory or reflectory response independent of neural control (*e.g.,* through the release of gaseous signaling molecule and potent vasodilator nitric oxide from capillary and venular endothelial cells), and/or secondary to sympathetic-fiber release of vasodilators(21,22). However, the mechanism of redistribution is not addressed in our experiments. Further mechanistic studies are therefore required to understand the complex behavior of pulsatile and non-pulsatile skin blood vessel in response to noxious stimulation.

The temporal profile of the relHI responses to electrical and heat stimulation differed in their dynamics (Fig. 5). Relative to the response to electrical stimuli that peaked early (within the first 10-s period of the stimulus), the response to heat stimulation was slower, with a peak response in the middle one-third of the stimulus. Moreover, more robust changes in response to electrical stimulation were observed compared to heat stimulation (Fig. 6). As discussed previously(11), different pain models activate different pain pathways with differences in central processing. For example, noxious electrical stimuli directly excite sensory and non-sensory nerves of the skin in an unnatural and synchronized fashion, bypassing the sensory nerve endings. In contrast, noxious heat stimuli activate nociceptors on Aδ- and C-fibers at their nerve endings. Possibly, the barrage of afferent input from electrical stimulation interacts instantaneously with central sites involved in autonomic response activation, while heat stimuli have slower response characteristics in this respect.

The decrease in RBV for both types of stimulation is in agreement with the dynamics of the relative blood flow in SVR and LVR – a decrease in RBV indicates a shift in energy

towards lower frequency bands. Although the decrease was statistically significant only for electrical stimulation, we postulate that the delayed onset of the response to heat stimulation may lead to a significant decrease in RBV at a slightly later time period which we cannot observe using the current protocol.

We applied random noxious stimuli in between individually determined pain threshold and pain tolerance values(11,12). Although there were some deviations in the reported pain scores with overestimation of pain at low stimulus intensities and underestimation at high pain scores, in general the subjects reported higher pain scores at greater pain intensities (Fig. 2). Possibly, a better dose-response relationship between NRS and hemodynamic responses could have been achieved if stimuli at escalating intensities would have been delivered to the subjects. However, we favored our current design to preclude any cognizant anticipatory effect of a known stimulus train on the study outcome.

Interestingly, we observed a linear stimulus intensity-ΔrelHI response relationship at reported NRS values > 5 (Fig. 6). This suggests that just reported stimuli at NRS intensities greater than 5 were perceived as painful enough to cause a significant autonomic response. However, somewhat to our surprise, even at the lowest intensity electrical stimulus, *i.e.* NRS 1, corresponding to the first perception of pain (pain threshold), a similar trend in the hemodynamic response was observed (Tables 1, 2 and 3). Since our study was performed in awake subjects, apart from the central processing of the afferent nociceptive input, some emotional or stress-related effects may have contributed to the hemodynamic responses we observed. The absolute increase in the response for all tested hemodynamic parameters demonstrates that on top of any stress-related effect that may have occurred in these trials, there is an additional response to pain, and this response increases in correlation with the stimulus intensity. Further studies are still needed to assess the response to pain under conditions in which conscious processing is absent or reduced.

To summarize, we applied the novel technique of dynamic light scattering to determine the effect of noxious stimulation on hemodynamic parameters in awake volunteers. While parameters that are commonly used such as HR were not able to detect noxious events, we observed that mDLS parameters such as RBV and relative blood flow could detect nociceptive stimuli and consequently could serve as objective biomarkers of nociception (acute pain). Moreover, these biomarkers provided some insight into the physical and physiological changes in hemodynamics that occur during noxious stimulation. Additional studies should address the ability of the mDLS sensor in detecting noxious stimuli during anesthesia or deep sedation and determine whether combining the hemodynamic parameters into one index would further increase the ability of the system to detect noxious events.

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CHAPTER 3

3

Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia

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Introduction

Accurate measurement of nociception during anesthesia remains a challenging task. Nociception, which is defined as the neural process of encoding and processing noxious stimuli (noxious stimuli are actually or potentially tissue damaging events)(1), will elicit behavioral, autonomic and hormonal responses in conscious and unconscious individuals. Detection of behavioral responses during anesthesia is often impossible because of the use of muscle relaxants. Hence, we rely mostly on the autonomic responses to assess the nociception level (NoL) of the patient. Most anesthesia healthcare providers, if not all, use changes in heart rate (HR) and blood pressure as markers of the occurrence of acute nociceptive events. Although these variables may suffice when intense nociceptive stimuli occur, mild and moderate stimuli are often not detected or detected too late(2). In recent years, various indices of nociception have been developed with varying success in actually detecting nociceptive events. These indices derive a numerical value from single variables (such as heart rate variability [HRV], skin conductance, skin vasomotor reflex, the electroencephalogram, pupil diameter) or a combination of signals(3–11). In the current study, we apply a new index of nociception, the NoL index(2). The NoL is a multiparameter nonlinear combination of HR, HRV, amplitude of the finger photoplethysmogram (AP), skin conductance level, fluctuations in skin conductance and their time derivatives, derived from random forest regression. Random forest is an algorithmic modeling approach that enables combining multiple parameters of different origin and discovering their complex nonlinear interactions(12,13). We measured the NoL, HR, and arterial blood pressure during induction of general propofol–remifentanil anesthesia, intubation, and incision. Our aims were to validate the NoL as measured in real time by assessing its ability to detect moderate and intense nociceptive stimuli under different target remifentanil blood concentrations. The NoL was compared with the more commonly used indices of nociception, mean arterial pressure (MAP), and HR.

Materials and Methods

The protocol was performed after obtaining approval from the local Human Ethics Committee Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands) and was registered at www.clinicaltrials.gov under number NCT01912118. All patients gave oral and written informed consent before enrolment into the study. The study was performed from July 2013 to June 2014.

Patients

American Society of Anesthesiology class I, II, or III patients (age, 18 to 80 yr) of either sex, scheduled for elective surgery under general anesthesia, were recruited to participate

in the study. Exclusion criteria included inability to give informed consent, pregnancy or lactation, body mass index more than 35 kg/m2, perceived difficult intubation, planned rapid sequence intubation, and use of β-adrenergic receptor antagonists. Preoperative preparation was according to local protocol.

Study Design

In this prospective randomized study, patients received total intravenous anesthesia with propofol and remifentanil. Seventy-two patients were randomly assigned to one of six possible remifentanil target concentrations: 0 (propofol only, n = 12), 1, (n = 12), 2 (n = 12), 3 (n = 12), 4 (n = 12), and 5 (n = 12) ng/ml, using a custom-built remifentanil target controlled infusion pump (Remifusor, University of Glasgow, United Kingdom) programmed with the remifentanil pharmacokinetic dataset published by Minto *et al.*(14). Similarly, propofol was infused using a target-controlled infusion system (Orchestra Base Primea, Fresenius Kabi, The Netherlands) programmed with the propofol pharmacokinetic dataset published by Marsh *et al.*(15). The target was adapted such that before intubation or skin incision the bispectral index (BIS) of the electroencephalogram (BISR VISTA, Covidien, Ireland) was maintained at 45 ± 5 for at least 10 to 15 min. If needed, a muscle relaxant (rocuronium, 0.5 mg/kg) could be given before intubation.

In the protocol, there were two additional study groups (n = 12, BIS, 70; remifentanil, 3 ng/ml; and n = 12, BIS, 30; remifentanil, 3 ng/ml). After enrollment of four subjects in this subprotocol, further inclusion of subjects was stopped because of safety concerns (*e.g.*, possibility of awareness, hemodynamic instability).

Data Collection

A finger probe containing sensors for measurement of the photoplethysmogram, the Galvanic skin response, skin temperature, and three-axis accelerometer was placed on the index finger of the right hand (Medasense Biometrics, Israel)(2,16). The signals from the probe were sampled at 50 Hz and recorded on a laptop computer using the PMD-10X system and software (Medasense Biometrics). All data were processed offline using MATLAB R2011b software (The Mathworks Inc., USA). The following variables were calculated from the finger probe as specified by Ben-Israel *et al*.(2): HR, HRV, AP, skin conductance level, and fluctuations in skin conductance. To measure the noninvasive beat-to-beat blood pressure, an appropriately sized finger cuff was applied to the mid-phalanx of the left index finger, which was connected to a Nexfin monitor (Edwards Lifesciences, USA). Refer the study by Martina *et al*.(17) for an elaborate explanation of the Nexfin system and calculation of blood pressure. The beat-to-beat finger arterial blood pressure was stored on disc for offline analysis. The PMD-10X and the Nexfin systems were time aligned before each study. Data were collected from induction of anesthesia until 3 to 5 min after incision. Specific events occurring during the study (start of induction, patient movement,

intubation, and incision) were logged in the PMD-10X software program enabling a direct link between stimulus and measurements.

Description of the Nociception Level Index

The NoL is based on a nonlinear combination of nociception-related physiologic parameters: HR, HRV (at the 0.15 to 0.4 Hz band power), amplitude of the photoplethysmograph wave, skin conductance level, number of skin conductance fluctuations, and their time derivatives(2). The NoL index was developed to correlate with a reference clinical score of nociception based on the estimated opioid concentration and stimulus strength (*i.e.*, the combined index of stimulus and analgesia [CISA]). A composite parameter was derived from random forest analysis(12,13), a nonlinear regression method, in which the physiologic signals with their derivatives were used as predictor variables and the CISA was used as the observed variable. The estimated multiparameter composite derived from the regression analyses was scaled from 0 to 100 to produce the NoL. The NoL index has been shown to provide a better indication of nociception than each of its component physiologic signals and to their linear combination(2). In the current study, the NoL index was calculated from the extracted signals by the PMD-10X software/hardware system using the algorithm derived from the learning study by Ben-Israel *et al*.(2). The NoL device has not received Food and Drug Administration clearance as yet and is still under investigation.

Data Analysis

Because this study was the first assessment of the NoL in a clinical perioperative setting using total propofol/remifentanil anesthesia, we were uninformed regarding the possible effect sizes of the three stimuli on the NoL. We somewhat arbitrarily set the sample size at 12 subjects per remifentanil treatment level or 72 patients in total, a number very similar to several previous studies linking physiologic signals to nociception(9,11). Statistical and data analyses were performed using MATLAB R2011b software (The Mathworks Inc.). Three distinct stimuli were defined in each patient: a nonnoxious event, incision, and intubation, which were regarded as nonnoxious, moderate noxious, and severe noxious stimuli, respectively(2,18,19). We graded the nociceptive intensity, nonnoxious event > incision > intubation, based on the previous studies that showed that the opioid concentration needed to suppress the autonomic response to intubation exceeds the concentration required to suppress the response to skin incision by a factor of (2.18,19). A nonnoxious event was defined as a 1-min interval within a 5-min window of absence of noxious stimulation; intubation was defined as the time interval around the insertion of the oropharyngeal tube into the trachea and included the preceding laryngoscopy; incision was defined as the time interval around the surgical skin incision. For each stimulus, two parameter values were defined, one before stimulation (before) and one after stimulation (after), which were the average of data before and after the stimulus along a certain

time interval. These time intervals were the first (before) and last (after) 30 s of the 1-min nonnoxious interval for the nonnoxious stimulus and the 30 to 60s before the stimulus (before) and the 10 to 180 s after the stimulus (after) for incision and intubation. Analysis was done on both the absolute MAP, HR, and NoL values and the difference between after and before values (*i.e.*, Δ). In case of use of vasoactive (*e.g.*, ephedrine and phenylephrine) and vagolytic (*e.g.*, atropine) drugs in these time windows, the data were discarded.

Statistical Analysis

The following statistical tests were performed to compare the performance of NoL, ΔNoL, MAP, ΔMAP, HR, and ΔHR:

1) Right-tailed paired *t* test to assess whether the average reaction (Δ) of the three variables to stimulation are significantly greater than 0. Two-tailed unpaired *t* test to assess whether the population values of the variables after stimulation were significantly different from the values obtained before stimulation. In addition, the effect of stimulation on BIS was tested using paired and unpaired *t* tests.
2) Receiver operating characteristic (ROC) curves were constructed to assess the ability of the individual variables (absolute values and Δ) to discriminate between noxious and nonnoxious events. CIs of the area under the ROC curves (AUCs) were calculated using the method suggested by Hanley and McNeil,20 which corrects for the use of correlated data.
3) Repeated measures ANOVA to test the ability of each of the variables to grade noxious stimuli, *i.e.*, to assess whether the variable values increased with an increasing stimulus strength: nonnoxious stimulus < moderate noxious stimulus (incision) < intense noxious stimulus (intubation). In case of a significant main and interaction terms, a Scheffe *post hoc* multiple comparison test was applied to test between pairs nonnoxious stimulus *versus* intubation, nonnoxious stimulus *versus* incision, and incision *versus* intubation.
4) For nonnoxious stimuli and intubation, the Spearman correlation coefficient was calculated to quantify the relation between HR, MAP, NoL, and the remifentanil target concentration. This was done separately for time intervals before and after stimulation. A quadratic polynomial was fitted by least square analysis to the data.

Results

Seventy-two patients participated in the study according to protocol (data from the subprotocol are not considered here). The characteristics of the 72 participating patients are given in Table 1. The complete dataset of one subject was lost because of technical problems. The data from 71 patients were used in the analysis. All patients completed the study without side effects. In about half of the patients, a muscle relaxant was administered before intubation. Before noxious stimulation (intubation/skin incision), BIS values were

on average of 45.0 ± 9.0 (mean ± SD), 45.6 ± 9.9, 47.2 ± 9.1, 42.6 ± 7.4, 44.7 ± 8.0, and 47.0 ± 9.8 in the 0, 1, 2, 3, 4 and 5 ng/ml remifentanil groups, respectively (repeated measures ANOVA: $P > 0.05$; grand mean, 45.5 ± 8.8). Because of technical (*e.g.*, monitor failure), logistic (*e.g.*, change of surgical plan), or other reasons (*e.g.*, hypertension/ hypotension or bradycardia in response to low/high remifentanil requiring the use of vasoactive/vagolytic drugs; lack of annotations) that caused an inadvertent breach of protocol, the datasets missed one of the noxious/nonnoxious stimuli in 20 to 25% of cases. The numbers of excluded events are given in Table 2.

Table 1. Patient characteristics for the six study groups and performed surgical procedures.

	REMI 0	**REMI 1**	**REMI 2**	**REMI 3**	**REMI 4**	**REMI 5**	**ALL**
n	12	12	12	12	12	12	72
M/F	6/6	3/9	9/3	4/8	3/9	8/4	33/39
Age (yrs) (range)	43 (20-75)	57 (24-74)	56 (37-69)	55 (21-74)	54 (26-76)	54 (31-73)	54 (20-76)
Height (cm)	176 ± 1	169 ± 6	181 ± 9	171 ± 9	170 ± 9	176 ± 13	174 ± 10
Weight (kg)	81 ± 16	67 ± 12	84 ±15	70 ± 11	69 ± 12	79 ± 16	75 ± 15
BMI	26 ± 5	24 ± 4	26 ± 4	24 ± 3	24 ± 3	26 ± 4	25 ± 4
Heart rate (bpm)*	79 ± 10	74 ± 15	72 ± 15	73 ± 10	70 ± 13	74 ± 18	73 ± 14
MAP (mmHg)*	90 ± 12	99 ± 14	96 ± 14	101 ± 19	96 ± 18	100 ± 10	97 ± 15
ASA 1 (*n*)	7	5	5	5	9	8	39
ASA 2 (*n*)	5	6	7	7	3	4	32
ASA 3 (*n*)	0	1	0	0	0	0	1
General surgery (*n*)	4	4	5	5	4	8	30
Gynecology (*n*)	4	4	2	1	1	4	16
Urology (*n*)	3	2	3	2	1		11
Orthopedics (*n*)	1		1		2		4
ENT (*n*)		1		1	2		4
Neurosurgery (*n*)		1					1
Oral surgery (*n*)			1				1
Plastic surgery (*n*)				3	2		5

All values are represented as mean ± SD or numbers (n), except age, which is represented as median (range).

*Values obtained at patient screening in the preoperative clinic.

ASA = American Society of Anesthesiologists; BMI = Body Mass Index; ENT = ear, nose and throat surgery; F = female; M = male; MAP = mean arterial pressure; REMI = remifentanil target concentration.

Table 2. Reason for missing or discarded data

	Device	*Number of subjects included in the analysis*	Number of subjects with missing data
			A / B /C
Non-noxious stimulus	PMD-10X™	63	0 / 0 / 9
	Nexfin device	56	7 / 0 / 9
	BIS monitor	56	7 / 0 / 9
Incision	PMD-10X™	58	1 / 5 / 8
	Nexfin device	53	3 / 5 / 8
	BIS monitor	56	3 / 5 / 8
Intubation	PMD-10X™	67	0 / 2 / 3
	Nexfin device	65	2 / 2 / 3
	BIS monitor	66	1 / 2 / 3

A = technical problems, B = clinical issues (hypotension/hypertension/bradycardia) and C = lack of annotation; BIS is the bispectral index of the electroencephalogram.

Response to Noxious Events

The effect of nonnoxious stimuli, incision, and intubation on BIS, HR, MAP, and NoL are given in figure 1. Nonnoxious stimuli had no effect on any of the variables when comparing before with after time intervals (mean difference [95% CI]): ΔBIS, −0.1 (−0.9 to 0.7); ΔHR, −0.13/min (−0.7 to 0.3/min); ΔMAP, −0.45 mmHg (−1.9 to 2.1 mmHg); and ΔNoL −1.1 (−3.6 to 2.0). Intubation caused an increase in HR, MAP, and NoL but not BIS: ΔBIS, 1.7 (−3.9 to 6.3; not significant [ns]); ΔHR, 7.0/min (1.4 to 12.0/min; paired *t* test, $P < 0.001$; unpaired *t* test, $P < 0.001$); ΔMAP, 13.0 (3.1 to 20; paired *t* test, $P < 0.001$; unpaired *t* test, $P < 0.001$); and ΔNoL, 18.0 (7.8 to 29.0; paired *t* test, $P < 0.001$; unpaired *t* test, $P < 0.001$). Incision had no effect on BIS and HR but caused increases in MAP and NoL, although, in contrast to MAP, the effects on NoL were significant in both paired and unpaired *t* tests: ΔBIS, 0.92 (−1.2 to 3.3; ns); ΔHR, 1.3/min (−0.46 to 3.1/min; ns); ΔMAP, 7.9 mmHg (−1.9 to 13.0 mmHg; paired *t* test, $P < 0.001$; unpaired *t* test, ns); and ΔNoL, 8.0 (0.4 to 16.0; paired *t* test, $P < 0.001$; unpaired *t* test, $P < 0.001$).

Comparing the three different stimuli (*i.e.*, assuming nonnoxious event ≠ incision ≠ intubation), a significant main and interaction effect was observed for HR, MAP, and NoL after (but not before) stimulation and Δs: HR $F(2,96) = 9.4$, $P < 0.001$; ΔHR $F(2,96) = 27$, $P < 0.0001$); MAP $F(2,80) = 28$, $P < 0.001$; ΔMAP $F(2,80) = 19$, $P < 0.0001$; NoL $F(2,96) = 23$, $P < 0.0001$; ΔNoL $F(2,96) = 46$, $P < 0.0001$. *Post hoc* analysis showed that only NoL (after stimulation) and ΔNoL graded the level of noxious intensity with nonnoxious NoL < incision NoL < intubation NoL. HR after stimulation and ΔHR could not differentiate between nonnoxious stimuli and incision ($P = 0.24$). ΔMAP could not discriminate between incision and intubation ($P = 0.07$). See also Supplemental Digital Content 1, tables 1 and 2, http://links.lww.com/ALN/B170.

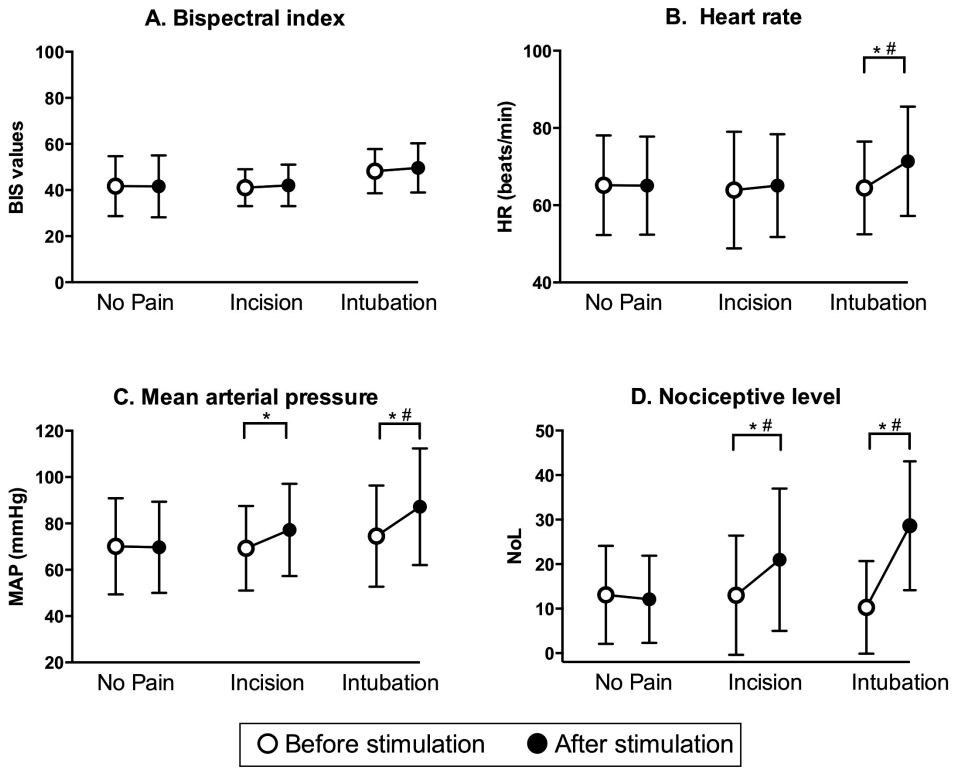

Figure 1. Bispectral Index (BIS)(**A**), heart rate (HR)(**B**), mean arterial pressure (MAP)(**C**) and nociceptive level (NoL)(**D**) before and after noxious stimulation for nonnociceptive conditions, incision and intubation. *Paired t test, $p < 0.001$. Open symbol = before stimulation; closed symbol = after stimulation.

The ROC curves, calculated (n = 71) for HR, MAP, and NoL (all after stimulation), and ΔHR, ΔMAP, and ΔNoL, are shown in figures 2 and 3. ROC areas under the curve sensitivity values at a specificity of 75% are given in table 3. ΔNoL outperformed all other variables in ability to discriminate between noxious (intubation or incision) and nonnoxious events with an AUC of 0.95 (95% CI, 0.91 to 0.99). The ΔNoL AUC was significantly larger compared with all other variables ($P = 0.0003$ *vs.* ΔHR; $P < 0.0001$ *vs.* ΔMAP; $P < 0.0001$ *vs.* HR; $P = 0.00004$ *vs.* MAP). Moreover, NoL after stimulation outperformed MAP and HR in classifying noxious stimuli (AUC, 0.82; 95% CI, 0.75 to 0.89, $P = 0.001$ *vs.* HR; $P = 0.035$ *vs.* MAP). The NoL outperformed HR and MAP and ΔNoL outperformed ΔHR and ΔMAP in terms of sensitivity, specificity, and positive and negative predictive values for the detection of noxious stimuli (table 3). For NoL a cutoff value between noxious and nonnoxious stimuli of 16 yielded a specificity and sensitivity of 80 and 73%.

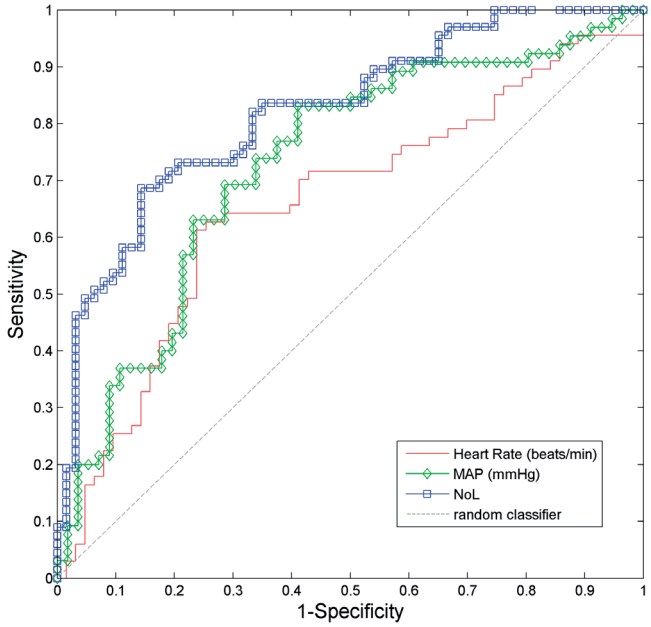

Figure 2. Discrimination between nociceptive (incision and intubation) and nonnociceptive stimuli: receiver operating curves of heart rate, mean arterial pressure (MAP) and the composite parameter, the nociceptive level (NoL).

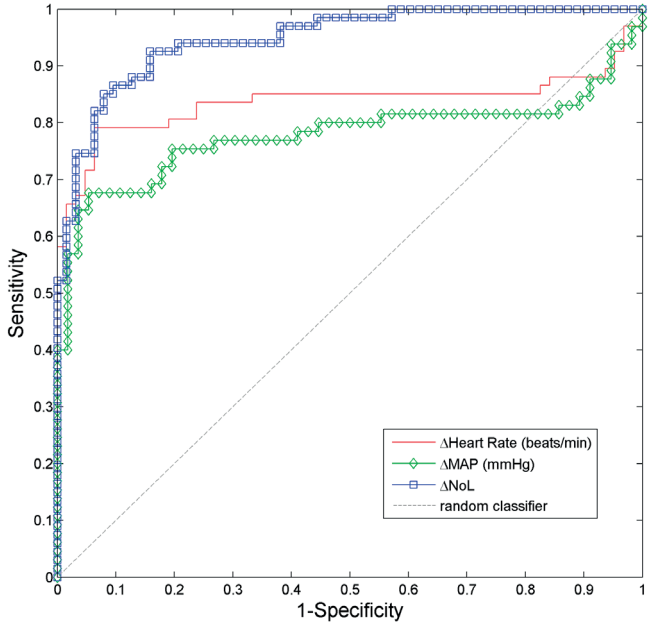

Figure 3. Receiver operating curves of the hemodynamic Δ signals and the Δ nociceptive level (ΔNoL). MAP = mean arterial pressure.

Table 3. AUC, Sensitivity, PPV and NPV of the NoL, ΔNoL, HR, ΔHR, MAP and ΔMAP at a Specificity of 75%.

Variable	AUC (95% CI)	Sensitivity(%)	Specificity(%)	PPV (%)	NPV(%)
HR	0.66 (0.56-0.75)	63	75	72	65
MAP	0.73 (0.64-0.81)	63	75	75	64
NoL	0.82 (0.75-0.89)*	73	75	75	72
ΔHR	0.84 (0.77-0.91)	84	75	78	81
ΔMAP	0.78 (0.70-0.86)	75	75	78	72
ΔNoL	0.95 (0.91-0.99)#	94	75	80	92
Random classifier	0.50	25	75	50	50

Statistical test was performed according to Hanley and McNeil(20). NoL, MAP and HR given were obtained after noxious stimulation.
*p = 0.001 vs HR. p = 0.036 vs MAP.
# p = 0.0003 *vs.* ΔHR; p < 0.001 *vs.* ΔMAP; p = 0.0001 *vs.* ΔNoL; p < 0.0001 *vs.* HR; p < 0.0001 *vs.* MAP.
AUC = area under the receiver operating characteristics curve; HR = heart rate; MAP = mean arterial pressure; NoL = nociceptive level; NPV = negative predictive value; PPV = positive predictive value.

Response to Intubation under Different Remifentanil Target Concentrations

The effects of increasing concentrations of remifentanil on HR (n = 57), MAP (n = 50), and NoL (n = 57) before and after noxious stimulation are shown in figures 4 to 6. The NoL before and after nonnoxious stimulation showed no significant correlation with the remifentanil concentration (rS = –0.047 and 0.024, $P > 0.05$; fig. 4, A and B). The before and after intubation NoL values showed a significant Spearman correlation with rS = –0.3, $P < 0.05$ (before, fig. 4C) and rS = –0.51, $P < 0.001$; after, fig. 4D). The analysis indicates that with increasing remifentanil concentrations, the NoL response to intubation decreases significantly with the smallest response observed at a remifentanil target concentration of 5 ng/ml (fig. 4D). HR before and after nonnoxious stimulation and intubation decreased significantly with increasing remifentanil concentrations ($P < 0.01$; fig. 5, A–D). A similar observation was made for MAP before and after nonnoxious stimulation and intubation ($P < 0.05$; fig. 6, A–D).

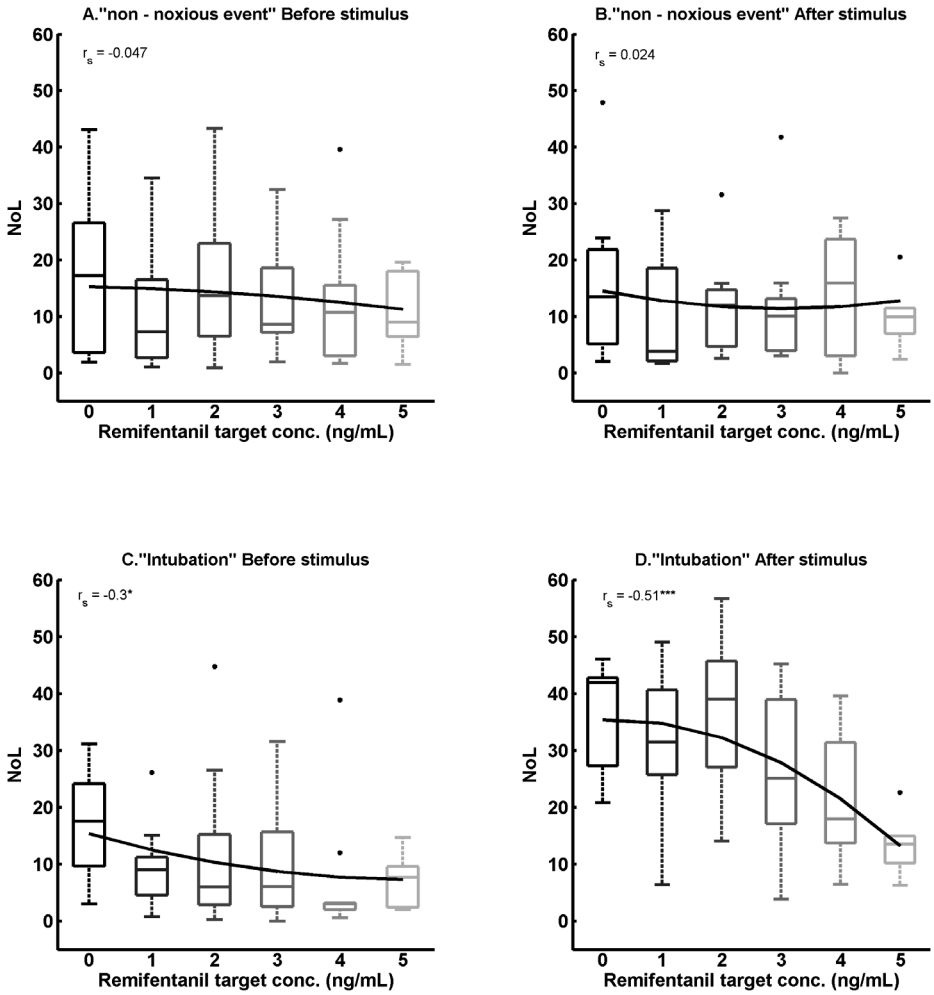

Figure 4. Boxplot of the effect of remifentanil on nociception level (NoL) before (**A**) and after (**B**) noxious stimulation for nonnociceptive conditions and before (**C**) and after (**D**) noxious stimulation for intubation. Boxplots represent the median and 25th and 75th percentiles, and the *whiskers* extend to the most extreme data points; outliers are plotted individually (*block dots*). The Spearman correlation is given (rS), with *$P < 0.05$ and ***$P < 0.001$. A quadratic polynomial is fitted to the data to guide the eye.

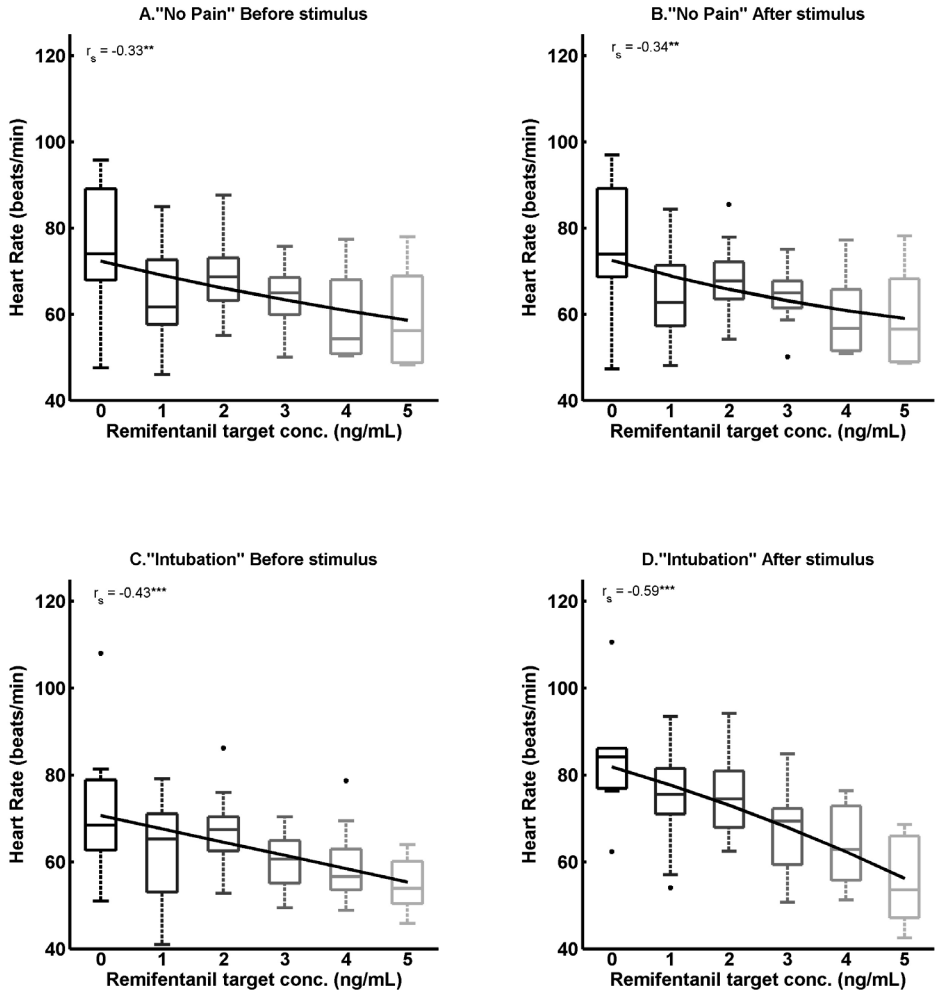

Figure 5. Boxplot of the effect of remifentanil on heart rate before (**A**) and after (**B**) noxious stimulation for nonnociceptive conditions and before (**C**) and after (**D**) noxious stimulation for intubation. Boxplots represent the median and 25th and 75th percentiles, and the *whiskers* extend to the most extreme data points; outliers are plotted individually (*black dots*). The Spearman correlation is given (rS), with $^{**}P < 0.01$ and $^{***}P < 0.001$. A quadratic polynomial is fitted to the data to guide the eye.

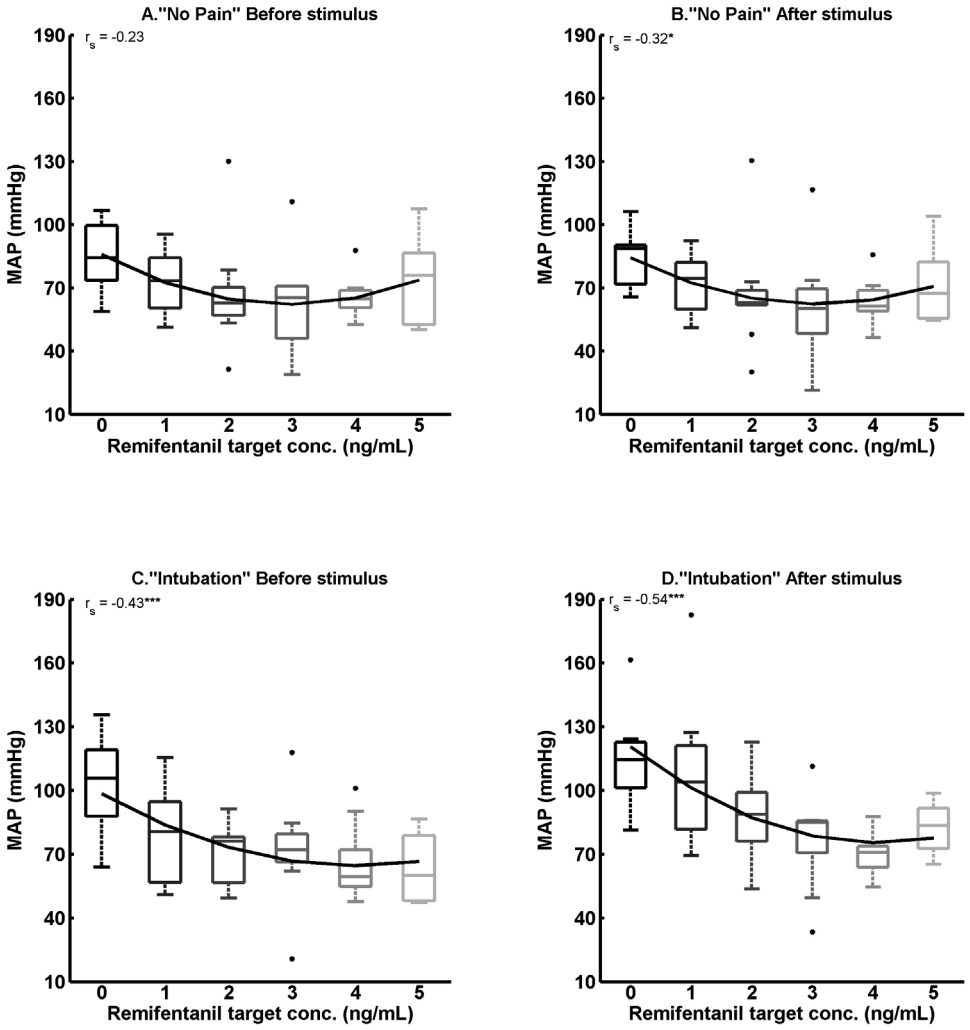

Figure 6. Boxplot of the effect of remifentanil on mean arterial pressure (MAP) before (**A**) and after (**B**) noxious stimulation for nonnociceptive conditions and before (**C**) and after (**D**) noxious stimulation for intubation. Boxplots represent the median and 25th and 75th percentiles, and the *whiskers* extend to the most extreme data points; outliers are plotted individually (*black dots*). The Spearman correlation is given (rS) with *$P < 0.05$ and ***$P < 0.001$. A quadratic polynomial is fitted to the data to guide the eye.

Discussion

In this validation study, the NoL, a novel multidimensional parameter, was used to detect nociceptive events during propofol–remifentanil anesthesia. The variables that make up the NoL cover both sympathetic and parasympathetic activities of the autonomous nervous system.(21) The main observations from our study are that 1) the NoL is able to detect intense noxious stimulation (intubation) and moderate nociceptive stimuli (incision). In this respect, the NoL outperformed the standard variables (HR and MAP) that were sensitive to intubation but to a lesser extent to incision. Furthermore, as based on the AUC of the ROC, the NoL was best in differentiating noxious from nonnoxious stimuli; and 2) the NoL was significantly correlated with the target remifentanil concentration after noxious stimulation. Similar observations were made for HR and MAP; however, in contrast to HR and MAP, the NoL was not affected by nonnoxious events.

Various previous studies have relied on single signals to assess nociception during surgery(3–11,22). For example, indices from the high-frequency component of HRV were used to evaluate surgical nociception and analgesia during anesthesia and to predict postoperative pain based on the measurements before extubation(3,22). Another example is the measurement of changes in skin conductance, which is based on the sympathetically induced secretion of sweat, which increases skin conductance(4). This response (*i.e.*, nociceptionrelated sweating) is unrelated to hemodynamic changes. All single indices aimed at detecting nociception share that they are surrogate markers of the autonomic nervous system and show a large within- and between-subject variability(2,23). Another approach in detecting nociception during surgery is the use of multiparameter indices(8–10). Several studies show that a multiparameter approach yields greater sensitivity and specificity in discriminating between noxious and nonnoxious stimuli than the single-signal approach(2,11,16). Examples of multiparameter indices are the Surgical Pleth or Stress Index (which combines HR and AP)(9), the response index of nociception (which combines parameters from the electroencephalographic and hemodynamic signals)(11), and the composite variability index (which combines the variability of the forehead electromyogram and BIS of the electroencephalogram)(11).

In the current study, we applied the multiparameter NoL to assess nociceptive responses at three levels of increasing nociceptive intensity. The NoL showed a remifentanil dose-independent increase in noxious response from −1.1 (nonnoxious stimulus) to 8.0 (incision) and 18.0 (intubation), with significant increases (Δ signal) occurring for incision and intubation (fig. 1). This contrasts with the two other variables that were tested, the commonly used HR and MAP, which on a population level did show significant increases at intense stimulation but not at moderate noxious stimulation. The ROC curves (figs. 2 and 3; table 2) showed that of all tested Δ signals, ΔNoL was best at differentiating

between noxious and nonnoxious stimuli (AUC, 0.95). Similar observations were made for NoL (AUC, 0.82) relative to HR (0.66) and MAP (0.73). Cutoff values of 16 for NoL yielded an acceptable sensitivity of 73% with specificity of 80% and could be interpreted as a cutoff for discriminating noxious from nonnoxious stimuli. Furthermore, when testing the effect of multiple target concentrations of remifentanil, the NoL, in contrast to HR and MAP, remained unaffected under nonnociceptive conditions. This indicates that the NoL was a more reliable measure of nociception *per se*, whereas HR and MAP are additionally affected by the hemodynamic effects of remifentanil (figs. 4–6). Treister *et al*.(16) studied the same index response to three intensities of noxious stimulation in awake volunteers. Although none of the signals that make up the NoL were able to discriminate between the different noxious intensities, they observed, in agreement with our findings, that the combination of parameters (*i.e.*, the NoL) was able to differentiate between pain and no pain and also between all three noxious intensities. This indicates that the NoL performs equally well in the awake and anesthetized individuals. Interestingly, single indices, such as HRV, perform better under conditions of general anesthesia than the awake state(24). Also in chronic pain patients, the ability to obtain objective and accurate measures of pain and nociception, next to subjective self-reports (that are often colored by a variety of biopsychosocial factors), is important(21). To assess the ability of the NoL to track nociception in patients with chronic pain, Ben-Israel *et al*.(25) studied patients with chronic radicular pain treated with spinal cord stimulation (SCS). The NoL values were in accordance with the efficacy of the SCS treatment as presented a correlation between reported pain score while turning the SCS device on and off. This indicates that the multivariate NoL may be used as an objective measurement of pain in patients with chronic pain and evaluate the efficacy of treatment.

The NoL is based on the advanced statistical and machine learning techniques to combine multiple signals into a single composite index. Machine learning methods rely on the concept that a specific algorithm that connects input to output can be trained to discover their optimal relationship. In our case, the link between input and output was established in a previous learn study, where the input were the records of physiologic signals collected during surgery under general anesthesia and the output the CISA, which is the linear combination of stimulus intensity and estimated analgesic plasma concentration(2). A detailed description of the CISA can be found in Ref. 2. The different autonomic variables that make up the NoL representIdifferent underlying systems, which have nontrivial nonlinear interactions. Adding their time derivatives to the equation (which is done to increase the ability to obtain a more reliable estimate of nociception) introduces an additional level of complexity by significantly enlarging the number of variables and creating additional nonlinear dependencies. Machine learning was performed using random forest regression analysis, a technique that is able to handle a large number of predictors to discover the optimal algorithm combining input to output, without the need

for an *a priori* specification of a stochastic data model (*i.e.*, the created algorithmic model treats the data mechanisms as unknown)(12,13). Random forest regression is applied in different areas of science and engineering such as the identification of the smallest possible set of genes that can still achieve a good predictive outcome in clinical tests, prediction of protein interactions, and forecasting murderous conduct by individuals on probation or parole(26–28).

An important issue is whether continuous measurement of nociception during surgery and treatment of signs of increased nociception will improve patient outcome. Chen *et al*.9 addressed this issue by studying the effect of surgical stress index–guided propofol–remifentanil anesthesia in patients undergoing elective ear, nose, and throat surgery. Compared with standard of practice, nociception-guided anesthesia reduced remifentanil consumption and unwanted movement and hemodynamic events. Parker *et al*.(29) showed that the catecholamine (stress) response during anesthesia and emergence, in patients undergoing lower extremity revascularization, contributed to the development of postoperative hypertension and possibly also to the occurrence of thrombotic events. Similarly, also anesthesia with overdoses in anesthetic and opioid delivery may be associated with a poor outcome(30,31). Cumulatively these data suggest that the prevention of overdosing or underdosing of opioid and anesthetic drug delivery by continuous monitoring of nociception (and possibly also indices from the electroencephalogram) may result in a more stable nociceptive condition with beneficiary effects on outcome. Evidently, further studies are needed to fully understand the complexities of anesthetic monitoring and outcome.

The current study has some limitations:

1) The level of anesthetic depth as measured by the BIS was fixed to values ranging between 40 and 50. Therefore, we remain unaware of the influence of variations in anesthetic depth at multiple target opioid concentrations on the NoL. Assuming a synergistic effect of remifentanil and propofol on nociception,32 we expect some effect of propofol on the NoL. Our subprotocol was intended to study this issue but was not completed. Data were collected in four patients (two at BIS 30 and two at BIS 70). The analysis of these data suggests no dependency on BIS value on the effect of intubation on the NoL (data not shown). Evidently, this issue requires further study.
2) Each subject only received one dose level of remifentanil. This precluded the assessment of the intraindividual variance in the response to remifentanil.
3) We used a finger cuff system (Nexfin) to noninvasively measure the beat-to-beat blood pressure rather than invasive blood pressure. This finger cuff technique is reliable(17), and Nexfin MAP measurements were second to the NoL in ability to detect nociceptive responses (fig. 2). Possibly adding the beat-to-beat MAP to the NoL algorithm would further improve the accuracy of the NoL.

4) We performed our studies in 72 patients. Because of technical, logistic, or other issues, nonnoxious, incision, and intubation events were obtained on average in 60 (83%) subjects. This may have affected the outcome of the study. Given the fact that the NoL performed as expected from results of previous studies, the loss of data did not affect the power of our study with respect to the NoL(2,16). Conversely, the loss of data may have caused the inability of MAP to detect moderate nociceptive stimuli (fig. 1).
5) Finally, we excluded patients on β-adrenergic-blocking drugs. Because β-adrenergic blockers and other vasoactive drugs affect the autonomic system at multiple sites, their effect on the accuracy of the NoL requires further study.

In conclusion, we applied a novel multidimensional index, the NoL, to detect nociception during conditions of no, moderate, and intense noxious stimulation in surgical patients under propofol–remifentanil anesthesia. We observed that compared with HR and MAP, the index was best at differentiating nociceptive from nonnociceptive conditions. In additionally, in contrast to MAP and HR, the NoL remained unaffected by the hemodynamic effects of increasing concentrations of remifentanil.

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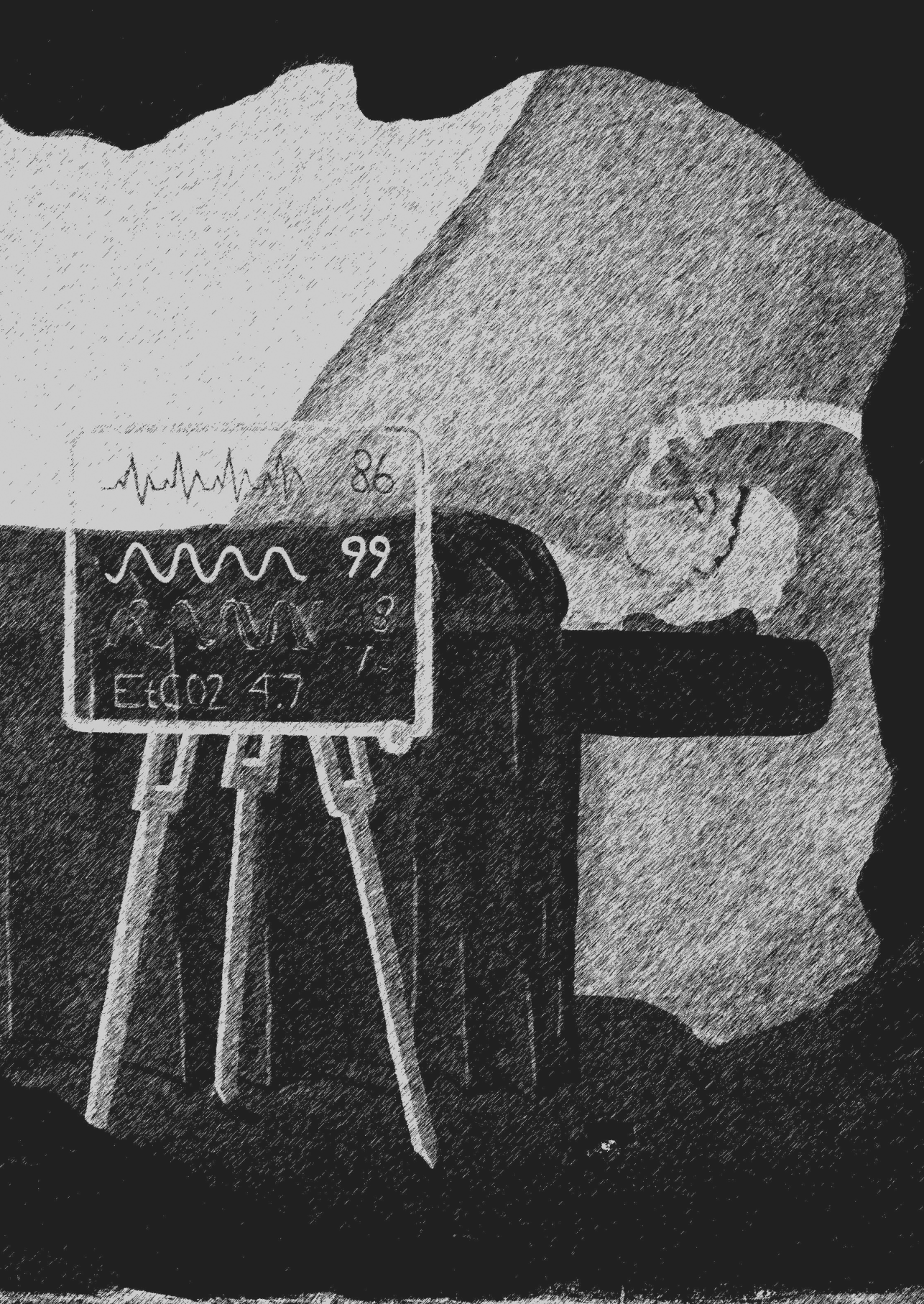
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Section 2

Monitoring of Neuromuscular Block

CHAPTER 4

Influence of reversal of a partial neuromuscular block on the ventilatory response to hypoxia: a randomized controlled trial in healthy volunteers

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Introduction

Residual neuromuscular blockade, defined by a train-of-four ratio less than 0.9, is associated with impaired function of respiratory and pharyngeal muscles with an increased risk of hypoventilation, hypoxia, upper-airway obstruction, and pulmonary aspiration(1–5). Importantly, Eikermann *et al*.(2) demonstrated that even when the train-of-four ratio fully recovered to unity, respiratory function tests (*e.g.*, forced vital capacity) may still be depressed in some patients. There is now robust evidence that nondepolarizing neuromuscular blocking agents additionally influence ventilatory control by acting within the peripheral chemoreflex loop at the carotid bodies(6–11). The carotid bodies are located at the bifurcation of the common carotid artery and are important sensors involved in maintaining respiratory homeostasis(12). For example, in case of hypoxia, carotid body activation results in hyperventilation aimed at increasing pulmonary oxygen uptake. The carotid body response to hypoxia (the acute hypoxic ventilatory response) is a life-saving reflex that is impaired by various drugs used in the perioperative phase, including opioids and anesthetics(13,14). In two pivotal studies in the early 1990s, Eriksson *et al*.(6,7) showed in humans that the nondepolarizing neuromuscular blocking agent vecuronium at a train-of-four ratio of 0.7 blunts the acute hypoxic ventilatory response by 15 to 60%. Because the acute hypoxic ventilatory response was significantly more depressed than the *hyperoxic* ventilatory response to carbon dioxide (which is a central chemoreflex response), an effect of vecuronium on the peripheral chemoreflex loop seems most likely. Animal studies give further proof for a selective effect of neuromuscular blocking agents at neuronal nicotinic acetylcholine receptors located postsynaptically on the afferent nerve that connects the oxygen sensing or glomus cells of the carotid bodies to the brainstem(9–11). Eriksson(8) showed later similar results for atracurium and pancuronium and additionally demonstrated that spontaneous return of the train-of-four ratio to values greater than 0.9 resulted in the recovery of acute hypoxic ventilatory response to values not different from control, although some subjects showed persistent depression of the hypoxic response. The picture that emerges from human and animal data from the Eriksson research group is that nondepolarizing neuromuscular blocking agents, irrespective of their chemical structure or receptor affinity, significantly impair the peripheral chemoreflex at the carotid bodies at train-of-four ratios less than 0.9. So far, no other laboratories replicated Eriksson's human studies. The aim of our study was twofold. We replicated the concept of the human studies originally performed by Eriksson *et al*.(6–8) with rocuronium to confirm their results for a nondepolarizing neuromuscular blocking agent not yet studied. Additionally, we measured the acute hypoxic ventilatory response, the hyperoxic hypercapnic ventilatory response after recovery of the partial neuromuscular block (as measured at the thumb), following reversal with neostigmine and sugammadex *versus* placebo. We hypothesized that the carotid body–mediated

hypoxic ventilatory response is fully restored following the return to a train-of-four ratio of 1, irrespective of reversal strategy.

Materials and Methods

Ethics

This single-center, double-blind, parallel, randomized controlled trial was performed at the Anesthesia and Pain Research Unit of the Department of Anesthesiology at Leiden University Medical Center (Leiden, The Netherlands) from May 2017 to September 2018. The protocol was approved by the local institutional review board (Commissie Medische Ethiek, Leiden, The Netherlands) and the Central Committee on Research Involving Human Subjects in The Hague, The Netherlands. The study was registered at the trial register of the Dutch Cochrane Center (Amsterdam, The Netherlands) under identifier 6427 (May 4, 2017). Before enrollment and after being informed about the study, all participants gave written informed consent. All study procedures were conducted according to good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki.

Subjects

Healthy male volunteers aged 18 yr or older and a body mass index less than 30 kg/m2 were eligible to participate in the study. Exclusion criteria were (1) known or suspected neuromuscular disorders impairing neuromuscular function; (2) suspected allergies to muscle relaxants, anesthetics, or narcotics; (3) a history (self or family) of malignant hyperthermia or any other muscle disease; (4) any medical, neurologic, or psychiatric illness (including a history of anxiety); (5) inability to give informed consent; and (6) signs (or history) of a possible difficult intubation. Subjects were asked not to eat or drink for at least 8 h before dosing with rocuronium. The subjects were not allowed to participate more than once in the study. The subjects were recruited and enrolled in the study by the study team.

Study Design

This study had a randomized, double-blind, placebo-controlled parallel design. Upon arrival in the research unit, all subjects received an intravenous line for administration of study drugs. Participants were randomized to receive placebo (2 ml of normal saline), 1 mg of intravenous neostigmine (combined with 0.5 mg of atropine), or 2 mg/kg sugammadex, following a continuous rocuronium infusion for 90 to 120 min aimed at a train-of-four ratio of 0.7. Before and during the rocuronium infusion, acute hypoxic and hyperoxic hypercapnic tests were performed. After the rocuronium infusion was stopped and a reversal agent was administrated, another set of ventilatory tests was performed. Throughout the study the subjects were monitored by electrocardiogram and oxygen saturation *via* a finger probe.

Initially, we had set out to obtain respiratory responses at two levels of neuromuscular blockade with train-of-four ratios 0.6 and 0.8. Especially at the deeper level of relaxation, we observed frequent upper-airway obstructions that, although short-lived and not hazardous, interfered with the control of end-tidal carbon dioxide and oxygen concentrations. We therefore decided to change the protocol to studying just one level of blockade in between the original targets. Additionally, we originally intended to study repetitive hypoxic exposures following reversal to measure the acute hypoxic ventilatory response at increasing train-of-four ratio values (from 0.7 to 1). However, we observed that the train-of-four ratio returned rather rapidly toward 1 and therefore decided to obtain one measurement of acute hypoxic ventilatory response at the time point at which the train-of-four ratio was first equal to 1. All changes were made after consultation with the data safety committee, were approved by the institutional review board, and documented in the trial registry.

Ventilatory Measurements

During ventilatory measurements, subjects were in the semirecumbent position. The ventilatory responses to hypoxia and hypercapnia were obtained using the dynamic end-tidal forcing technique. The technique is described in detail elsewhere.15,16 In brief, subjects breathed through a facemask that was attached to a pneumotachograph and pressure transducer system (catalog no. 4813; Hans Rudolph Inc., USA) and to a set of mass flow controllers (Bronkhorst High Tech, The Netherlands) for the delivery of oxygen, carbon dioxide, and nitrogen. The mass flow controllers were controlled by a computer running software (RESREG/ACQ, Leiden University Medical Center, The Netherlands) that steers end-tidal gas concentrations (by varying the inspired concentration) and collects respiratory variables. The inspired and expired oxygen and carbon dioxide partial pressures were measured at the mouth using a capnography (Datex Capnomac, Finland); heart rate and arterial oxygen saturation were measured by pulse oximetry (Masimo Corporation, USA). The following variables were collected on a breath-to-breath basis and averaged over 1 min for further analysis: minute ventilation (V_E), end-tidal carbon dioxide concentration (ET_{CO_2}), end-tidal oxygen concentration (ET_{O_2}), and arterial oxygen saturation (SpO_2). To obtain the isocapnic hypoxic ventilatory response, we performed steps into hypoxia by lowering the ET_{O_2} to 52 mmHg such that the SpO_2 dropped to 80± 2%. The hypoxic test took about 7 to 9 min, *i.e.*, 2 to 4 min of normoxia (ET_{O_2} 100 mmHg) followed by 5 min of hypoxia. Throughout the experiment the ET_{CO_2} was kept constant at 1 to 2 mmHg above resting values. To obtain the hyperoxic hypercapnic ventilatory response, we applied three 5- to 7-min steps in ET_{CO_2} with step sizes of 7.5, 10, and 15 mmHg. To suppress the contribution of the carotid bodies to the hypercapnic response, all hypercapnic tests were performed in hyperoxia (inspired oxygen fraction, 0.5).15 The hypoxic ventilatory sensitivity was calculated by linear regression of the SpO_2–V_E data using the last 2 min of normoxia and hypoxia. The hypercapnic ventilatory sensitivity was calculated by linear

regression of the ET_{CO_2}–V_E data using the last 2 min of each hypercapnic step. This analysis provided the slope of the hypercapnic ventilatory response (S) and the extrapolated *x*-axis intercept (apneic threshold, B). Next, we calculated ventilation at an extrapolated ET_{CO_2} of 55 mmHg (V_E55) using the following equation $V_E55 = S \times (55 - B)$. Ventilation at an extrapolated ET_{CO_2} of 55 mmHg takes the slope and the position of the hypercapnic ventilatory response into account and hence gives a reliable reflection of the effect of the intervention on hypercapnic ventilatory control (see fig. 2 of van der Scrier *et al.*).17 To ensure that responses were unaffected by previous responses, we allowed rest periods between measurements. Additionally, minute ventilation was assessed in real time on-screen, and only when ventilation had returned to baseline levels was the next ventilatory measurement initiated.

Experiments were performed at baseline (before any drug administration), at a stable neuromuscular block with train-of-four ratio equals 0.7, and after recovery to a train-of-four ratio equals 1. The sequence of hypoxic and hypercapnic tests was randomized at baseline and during rocuronium infusion; however, following return of the train-of-four ratio to 1 after reversal, first one hypoxic test was obtained followed by the hypercapnic test.

Drug Administration

All drugs were given intravenously. For rocuronium (Esmeron, MSD BV, The Netherlands), the dosing was dependent on the measured train-of-four ratio. In all subjects the initial bolus dose was 5 mg, after which a rocuronium continuous infusion was started at 0.42 mg/min. Additional bolus doses of 1 to 5 mg were given, and/or the infusion rate was modified when the train-of-four ratio remained above the target. In case of an overshoot with train-of-four ratios of less than 0.7, the infusion was lowered until the target was reached. At the desired train-of-four ratio target, we waited 10 to 15 min, and when the train-of-four ratio remained stable, the first respiratory test was performed. Otherwise the infusion rate was further adapted until the target was reached. On average, 55± 15 mg rocuronium was given throughout the experiment. The rocuronium dosing was based on simulations using the pharmacokinetic data set of Kleijn *et al.*(18) The reversal agents 1 mg of neostigmine Hameln Pharmaceuticals Ltd., United Kingdom), 2 mg/kg sugammadex (Bridion, MSD BV), and 2 ml of placebo (NaCl 0.9%) were given as a bolus infusion when the rocuronium infusion was stopped. In case of an upper-airway obstruction or severe respiratory depression (with SpO_2 less than 70%) due to a more intense neuromuscular block than intended, the subject received 2 mg/kg sugammadex, and the experiment was ended.

Measurement of the Neuromuscular Block

Neuromuscular block was measured by electromyography at the adductor pollicis muscle, using the CARESCAPE B450 monitor combined with the electromyography–neuromuscular transmission module (both General Electric, Finland). After degreasing the skin with alcohol, the electrodes were placed at the wrist according to the guidelines of the manufacturer (in the arm opposite to the arm with the intravenous line). Before administration of rocuronium, a series of measurements were obtained at a stimulus strength of 30 mA. Stable recordings were verified and defined as a difference in train-of-four ratio of less than 5% in three consecutive measurements. All subsequent measurements were obtained at 1-min intervals. Skin temperature was maintained throughout the study by keeping a constant room temperature.

Randomization and Allocation

Randomization (placebo:neostigmine:sugammadex equals 1:1:1) was performed by an independent third party (research nurse not involved in the study) using a computer-generated randomization list. On the day of the experiment, each subject was allocated to treatment, and all study medication was delivered to the laboratory by the same nurse in unmarked sequentially numbered syringes of equal size and volume. In case of neostigmine administration, the syringe additionally contained 0.5 mg of atropine. The study was independently monitored, ensuring all Good Clinical Practices requirements were met.

Statistical Analysis

No formal sample size analysis was performed because we based our samples size on the previous studies of Eriksson *et al.*6–8 We defined the acute hypoxic response (AHR), slope of the hypercapnic ventilatory response (HCVR), and ventilation at an extrapolated ET_{CO_2} of 55 mmHg (V_E55) obtained at baseline as AHR_1, $HCVR_1$, and V_E55_1, respectively. Similarly, at a train-of-four ratio of 0.7, the responses are denoted AHR_2, $HCVR_2$, and V_E55_2, and after recovery of the neuromuscular block, the responses are denoted AHR_3, $HCVR_3$, and V_E55_3.

We calculated the ratio of acute hypoxic response and ventilation at an extrapolated ET_{CO_2} of 55 mmHg relative to their baseline values, with $AHR_{2R} = AHR_2/AHR_1$, $AHR_{3R} = AHR_3/AHR_1$, $V_E55_{2R} = V_E55_2/V_E55_1$, and $V_E55_{3R} = V_E55_3/V_E55_1$. Next, we calculated the ratios $F2 = AHR_{2R}/V_E55_{2R}$ and $F3 = AHR_{3R}/V_E55_{3R}$ as carotid body index (*i.e.*, markers of hypoxic chemosensitivity).(7) In some participants V_E55_3 values exceeded baseline ventilation at an extrapolated ET_{CO_2} of 55 mmHg values with consequently V_E55_{3R} values of more than 100%. We consider this excitatory phenomenon a procedural effect because the hypercapnic test after reversal was always performed after the hypoxic test. Because this may have underestimated the effect of reversal treatment on F3, we calculated

correctedV_E55_{3R} and F3 values by constraining V_E55_{3R} to 100% in case values of more than 100% were observed.

All data were checked for normality by evaluation of their empirical distribution (*i.e.*, by histogram). The effects of treatment on acute hypoxic response, slope of the hypercapnic ventilatory response, and ventilation at an extrapolated ET_{CO_2} of 55 mmHg were analyzed by one-way ANOVA (factor: treatment) with *post hoc* Holm–Sidak multiple comparison test to compare treatment effect (either measurement 2 or 3) to control (baseline) data. The hypoxic and hypercapnic ratios F were compared to 1 using two-tailed paired *t* tests. These analyses were performed (using a two-tailed approach) on the complete data set and on the three distinct reversal treatments, allowing within-group comparison. To test our hypothesis that at a train-of-four ratio of 1 the responses fully returned to baseline levels irrespective of the reversal strategy, an analysis of covariance was performed on AHR3, HCVR3, VE553, with the baseline as covariate and treatment (placebo, neostigmine, sugammadex) as fixed effect. To compare the F3 ratios among treatments, a one-way ANOVA was performed. If a significant main effect was observed, protected *post hoc* tests were performed. The statistical analysis was performed using GraphPad Prism version 7 for Mac OS X (GraphPad Software, USA) and SPSS Statistics for Windows (IBM, USA), version 23.0. *P* values of less than 0.05 were considered significant. All values are means } SD unless otherwise stated; the data in the figures are means ± 95% CI.

Results

In the amended protocol 40 subjects were randomized (fig. 1). All subjects completed the protocol without serious adverse events. Four subjects developed upper-airway obstruction: three during the administration of rocuronium and one during recovery following placebo reversal. All four were treated with sugammadex, after which they fully recovered; they were taken out of the study, and each was replaced by another subject. The characteristics of the 36 subjects that completed the study are given in table 1.

Data from two subjects (one in the neostigmine group and the other in the sugammadex group) were unreliable due to lack of calibration. Consequently, the data from 34 subjects were analyzed. Apart from upper-airway obstruction, adverse effects included diplopia (80%), difficulty swallowing (40%), and ptosis (10%). After reversal, all subjects recovered fully. None of the subjects reported the occurrence of distress or anxiety during relaxation.

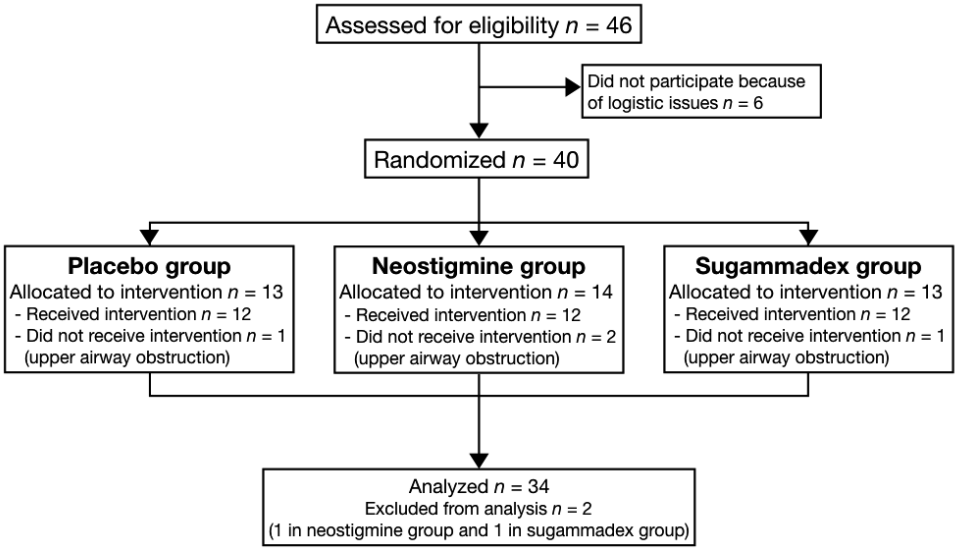

Figure 1. Consort flow diagram.

Table 1. Subject characteristics

		Reversal group		
	All subjects	**Placebo**	**Neostigmine**	**Sugammadex**
Age (median) [range]	22 [18-29] year	20 [19-29] year	23 [18-29] year	23 [19-25] year
Weight (mean ± SD)	80 ± 10 kg	79 ± 9 kg	77 ± 10 kg	86 ± 10 kg
Height (mean ± SD)	185 ± 8 cm	186 ± 10 cm	187 ± 9 cm	187 ± 8 cm
BMI (mean ± SD)	23.1 ± 2.1 kg·m^{-2}	22.6 ± 1.5 kg·m^{-2}	22.2 ± 2.1 kg·m^{-2}	24.7 ± 2.2 kg·m^{-2}

Influence of Low-dose Rocuronium and Reversal on Ventilatory Control

Upon the administration of rocuronium, the train-of-four ratio decreased slowly and reached a steady state of 0.68 ± 0.01 (fig. 2) within 45 min, after which the respiratory tests were performed. During the hypoxic tests, the ET_{CO_2} averaged to 41.1 ± 2.5 mmHg in control studies, 41.5 ± 2.6 mmHg in rocuronium studies, and 41.4 ± 2.6 mmHg in reversal studies. Hypoxic ventilator sensitivities during control, during relaxation, and after reversal were 0.55 ± 0.22 (AHR_1), 0.31 ± 0.20 (AHR_2), and 0.45 ± 0.16 (AHR_3) l · min−1 · %−1 (AHR_2 *vs.* AHR_1, $P < 0.001$; AHR_3 *vs.* AHR1, $P < 0.001$; table 2), respectively. AHR_2 was depressed by 42%, and V_E55_2 was depressed by 11% (tables 2 and 3).

Table 2. Acute Hypoxic Response and Slope of the Hypercapnic Ventilatory Responses Obtained at Baseline, during Infusion of Low-dose Rocuronium and after Reversal with Placebo, Neostigmine, or Sugammadex.

Treatment	**AHR_1** ($L.min^{-1}.\%^{-1}$)	**AHR_2** ($L.min^{-1}.\%^{-1}$)	**AHR_3** ($L.min^{-1}.\%^{-1}$)	**$HCVR_1$** ($L.min^{-1}.mmHg^{-1}$)	**$HCVR_2$** ($L.min^{-1}.mmHg^{-1}$)	**$HCVR_3$** ($L.min^{-1}.\%^{-1}$)
All treatments	0.55 ± 0.22	0.31 ± 0.20	0.45 ± 0.16	2.02 ± 0.66	1.51 ± 0.48	2.20 ± 0.96
Mean difference (95% CI)		-0.23 (-0.30 to -0.16) $p < 0.001$ vs. AHR_1	-0.10 (-0.15 to -0.05) $p < 0.001$ vs. AHR_1		-0.50 (-0.63 to -0.37) $p < 0.001$ vs. $HCVR_1$	0.19 (-0.02 to 0.40) $p = 0.094$ vs. $HCVR_1$
Placebo	0.66 ± 0.21	0.34 ± 0.22	0.49 ± 0.13	2.34 ± 0.69	1.68 ± 0.44	2.33 ± 0.88
Mean difference (95% CI)		-0.33 (-0.49 to -0.17) $p = 0.003$ vs. AHR_1	-0.18 (-0.26 to -0.10) $p = 0.002$ vs. AHR_1		-0.66 (-0.94 to -0.38) $p = 0.001$ vs. $HCVR_1$	-0.01 (-0.38 to 0.36) $p = 0.965$ vs. $HCVR_1$
Neostigmine	0.43 ± 0.23	0.29 ± 0.20	0.36 ± 0.20	1.81 ± 0.71	1.24 ± 0.47	2.05 ± 1.11
Mean difference (95% CI)		-0.15 (-0.20 to -0.10) $p < 0.001$ vs. AHR_1	-0.07 (-0.18 to 0.02) $p = 0.074$ vs. AHR_1		-0.56 (-0.77 to -0.35) $p = 0.001$ vs. $HCVR_1$	0.24 (-0.03 to 0.51) $p = 0.106$ vs. $HCVR_1$
Sugammadex	0.54 ± 0.16	0.31 ± 0.17	0.48 ± 0.13	1.88 ± 0.48	1.60 ± 0.47	2.24 ± 0.95
Mean difference (95% CI)		-0.23 (-0.29 to -0.17) $p < 0.001$ vs. AHR_1	-0.05 (-0.13 to 0.03) $p = 0.241$ vs. AHR_1		-0.27 (-0.47 to -0.07) $p = 0.004$ vs. $HCVR_1$	0.37 (-0.10 to 0.84) $p = 0.149$ vs. $HCVR_1$
Main treatment effect (ANCOVA)			$p = 0.299$			$p = 0.938$

The values are mean ± SD. AHR is the acute isocapnic hypoxic response; HCVR is the hyperoxic hypercapnic ventilatory response slope. AHR1 and HCVR1 are response obtained at baseline, AHR2 and HCVR2 are response obtained during infusion of rocuronium, AHR3 and HCVR3 are responses obtained following reversal. All within group statistical comparisons are relative to the baseline value (AHR1 or HCVR1). To assess the treatment effect on AHR3 and HCVR3, an analysis of covariance (ANCOVA) with baseline values (AHR1, HCVR1) as covariate and treatment as fixed effect was performed.

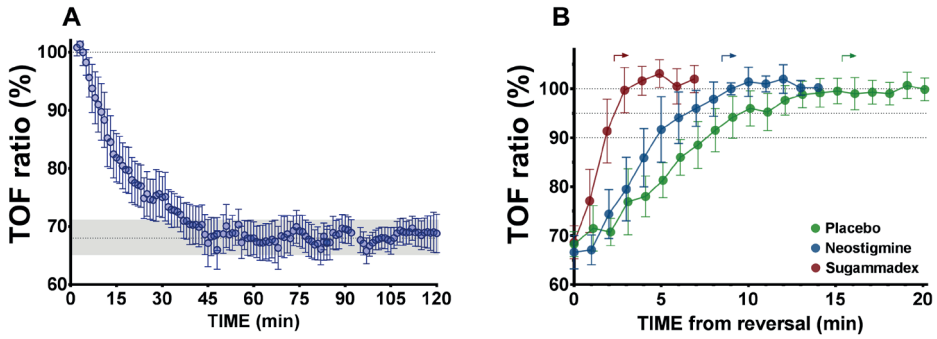

Figure 2. (**A**) Average train-of-four (TOF) ratio values during infusion of low-dose rocuronium (n = 36). Hypoxic and hypercapnic experiments were performed from t equals 45 to t equals 120 min (average TOF ratio, 68 ± 1%), after which reversal agents were given. (**B**) Effect of reversal with placebo (*green symbols*), neostigmine (*blue symbols*), and sugammadex (*red symbols*) on TOF ratios. The *arrows* indicate the mean times at which data collection of the hypoxic ventilatory response was started (hypoxic responses took 7 to 9 min). The values are means ± 95% CI.

Table 3. Ventilation at Extrapolated End-tidal Carbon Dioxide Concentration of 55 mmHg Measured at Baseline, during Low-dose Rocuronium Infusion and after Reversal with Placebo, Neostigmine, or Sugammadex.

Treatment	$VE55_1$	$VE55_2$	$VE55_3$
All treatments (L/min)	32 ± 9	28 ± 7	37 ± 11
Mean difference (95% CI)		-3.9 (-5.5 to -2.3) p < 0.001 vs. $VE55_1$	5.0 (3.5 to 6.5) p < 0.01 vs. $VE55_1$
Placebo (L/min)	35 ± 11	30 ± 8	39 ± 11
Mean difference (95% CI)		-5.5 (-9.1 to -1.9) p = 0.020 vs. $VE55_1$	3.7 (-1.0 to 8.4) p = 0.159 vs. $VE55_1$
Neostigmine (L/min)	29 ± 7	26 ± 7	34 ± 9
Mean difference (95% CI)		-3.0 (-5.0 to -1.0) p = 0.026 vs. $VE55_1$	4.9 (2.6 to 7.2) p < 0.01 vs. $VE55_1$
Sugammadex (L/min)	31 ± 8	27 ± 7	37 ± 14
Mean difference (95% CI)		-3.2 (-5.2 to -1.2) p = 0.038 vs. $VE55_1$	6.6 (-0.2 to 13.4) p = 0.092 vs. $VE55_1$
Main treatment effect (ANCOVA)			**p = 0.679**

The values are mean ± SD. VE55 is ventilation at an extrapolated extrapolated end-tidal carbon dioxide concentration of 55 mmHg. VE551 is hypercapnia ventilation measured at baseline, VE552 is hypercapnia ventilation measured during infusion of rocuronium, VE553 is hypercapnic ventilation measured following reversal. To assess treatment effect on VE553, an analysis of covariance (ANCOVA) with the baseline value as covariate (VE551) and treatment as fixed effect was performed.

Consequently, the effect of low-dose rocuronium on AHR_2 may be attributed largely to carotid body impairment with carotid body index F2 = 0.67 ± 0.32 ($P < 0.001$; table 4). Following reversal, AHR_3 was still depressed by 18%, but V_E55_3 was on average 15% greater than the value measured at baseline; V_E55_3 exceeded baseline values in 29 subjects. After adjustment for this excitatory effect, the corrected carotid body index F3 value averaged 0.89 ± 0.34 ($P = 0.076$).

Neostigmine, Sugammadex, and Placebo Reversal

Subject characteristics were similar among the three treatment groups (table 1). The train-of-four ratio recovery profiles for the three treatments are given in figure 2B. The times from reversal until the start of the hypoxic studies were 2.5 ± 0.7 (range 1 to 3) min, 8.2 ± 3.2 (4 to 16) min, and 15.1 ± 4.6 (12 to 25) min, for reversal with sugammadex, neostigmine, and placebo, respectively (*arrows* in fig. 3B). Although the magnitude of the control hypoxic responses among the three treatment groups varied (AHR_1 in table 2), these variations were not significantly different ($P = 0.175$), and partial relaxation by low-dose rocuronium resulted in a similar reduction by 38 to 46% (AHR_2) in the three treatment groups.

When considering the complete study population, reversal to a train-of-four ratio equals 1 led to an AHR3 of 0.45± 0.16 l · min−1 · %−1 ($P < 0.001$ *vs.* AHR_1) or a residual 18% depression compared to baseline. Within-group comparisons are given in table 2. The treatment effect (between-group comparison) did not reach the level of significance (analysis of covariance main effect $P = 0.299$), indicating that the three reversal strategies had a similar effect on the acute hypoxic ventilatory response. Relative to control levels, all treatments produced a similar increase in the hypercapnic ventilatory response (analysis of covariance main effect $P = 0.938$) and ventilation at an extrapolated ET_{CO_2} of 55 mmHg (analysis of covariance main effect $P = 0.679$; tables 2 and 3). Both uncorrected and corrected AHR3R values and corresponding F3 values are given in table 4 and figure 3. The uncorrected and corrected F3 values in the complete population were 0.78 ± 0.35 ($P = 0.001$) and 0.89 ± 0.34 ($P = 0.076$), respectively. Neither for the corrected nor for the uncorrected F ratios a significant treatment effect was observed (F3 uncorrected, ANOVA main effect $P = 0.231$; F3 uncorrected ANOVA main effect $P = 0.232$). Corrected F3 values less than 0.95 were observed in 10 subjects in the placebo group, 7 in the neostigmine group, and 5 in the sugammadex group.

Table 4. Ratios of the Acute Hypoxic Response (AHR) and Ventilation at an Extrapolated End-tidal Carbon Dioxide Concentration of 55 mmHg (VE55) Relative to Baseline (%) Obtained during Infusion of Low-dose Rocuronium (AHR2R and VE552R) and after Reversal with Placebo, Neostigmine, or Sugammadex (AHR3R and VE553R) and Carotid Body Indices Obtained during Low-dose Rocuronium Infusion (F2) and after Reversal (F3).

	Low-dose rocuronium (TOF-ratio = 0.7)			Reversal (TOF-ratio = 1)				
Treatment	**AHR_{2R}**	**$VE55_{2R}$**	**F_2**	**AHR_{3R}**	**$VE55_{3R}$** (uncorrected)	**$VE55_{3R}$** (corrected)	**F_3** (uncorrected)	**F_3** (corrected)
All treatments	57 ± 26	89 ± 11	0.66 ± 0.32	86 ± 25	115 ± 23	98 ± 7	0.78 ± 0.35	0.89 ± 0.34
Discrepancy (vs. 1) (95% CI)			-0.34 (-0.45 to -0.23) p < 0.001				-0.22 (-0.34 to -0.10) p = 0.001	-0.11 (-0.23 to 0.01) p = 0.076
Placebo	54 ± 33	85 ± 11	0.65 ± 0.43	76 ± 16	115 ± 24	97 ± 8	0.68 ± 0.16	0.79 ± 0.25
Discrepancy (vs. 1) (95% CI)			-0.34 (-0.62 to -0.06) p = 0.019				-0.32 (-0.42 to -0.22) p < 0.001	-0.21 (-0.31 to 0.11) P < 0.001
Neostigmine	62 ± 25	90 ± 12	0.69 ± 0.28	87 ± 27	117 ± 14	100 ± 0	0.75 ± 0.25	0.87 ± 0.27
Discrepancy (vs. 1) (95% CI)			-0.31 (-0.50 to -0.12) p = 0.004				-0.25 ± 0.16 p = 0.008	-0.13 (-0.30 to 0.04) p = 0.128
Sugammadex	56 ± 16	90 ± 12	0.64 ± 0.23	95 ± 29	112 ± 30	96 ± 8	0.93 ± 0.53	1.03 ± 0.5
Discrepancy (vs. 1) (95% CI)			-0.36 (-0.52 to -0.20) p < 0.001				-0.07 ± 0.35 p = 0.661	0.03 (-0.30 to 0.36) p = 0.842
Main treatment effect (anova)							**p = 0.231**	**p = 0.232**

The values are means ± SD. To assess treatment effect on the F ratios, a one-way ANOVA was performed. TOF, train of four.

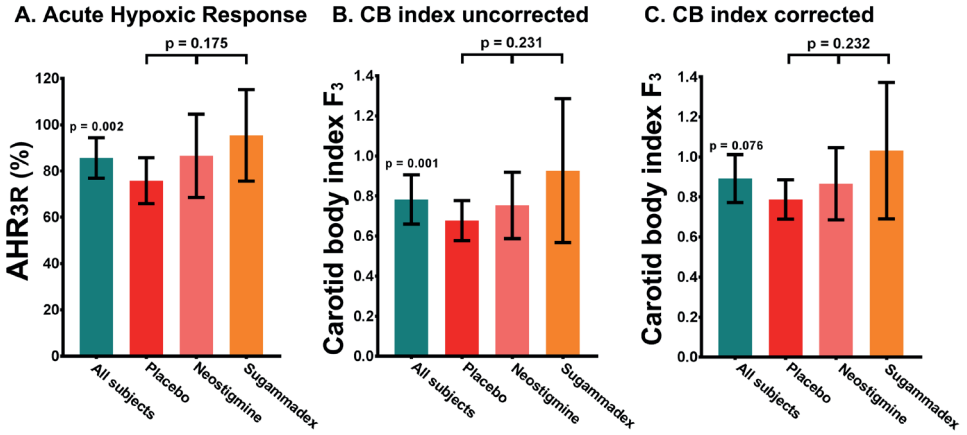

Figure 3. Influence of three reversal strategies on the acute hypoxic response and carotid body index F3. (**A**) AHR3R indicates the acute hypoxic ventilatory response after reversal as a percentage of the baseline response. (**B**) Uncorrected carotid body index F3, which is the ratios AHR3R/VE553R or the ratio of the changes in acute hypoxic response and ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg (VE55), relative to baseline, after reversal and full recovery of neuromuscular function at the thumb. (**C**) Corrected carotid body index F3, with VE553R constrained to 100% in case of values exceeding 100%. The values are the means ± 95% CI. Between-treatment comparisons were done by analysis of covariance with baseline value as covariate. CB, carotid body.

Discussion

The main outcomes of our experimental study are summarized as follows:

1) Rocuronium-induced partial neuromuscular blockade (train-of-four ratio ≈ 0.7) blunts the isocapnic hypoxic response by 42%, whereas hypercapnic ventilation was reduced by just 11% (table 3). As estimated from the carotid body index (F2 = 0.67), the depression of the hypoxic response is primarily due to an effect on the peripheral chemoreflex loop. The additional depression of the hypoxic response is most probably related to mild respiratory muscle weakness.
2) Reversal of the neuromuscular block to a train-of-four ratio of 1 did not result in a complete return of the acute hypoxic response to baseline values (AHR_3 = 86 ± 25% of baseline, P = 0.002). We therefore reject the null hypothesis that full reversal of the neuromuscular block at the thumb results in a complete return of the acute hypoxic ventilatory response. Interestingly, this residual effect was independent of reversal strategy with 62% of subjects that still had AHR_3 values less than 95% of baseline (placebo n= 10, neostigmine n = 7, and sugammadex n = 5).

Partial Neuromuscular Blockade

In the first part of our study, we convincingly replicate the findings of Eriksson *et al.*(6–8) and show that partial neuromuscular block reduces the acute hypoxic response primarily *via* an effect at the carotid bodies. As proposed by Eriksson *et al.*(7), the separation between carotid body and muscle effects on ventilatory control was performed by calculating the carotid body index F2, which is the ratio AHR_{2R}/V_E55_{2R} or the ratio of relative changes in hypoxic response and ventilation at an extrapolated ET_{CO_2} of 55 mmHg. Because ventilation at an extrapolated ET_{CO_2} of 55 mmHg was obtained at hyperoxia, ventilation at an extrapolated ET_{CO_2} of 55 mmHg is minimally influenced by carotid body activity. Hyperoxia silences the contribution of the carotid bodies to hypercapnic ventilation, which is 10 to 20% under normoxic conditions *versus* 0 to 5% under hyperoxic conditions(15). Impairment of the hypoxic response *via* the respiratory muscles rather than carotid bodies would have resulted in carotid body index values not different from 1.7 The rocuronium F2 value of 0.66 (95% CI, 0.55 to 0.77) is smaller than the F value earlier observed for vecuronium (F = 0.84).7,8 This suggests a greater potency of rocuronium at impairing the carotid bodies compared with vecuronium.

Our data indicate a small non–carotid body–related effect on the hypoxic response during low-dose rocuronium infusion. Although this is most probably due to respiratory muscle weakness (illustrated by the decrease in V_E55_2), we cannot exclude other causes. Theoretically, one such cause could be a decrease in arousal level from deafferentation related to reduced muscle spindle input to central sites. There is ample evidence that peripheral deafferentation from spinal or epidural anesthesia changes the brain sensory and arousal states(19,20). A reduction in arousal level will decrease hypoxic response(14). Because we did not detect any obvious changes in arousal during partial muscle relaxation, we conclude that the non–carotid body–related effect of low-dose rocuronium on hypoxic response was related to mild respiratory muscle weakness. Although in line with the findings of Eikermann *et al*.(2) on rocuronium, our data differ from those of Eriksson *et al*.(6–8), who observed no effect of partial neuromuscular block on the slope of the hypercapnic ventilatory response. These differences may be attributed to differences in protocol or differences in drug sensitivity with greater rocuronium sensitivity in relaxation of respiratory muscles compared with other relaxants.

Reversal of the Partial Neuromuscular Blockade

The between-group comparison indicated that despite full reversal of partial neuromuscular block as evidenced by the measurement of the train-of-four ratio of 1 and a fully restored ventilation at an extrapolated ET_{CO_2} of 55 mmHg, impairment of the peripheral chemoreflex persisted in the majority of subjects, irrespective of the reversal strategy. It is further of interest to discuss the within-group comparisons.

Placebo. Following placebo reversal and recovery of the train-of-four ratio to values more than 0.90 as measured at the thumb, the hypoxic response was just 76% of control, whereas ventilation at an extrapolated $ET_{CO_2}$of 55 mmHg was fully restored. The resultant reduced carotid body index indicates that despite the return of muscle function at the thumb, carotid body function remained suboptimal. A possible explanation is a difference in rocuronium affinity for muscle *versus* neuronal nicotinic acetylcholine receptors. *In vitro* experiments give evidence for the distinct pharmacologic properties of rocuronium at various human muscle and neuronal nicotinic acetylcholine receptor subtypes expressed on *Xenopus* oocytes(21). However, functional affinity of nondepolarizing muscle relaxants was higher for muscle type receptors, with half-maximum inhibitory concentrations in the nanomolar concentration range for muscle nicotinic acetylcholine receptors *versus* micromolar range for neuronal nicotinic acetylcholine receptors. This seems to contradict our findings. Still, reversal of rocuronium-impaired carotid body function is a dynamic process that is influenced by several factors, such as acetylcholine receptors receptor kinetics at pre- and postsynaptic sites (including involvement of specific receptor subtypes), local blood flow, local acetylcholine and acetylcholinesterase concentrations, interaction with other (including muscarinic acetylcholine, dopamine, purinergic) receptors, receptor (de)sensitization, neuronal dynamics, *etc*. Currently, little is known about this complex process, and we postulate that reversal of the rocuronium effect at carotid bodies is slower than at peripheral muscles. This might not be so for the other non-depolarizing neuromuscular blockers, because Eriksson(8) showed full recovery of hypoxic responses and F values following spontaneous return of the train-of-four ratio to values of more than 0.9 after partial muscle relaxation induced by vecuronium, atracurium, and pancuronium.(8)

Neostigmine. Seven subjects (64%) had corrected F3 values less than 0.95 following reversal. Consequently, we argue that although neostigmine was effective in restoring muscle function at the thumb, it did not concurrently restore the hypoxic response in all subjects. We cannot exclude a possible role for atropine in this suboptimal reversal. Animal data indicate that atropine, a muscarinic acetylcholine receptor antagonist, significantly attenuates the carotid body response to hypoxia.(22,23) Because data derived from human carotid bodies detected expression of just neuronal nicotinic acetylcholine receptors(24), a possible inhibitory effect of atropine on the hypoxic response in our sample seems unlikely. What remains is the possibility that the neostigmine dose (13 μg · kg−1) was sufficient to reverse respiratory muscle impairment but insufficient for full reversal of carotid body function in some subjects. Dose-response studies are needed to determine the dose required to restore carotid body function in all individuals following rocuronium relaxation.

Sugammadex. Five subjects (45%) had corrects F3 values less than 0.95. Consequently, even with sugammadex reversal and restoration of muscle function at the thumb, the hypoxic response may not be restored in all patients.

Our data indicate that reversal to a train-of-four ratio of 1 does not fully reverse blunting of the acute hypoxic response in most subjects. Because our protocol was unable to determine the timing at which the response returned to baseline values (*i.e.*, AHR3 > 0.95 × AHR1), further studies are urgently needed to establish the dynamics of the return of the hypoxic response toward baseline following reversal strategies (neostigmine/atropine, sugammadex) or spontaneous recovery.

Trial Limitations

Although we randomized the hypoxic and hypercapnic tests during relaxation, we refrained from randomization following reversal. Although this was done to ensure that the hypoxic tests were performed at similar stages of reversal, this may have affected the hypercapnic test results. Indeed, ventilation at an extrapolated ET_{CO_2} of 55 mmHg values following reversal were on average 15% larger than control values. This observation made us decide to correct for this excitatory effect by constraining the upper limit of VE553R to 100% to prevent overestimation of the effect of the three reversal agents. Uncorrected and corrected F3 values differed by about 10%. However, because 22 of 34 subjects had a corrected F3 value of less than 0.95, we do not believe that this correction affected the clinical interpretation of the data.

Our method of measuring muscle relaxation may have been suboptimal. Although mechanomyography is considered the gold standard in neuromuscular monitoring, electromyography is generally regarded a good and accurate alternative to mechanomyography(25) and lacks the staircase effect that troubles acceleromyography or mechanomyography(26). However, measurements may have been influenced by the fact that our subjects were awake, which may have caused occasional (unnoticed) thumb movements disturbing the measurements with possibly some overestimation of the train-of-four ratio. In addition, supramaximal stimulation was not used to avoid a possible confounding effect of discomfort on respiratory measurements.

Finally, train-of-four ratios were not corrected for baseline train-of-four ratio, which may have caused overestimation of the recovery of the neuromuscular block at the time of measurement.

However, this effect was relatively small (1 to 2%).

In conclusion, we successfully replicated the original study by Eriksson *et al.(*6) showing an inhibitory effect of rocuronium at the carotid bodies. Our reversal data point toward persistence of carotid body impairment despite recovery of the train-of-four ratio to values of more than 0.9 at the thumb. These are important and clinically relevant observations. However, given the complexity of this experimental study, we highlight the need for further investigations. We encourage others to replicate our study and address the effect of spontaneous return of neuromuscular function following rocuronium relaxation on carotid body function. Finally, we would like to stress that in clinical practice, residual anesthetic and muscle relaxant levels synergistically affect breathing postoperatively. Further research should investigate such interactions with special emphasis on mechanisms and sites of action.

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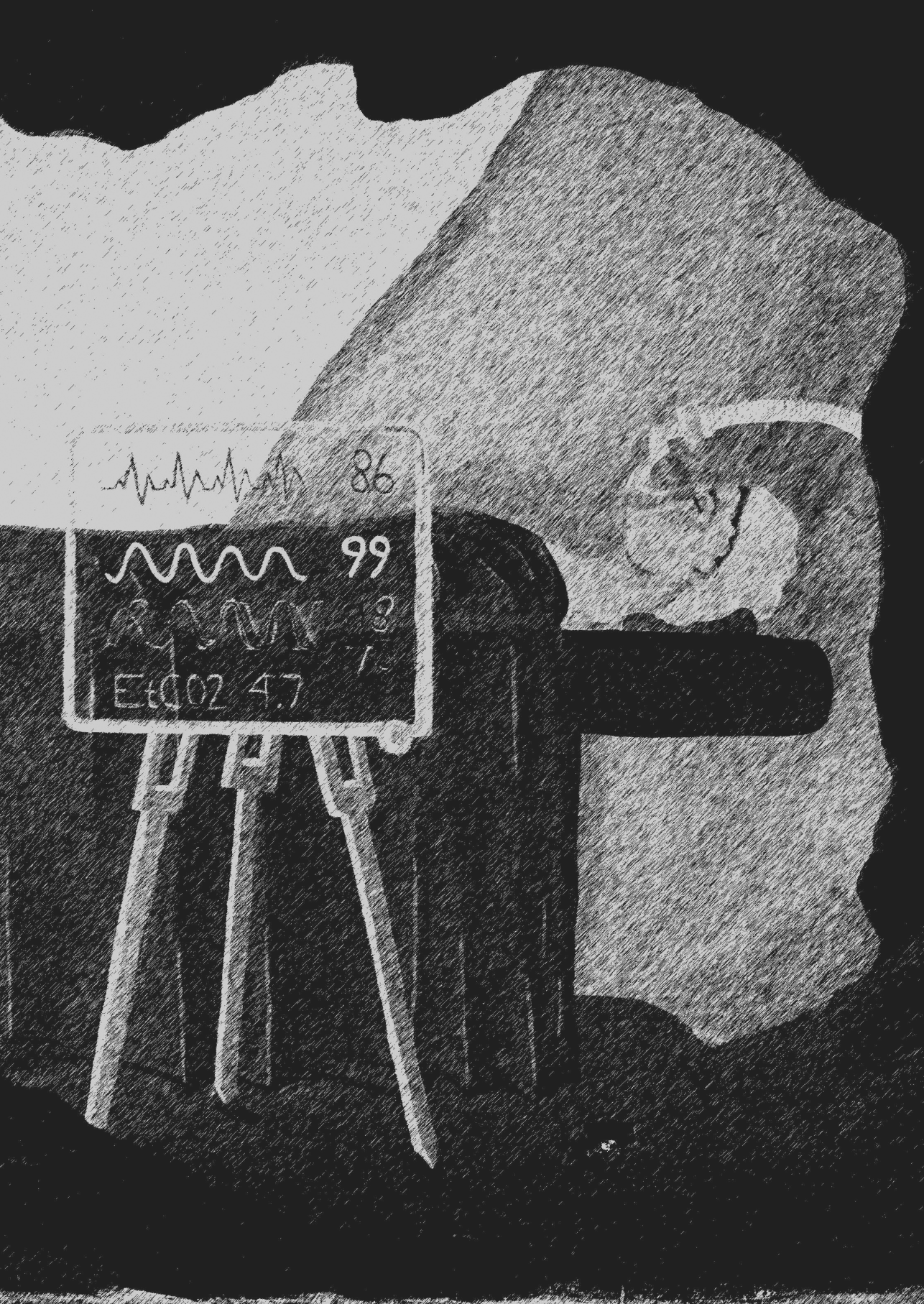
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Section 3

Postoperative Respiratory Monitoring

CHAPTER 5

5

Frequent respiratory events in postoperative patients aged 60 years and above

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Introduction

In current clinical practice, moderate–severe pain in postoperative patients is treated with potent opioids. While effective against pain in most patients, opioids come with serious side effects, of which opioid-induced respiratory depression is potentially life-threatening(1). In a review of the literature, we recently retrieved 132 case studies since 1980 in adult and pediatric patients that described the occurrence of postoperative respiratory depression from opioid treatment(2,3). Apart from these case studies, there was limited information on the prevalence of respiratory events in the postoperative period, with a few studies using continuous monitoring beyond measurements in the postanesthesia care unit (PACU) that showed frequent episodes of hypoxemia and/or bradypnea(4,5). In clinical practice, measurements are often restricted to the PACU, where currently pulse oximetry is the most important monitor of ventilation. However, oxygen saturation is not a direct measure of ventilation (but a measure of gas exchange in the lungs), and supplemental oxygen may obscure or delay the detection of respiratory events when oxygen saturation is used as a proxy for respiratory depression(6). Given these facts, continuous measurement of ventilation, rather than oxygen saturation, is presumably a more accurate tool to detect respiratory events, and also to prevent such events(2,4,7,8). A practical method to determine breathing activity is to measure respiratory rate (RR). RR can be assessed by multiple methods, including intermittent manual counting of thoracic movement and electrocardiography (ECG)-derived technologies, which are both error-prone and may lead to the underdetection of respiratory events(9). For example, upper-airway obstruction is often not detected, due to the persistence of thoracic movements. Continuous monitoring of respiration is thus best accomplished by electronic devices detecting airflow at the mouth, as this gives a noninvasive indication of gas movement into and out of the lungs.

In the current study we measured RR in postoperative patients using the RespiR8 (Anaxsys, Send, UK), which was developed to measure RR based on the humidity of exhaled air. In a previous validation study, we showed that the RespiR8 monitor is as reliable as capnometry to measure RR in the range observed in clinical practice(9). Here, we measured RR during the 6 hours following surgery in the PACU, as well as on the ward. We tested an elderly population, 60 years of age and older, as there is evidence that elderly patients are at an elevated risk of respiratory events following opioid administration(10). Our main aim was to use continuous RR monitoring of the postoperative patient using the RespiR8 device in the PACU and on the ward to quantify the occurrence of respiratory events, split into bradypneic (RR 1–6 breaths/minute) and apneic (RR 0 breaths/minute for at least 1 minute) events. Additionally, we aimed to identify patient risk factors, such as neck circumference or body-mass index, that could predict the occurrence of an event.

Materials and methods

Study design and population

The protocol was approved by the Ethics Committee of Leiden University Medical Center (the Netherlands) and by the National Research Ethics Service Committee, East Midlands (UK). All study procedures were conducted according to Good Clinical Practice guidelines and adhered to the tenets of the Declaration of Helsinki. This was a multicenter study performed at two sites: LUMC, Leiden, the Netherlands, and Nottingham University Hospital NHS Trust (Nottingham, UK). The study has been registered in the Netherlands Trial Register (NTR4778).

Of 115 recruited patients at the preoperative screening facility, 80 patients were enrolled in the study. All 80 study participants provided oral and written informed consent prior to study procedures and prior to their scheduled surgery. Inclusion criteria were age $60 years, elective surgery under general anesthesia for at least 60 minutes, and ability to read and understand the patient-information and consent form. Exclusion criteria were head, neck, and facial surgery or other conditions prohibiting application of the RespiR8 mask postoperatively. Possible risk factors for apnea were recorded, such as sex, body-mass index, neck circumference, history of snoring, or diagnosis of obstructive sleep apnea. It was expected that at least 50 subjects would be required to observe a significant proportion of patients with at least one apnea event.

Measurements

All patients were extubated in the operating theater and transported to the PACU. In the PACU, patients were connected to standard clinical monitoring equipment, including three-lead ECG and pulse oximetry. All patients received conventional clinical care in the PACU facility, and were discharged to the ward based on local protocol.

RR was measured automatically and continuously using the RespiR8 monitor. The device performs a calculation using a three-breath averaging algorithm, and is expressed as breaths/minute. The RespiR8 sensor is integrated in a standard oxygen face mask that is placed upon arrival in the PACU, but does not functionally require a flow of exogenous oxygen. In cases where supplemental oxygen was required (ie, oxygen saturation ,94%), 5–10 L/minute oxygen was administered. Supplemental oxygen was stopped before patients were discharged to the ward. RR measurements continued on the ward, and were temporarily discontinued in cases of eating/drinking, talking, or during other conditions where the face mask was removed. A research nurse remained with the patient during the complete 6-hour study period. Data were digitally recorded as average breaths/minute, and each data point represents a 1-minute average. A visual alarm was triggered when bradypnea (1–6 breaths/minute) or apnea (0 breaths/minute) was detected.

Statistical analysis

Statistical testing was performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA, US) and SPSS 20 (IBM, Armonk, NY, US). Data are presented as average ± standard deviation or median (interquartile range), unless otherwise stated. Bradypnea was defined as an RR of 1–6 breaths/minute, and apnea was defined as an absence of inspiratory flow at the mouth for at least 1 minute. Comparisons were made by Student's *t*-tests or nonparametric tests, and linear regression was used to correlate described variables. *P*-values ,0.05 were considered significant.

Results

Of the 80 patients enrolled in the study, data from 68 patients were able to be used for analysis. One patient was admitted to the intensive care unit directly after surgery and thus excluded; data acquisition failed in four patients, and seven patients withdrew their informed consent postoperatively. Characteristics of the remaining 68 patients are given in Table 1. Ten patients were recruited at the UK site, and 58 patients were recruited at the Netherlands site.

All patients received general anesthesia; 19 patients (28%) received an additional epidural or local technique. These 19 patients did not receive additional opioids in the operating theater or in the PACU. Of the remaining 49 patients, 35 (71%) received intravenous morphine as an opioid for postoperative pain relief. Typically, they received an opioid loading dose during surgery and received further increments of morphine titrated to their need in the PACU. Five patients subsequently received an intravenous patient-controlled morphine device; four of these patients used the device on the ward. Consequently, of the entire study population, only four patients used additional opioids on the ward. Patients who did not receive any opioids postoperatively were treated with acetaminophen and nonsteroidal anti-inflammatory agents at regular intervals (see also Table 1). Patients who received a muscle relaxant during surgery were adequately monitored and effectively reversed with either sugammadex or neostigmine according to standardized clinical protocol.

No serious adverse events occurred during the study. Nine adverse events were recorded, which were all judged to be not study-related. Adverse events included nausea and the occurrence of moderate pain, all occurring on the ward. All events were treated and resolved within the study period: pain was treated with a nonsteroidal anti-inflammatory agent, nausea with antiemetic medication.

Table 1. Patient characteristics, surgery and pain relief

Number of patients analyzed	68
Sex, male/female	38/30
Age (years)	70 [60 - 83]
BMI (kg/m^2)	26.7 [17.2 - 40.1]
Weight (kg)	79.6 (13.4)
Neck circumference (cm)	38.7 (4.4)
History of snoring, n (%)	38 (56)
Diagnosis of obstructive sleep apnea, n (%)	0
ASA status, n (%)	
ASA I	6 (9)
ASA II	57 (84)
ASA III	4 (6)
Unknown	1 (1)
Type of surgery, n (%)	
General	39 (57)
Orthopedic	11 (16)
Urology	15 (22)
Gynecology	3 (4)
Anesthesia technique, n (%)	
General	68 (100)
General + epidural or locoregional	19 (28)
Type of anesthesia, n (%)	
Total intravenous	37 (54)
Inhalational	21 (31)
Unknown	10 (15)
Intraoperative opioid	
Remifentanil	17 (25)
Sufentanil	38 (56)
Other	3 (4)
Unknown	10 (15)
Postoperative pain relief, n (%)	
IV morphine (OT/PACU)	35 (51)
PCA (morphine)	5 (7)
Morphine administred in PACU (mg)	10.3 (4.3)
Time in PACU (minutes)	120 (53.8)
Patients who received opioid on the ward	4 (6) + 5 PCA

Values expressed as mean (SD) or mean [range], unless otherwise stated.
ASA, American Society of Anesthesiologists; IV, intravenous; OT, operating theater; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia.

RR monitoring using the RespiR8 device was successful during the first 6 postoperative hours. Almost 24,000 RR data points were collected (408 hours, 6 hours per patient); 482 data points (ie, 482 minutes or 2% of measurement time) were missing, due to face-mask removal because of eating/drinking or other unspecified reasons. A histogram with the distribution of data points is shown in Figure 1. The median RR was 13 (10–15, range 0–39). In total, 877 measurements (3.6%) were bradypneic. On 262 data points, apnea was detected (RR 0 breaths/minute for at least 1 minute, 1.1%). Examples of RR values in the PACU and on the ward are shown in Figure 2. This shows one patient without any events in the PACU or on the ward (Figure 2A), one patient with multiple bradypneic events in the PACU and on the ward (Figure 2B), and finally one patient with apneic events in the PACU and on the ward (Figure 2C). None of the included patients in this study required verbal stimulation to breathe, mechanical support of ventilation, tracheal intubation, or the need for an opioid-reversal agent.

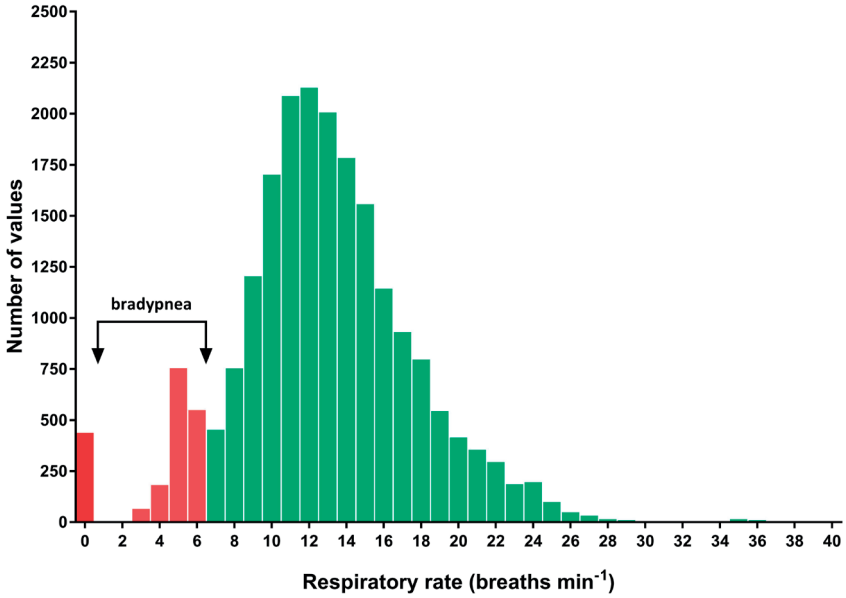

Figure 1. Observed respiratory rates.
Respiratory rate data were collected at 1-minute intervals, and represent a data set of almost 24,000 observations from 68 patients.

Eleven patients (16%) experienced no respiratory events, and 53 patients (78%) experienced at least one bradypneic event during the 6-hour study, with a median number of events per patient of ten (3.5–24). The median duration of these events was 1.4 minutes (1–1.6 minutes, range 1–4.3 minutes). A total of 39 patients (57%) experienced at least one apneic event, with a median number of events per patient of three (1–11, range 1–28).

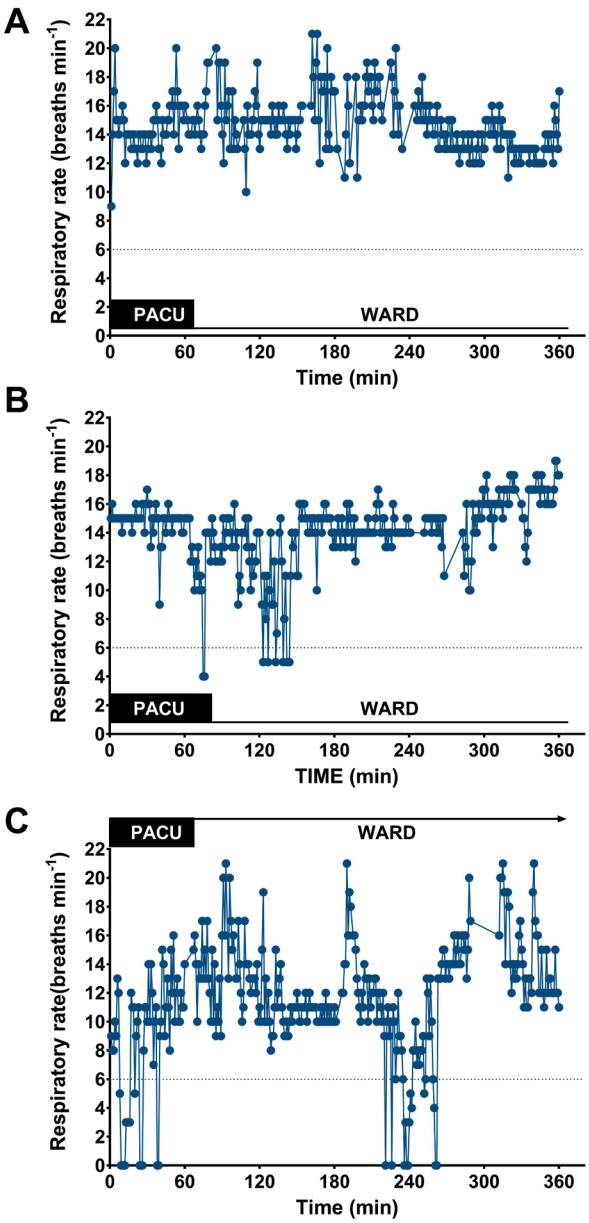

Figure 2. Examples of collected respiratory rate measurements in three patients (**A**–**C**). Respiratory rate data were collected at 1-minute intervals. Dotted, horizontal lines indicate the border for bradypnea. Time spent in the post-anesthesia care unit (PACU) and on the ward is indicated.

The median duration of an apneic event was 1.6 minutes (1–1.9 minutes, range 1–5 minutes). A total of 35 patients (51%) experienced both apneic and bradypneic episodes,

while just four patients (6%) had an apneic event without any bradypneic episodes. Finally, 18 patients (26%) had only bradypneic events.

Patients who experienced bradypnea or apnea did not differ from patients without bradypnea or apnea with respect to age, body-mass index, sex, American Society of Anesthesiologists (ASA) status, positive history of snoring, type of surgery, or PACU time. Neck circumference was significantly larger in patients with apneic events than in patients without apneic events: 39.6 (0.7) cm versus 37.4 (0.8) cm (*P*,0.05), and neck circumference correlated significantly with the duration of apnea (*P*,0.05). In contrast, neck circumference was not different for patients with or without bradypneic events: 38.7 (0.6) cm versus 38.8 (1) cm (*P*.0.05). None of the studied patient characteristics (age, body-mass index, sex, ASA status, positive history of snoring, type of surgery, PACU time) were correlated with the number or duration of bradypneic or apneic events (data not shown).

The occurrence of apneic and bradypneic events in the PACU was a predictor of events on the ward (bradypnea, *r*2=0.4, *P*,0.001; apnea, *r*2=0.2, *P*,0.001; Figure 3). Additionally, we observed a positive correlation between the occurrence of bradypneic events and apneic events (*r*2=0.4, *P*,0.0001), indicative that both conditions frequently concurred. A weak correlation was observed between morphine dose and number of observed bradypneic (*r*2=0.2, *P*,0.05) and apneic (*r*2=0.3, *P*,0.05) events in the PACU, but not to the number of events on the ward (Figure 4). Finally, we observed no difference in the number of apneic and bradypneic events in patients who had received general anesthesia combined with an epidural or local block and patients who received just general anesthesia (Mann–Whitney test, *P*.0.05).

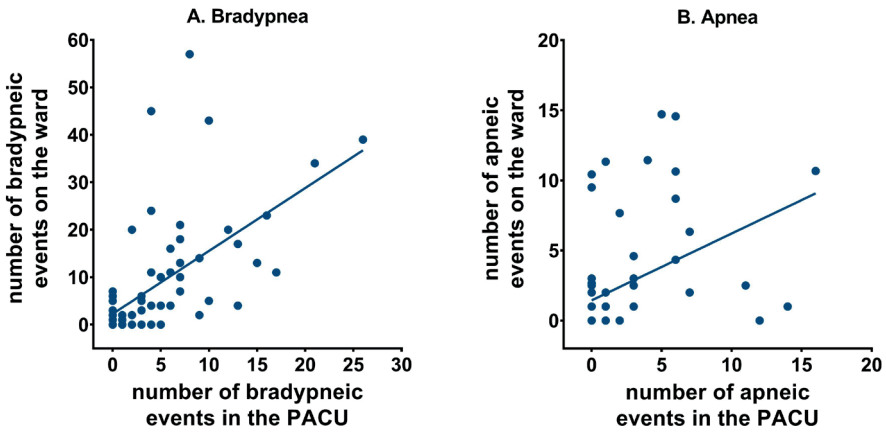

Figure 3 Correlation between respiratory events measured in the postanesthesia care unit (PACU) and on the ward. (**A**) Bradypneic events, r_2=0.4 (*P*,0.0001); (**B**) apneic events, r_2=0.2 (*P*,0.001).

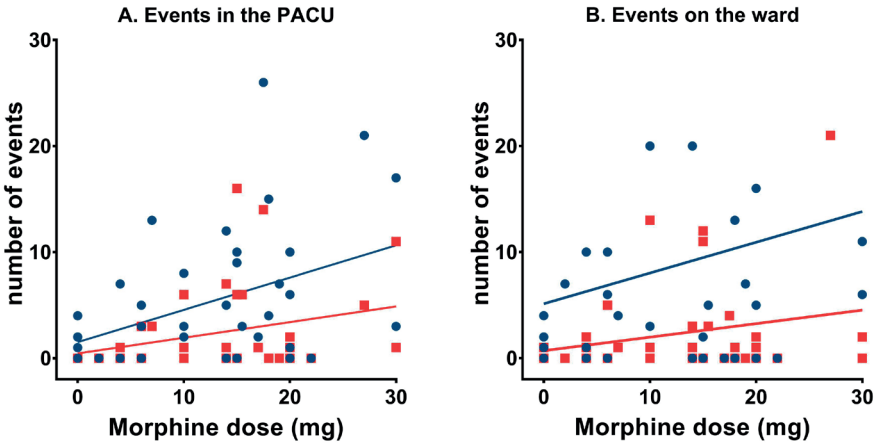

Figure 4 Correlation between morphine dose administered in the operating theatre and in the post-anesthesia care unit (PACU).
Number of bradypneic (blue circles) and apneic (red squares) events in the PACU (**A**) and on the ward (**B**). (**A**) Bradypnea, r_2=0.2 (*P*,0.05); apnea, r_2=0.3 (*P*,0.05). (**B**) Bradypnea, r_2=0.1 (*P*.0.05); apnea, r_2=0.2 (*P*.0.05).

Discussion

We studied respiratory rates in postoperative patients aged 60 years and older following major elective surgery in the PACU and on the ward using the RespiR8 device. Continuous and reliable RR measurements were obtained during the first 6 postoperative hours for 98% of the time; data loss because of face-mask removal occurred in 2% of measurements. A respiratory event occurred in 84% of patients, with frequent bradypneic and apneic events in 78% and 57% of patients, respectively, with a median of 10 bradypneic events per patient and 3 apneic events per patient.

Various techniques to measure RR continuously in spontaneously breathing patients have been developed in recent years. These techniques include CO_2 measurements at the mouth and nose, measurement of acoustic signals on the skin of the throat, impedance measurements from ECG, and measurements of thoracic and abdominal wall movement(11–16). Recently a new noninvasive technique was published that uses a radar system mounted above the patient's bed to measure RR(17). In this study, we used the RespiR8, a small and mobile device that relies on the detection of humidity in the exhaled air (see Niesters et al9 for a detailed description of the RespiR8 measurement technique). The current study, as well as our previous validation study, shows that the device allows long-term reliable assessment of RR(9). In our sample of 68 patients, the device detected multiple events of low RR and events with complete cessation of airflow at the mouth.

It is important to realize that the system does not provide information on the cause or location (central or obstructive) of the respiratory event.

Additionally, it is important that although respiratory events were frequent, they were short-lived and did not necessitate any intervention, such as verbal stimulation to breathe, mechanical ventilation, intubation, admission to the intensive care unit (ICU), or any pharmacological intervention. We relate this to the fact that our sample was relatively small and opioid use on the ward minimal. Our data are supportive of the recommendation from national anesthesia societies for the continuous monitoring of RR in spontaneously breathing patients who receive potent opioids for pain relief(7,8). An important observation was that early respiratory events in the PACU predict events on the ward. Since opioid use on the ward was limited in our patient population, this observation suggests that in some patients, respiratory instability persists beyond their stay in the PACU. Such prolonged periods of instability may be related to underlying disease, surgical stress, residual anesthetics and relaxants, opioid use in the PACU, or any combination of these factors. Irrespective of the cause, the early detection of respiratory events can serve as a clinical warning sign, and especially the population with early respiratory instability may require RR monitoring on the ward, and also in patients who do not consume large amounts of opioids.

The amount of morphine use was only weakly correlated with the occurrence of respiratory events in the PACU; no correlation was observed for events on the ward. The latter was expected, given the fact that opioid use on the ward was restricted to just four patients. The weak correlation is somewhat surprising, given the fact that the average morphine dose was relatively high (0.22 mg/kg). Still, as suggested, factors other than opioid consumption alone may have played a causal role in the generation of respiratory events in our patient population. Whether our findings are related to the age-group we tested remains unknown. We recently observed more frequent apneic events in an elderly population following oxycodone 20 mg intake (with and without additional ethanol) relative to a younger population(10). We relate these latter findings as well as our current results to higher opioid sensitivity and altered pharmacokinetics in the elderly, but additionally to alterations in the metabolic state, greater stress response to surgery and anesthesia, loss of resilience, reduced circulating volume and lean-muscle mass, and reduced reserve capacity in the elderly(18–20). These factors may be more pronounced in a certain subcategory of elderly patients (“the frail”), which would account for the occurrence of respiratory events in many but not all patients. At present, we have no reliable way of predicting which elderly patients are at increased risk of postoperative respiratory events. These findings warrant intensified, continuous monitoring of the respiratory status of postoperative elderly patients. Further studies are needed to understand fully the age effect on the control of breathing following major surgery under general anesthesia.

Patients who experienced apneic events had larger neck circumference than patients who did not have such events. In contrast, no such dichotomy was observed for bradypneic events. Neck circumference is an important predictor of upper-airway obstruction in sleep and sedation(21). This explains why patients with relatively greater neck circumference had more apneic episodes, most probably related to upper-airway obstruction, but not bradypneic events, as these are a measure of central respiratory instability.

Our study has a number of limitations. We aimed to evaluate the clinical use of the RespiR8 device and quantify the occurrence of respiratory events. Consequently, this study was not powered to detect any clinical consequences of the recorded respiratory events. Oxygen saturation and the use of supplemental oxygen in the PACU or on the ward were not recorded. Additionally, there was no assessment of mental state to detect the occurrence of delirium or postoperative cognitive decline. It is thus unclear what the clinical significance of the recorded events was. Future, longitudinal studies of respiratory events in elderly postoperative patients should address these issues. Also, the use of opioids on the ward was particularly low. This may have accounted for the absence of severe pain on the ward, but we cannot exclude that the patient's age played some role as well (e.g. fear of opioid use on the ward in elderly patients). It seems likely that we would have found a stronger correlation between opioid use and respiratory events with a higher total dose of administered morphine. This has been observed in patients aged 65 years and older on intravenous patient-controlled morphine. Interestingly, in that study, respiratory events (RR ,10 breaths/minute for at least 2 minutes) occurred in 78% of patients.4 This incidence is remarkably similar to data obtained in our study, and suggests that there are inherent opioid-dependent and nonopioid-dependent factors that predispose to postoperative respiratory events. Additionally, the RespiR8 sensor is based on exhaled humidity(9). The presence of shallow (opioid-induced) breathing patterns or the application of (dry) oxygen flow may change RespiR8 performance, and should be taken into account when interpreting our data. Finally, periods of sleep or sedation were not recorded. Both sleep and sedation can affect breathing patterns, and could be informative when analyzing longitudinal RRs.

In conclusion, this is the first long-term data-collection study on postoperative RRs in adults aged 60 years and older using the RespiR8 system. Almost 80% of patients experienced at least one bradypneic period during the 6-hour postoperative period, and almost 60% of patients had at least one apnea event. These events occurred well into the postoperative period, even in the absence of opioid administration. Known risk factors did not predict which patients were at risk for postoperative respiratory depression. Our data demonstrate the magnitude of respiratory disturbances in a postoperative elderly population, which may relate to presently unknown patient specific factors. Continuous respiratory monitoring during this time frame is warranted in this vulnerable patient population.

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CHAPTER 6

6

Recognition of respiratory compromise-related postoperative respiratory events with the Integrated Pulmonary Index algorithm

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Introduction

Respiratory compromise can be defined as a state in which there is a high likelihood of decompensation into respiratory insufficiency, respiratory failure or arrest, when early identification and intervention may prevent further deterioration(1). Respiratory compromise is a primary cause of postoperative complications, often leading to intensive care unit admission and increased risk of brady-tachyarrythmias and cardio-respiratory arrest(2). In addition to impaired central drive due to peri-operative opioid analgesia, certain patient comorbidities are associated with increased risk of respiratory compromise. (3-5). These comorbities include, but are not limited to: age ≥ 65 years, obstructiuve sleep apnea, chronic obstructive pulmonary disease, bronchoconstriction, idiopathic pulmonary fibrosis, pulmonary embolism, congestive heart failure, acute postoperative renal failure, diabetes, coronary artery disease and hypertension(3-5).

Rapid recognition of respiratory events in the immediate postoperative period can reduce the risk or prevent progression of respiratory compromise. However, spot checks of respiratory rate and peripheral capillary oxygen saturation (SpO_2) – a common care standard for monitoring patients – do not provide adequate clinical assessment of ventilatory status(6), leaving the patient unmonitored over 95% of the time(7), and recent literature on the incidence of postoperative respiratory events would appear to justify an enhanced patient monitoring protocol. For example, one study designed to quantify postoperative respiratory events (bradypnea and apnea) and the risk factors for these events in 68 patients ≥60 years showed that almost 80% of the patients experienced at least one bradypneic period during the 6-hour postoperative period and almost 60% had at least one apnea event(8). Patients with apnea had significantly larger neck circumferences than did those without apnea(8). These results suggest that continuous respiratory monitoring of patients is warranted on the ward after transfer from the PACU, particularly for patients with risk factors such as opioid administration and a larger neck circumference(8).

Continuous monitoring of oxygenation and ventilation using pulse oximetry and capnography, respectively, allows clinicians to identify trends in respiratory parameters not captured by intermittent monitoring and promotes timely medical intervention that may prevent respiratory arrest. The Integrated Pulmonary Index ™ (IPI) algorithm utilizes an artificial intelligence algorithm that combines the real-time measures of four parameters (i.e., multiparametric) – end-tidal CO_2 (ET_{CO2}); respiratory rate; pulse rate; and SpO_2 – into a single, easy-to-use 1-10 scale to provide an indication of changes in patients' ventilatory status(9-10). Table 1 shows interpretive criteria. Lower numbers represent poorer respiratory status. Ten is considered normal; values between one and four reflect critical events that require intervention.

Table 1. IPI Patient Status Scale

	IPI	Patient status
	10	Normal
	8-9	Within normal range
	7	Close to normal range; requires attention
	5-6	Requires attention and may require intervention
	3-4	Requires intervention
	1-2	Requires immediate intervention

Capnography and the IPI algorithm are valuable tools for monitoring patients who may be at increased risk for respiratory compromise following surgery(11-16) and to increase the opportunity for treatment before cardio-respiratory arrest(17). We conducted a study to evaluate the clinical utility of the IPI algorithm for detecting respiratory events in the postoperative patients and to determine the incidence of respiratory events in these patients.

Patients and Methods

Following IRB approval and obtaining informed consent, 40 patients scheduled for elective surgery under general anesthesia were included in the study. Continuous IPI algorithm measurements (data storage frequency 0.5 Hz) using the Capnostream 20p patient monitor (Medtronic) began immediately after admission to the PACU and continued until 8 am of the first postoperative day. Known risk factors for respiratory compromise including sleep apnea and opioid administration were identified for each patient by history and chart review.

Results

Demographic data from the 40 patients are shown in Table 2. One patient discontinued participation due to discomfort with the ET_{CO_2} sampling cannula. The mean age was 57.2 years (range: 31.5 to 75.8) and the mean body mass index (BMI) was 26 kg/m^2 (range: 16.6 to 38.2). The large majority of patients received total intravenous anesthesia and opioid analgesia. The most common surgical procedure was post-mastectomy autologous fat graft.

Table 2. Patient and Surgery Characteristics

Patient Characteristics	
Number of patients analyzed	40
Gender (male/female)	22/18
Age (years)	57.2 ± 12.2 (range: 31.5 – 75.8)
Weight (kg)	80.9 ± 17.4 (range: 54.5 – 135)
Height (m)	1.76 ± 0.1 (range 1.54 – 1.92)
BMI (kg/m^2)	26.0 ± 4.6 (range: 16.6 – 38.2)
Surgery Characteristics	
Duration of anesthesia (min)	277 ± 146 (range 48 - 659)
Type of surgery, n (%)	
General	10 (25)
Nephrectomy	8 (20)
Post-mastectomy autologous fat graft	13 (32.5)
Vascular	4 (10)
Other	5 (12.5)
Type of anesthesia, n (%)	
Total intravenous	35 (87.5)
Balanced	5 (12.5)
Neuromuscular block reversal, n (%)	
None	30 (75)
Neostigmine	2 (5)
Sugammadex	8 (20)
Postoperative pain relief, n (%)*	
None	11 (27.5)
Morphine	26 (65)
Methadone	5 (12.5)
Esketamine	1 (2.5)

*Total greater than 100% because some patients received more than one type of analgesic

Approximately 700 hours of postoperative IPI algorithm values were obtained, representing a data set of 1,152,427 observations with an average of 17 hours per patient (range: 12 to 22 hours); 5.8% of measurements were missing (e.g., sensor off). Thirty-nine of the 40 patients had at least one critical IPI event (defined as values between 1 and four), three patients displayed low IPI algorithm values during more than 15% measurement time and critical IPI events occurred in 3.6% of all measurements (Figure 1). These findings appeared unrelated to the presence of sleep apnea or opioid administration schedules. Although the critical IPI events likely required caregiver interventions, this was not recorded because the study was observational. Multivariate regression analysis was performed to predict the percentage of critical events from age, gender, BMI and the duration of anesthesia (Figure 2). Age and BMI addes significantly to the prediction. Figure 3 shows graphs of IPI algorithm recordings from three patients, demonstrating different IPI algorithm results. No serious adverse events occurred during the study.

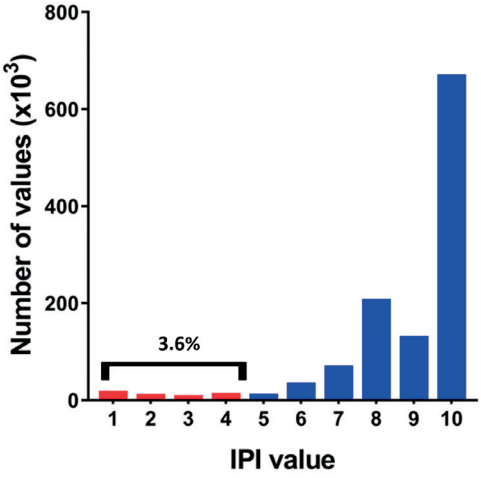

Figure 1. Histogram of observed Integrated Pulmonary Index (IPI) algorithm values. IPI algorithm values were obtained at a 0.5 Hz interval and represent a data set of 1,153,427 observations collected from 40 patients. Critical IPI events, values 1-4, are labeled red

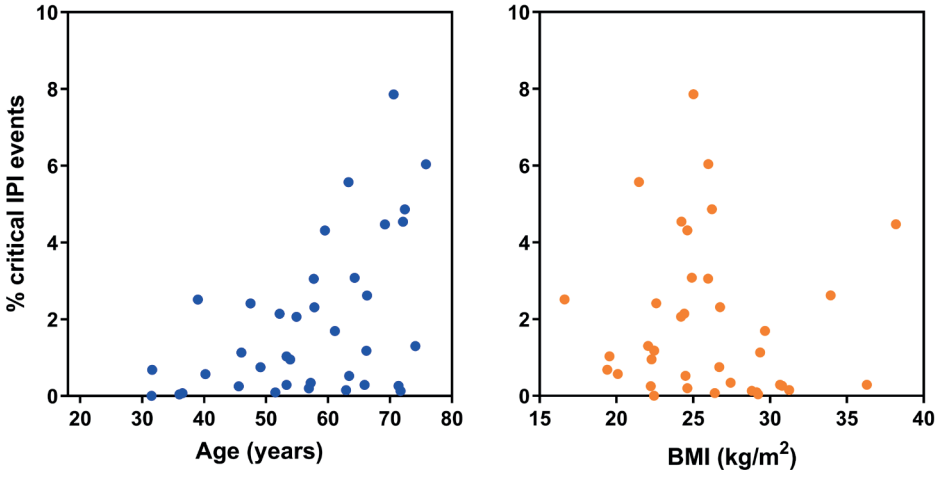

Figure 2. Correlation plots of age (left panel) or BMI (right panel) and percentage of critical IPI events (range 1-4, as percentage of total recording period) per patient. Multivariate regression analysis was performed to predict the percentage of critical IPI events from age, gender, BMI and the duration of anesthesia. These variables predicted the occurrence of critical IPI events, $F(4,32)= 4.523$, $P = 0.005$. More specifically, age and BMI added significantly to the prediction ($P < 0.05$).

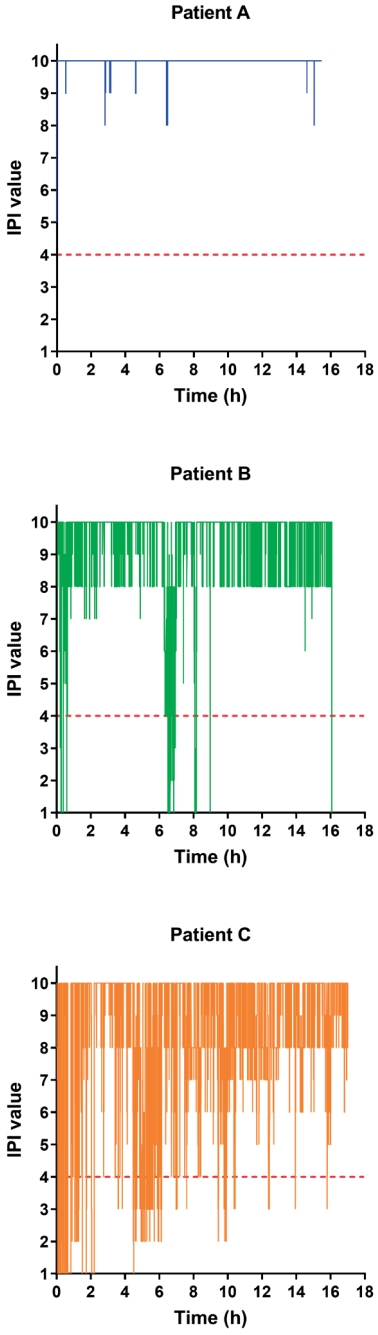

Figure 3. Example graphs of IPI algorithm recordings from three patients. (**A**) During the 17-hour recording period, no critical IPI events were observed. (**B**) Some critical IN events were registered during the 17-hour study period. (**C**) Frequent and prolonged episodes of critical IPI events occurred during the 17-hour recording period. Critical IPI events are defined as values between 1-4; the cut-off is indicated in the graphs with a red dashed horizontal line.

Discussion

This study involved 40 patients with an average age of 57 and an average BMI of 26 kg/m^2 who were scheduled for elective surgery under general anesthesia. Following their respective procedures, most of the patients were provided pain relief with morphine, methadone or esketamine. They were monitored using the IPI algorithm in a postoperative setting for an average of 17 hours. Results from the study showed the IPI algorithm was easy to use and almost all patients displayed at least one critical event, likely requiring intervention. However, critical IPI events and low IPI values appeared to be unrelated to the presence of sleep apnea or opioid administration, which are known risk factors for respiratory compromise. In contrast, older age and higher BMI were significant predictors of critical IPI events.

Conclusion

These results show that critical IPI events are common during the immediate postoperative period and demonstrate the clinical utility of the IPI values for detecting respiratory events in postoperative patients. Based on these results, interventional studies are planned to assess the performance of the IPI values as an early warning sign of respiratory compromise.

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CHAPTER 7

Effect of postoperative respiratory monitoring using the Integrated Pulmonary Index compared to standard care on adverse respiratory events and resultant nurse interventions in the post anesthesia care unit: a randomized controlled trial

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Introduction

Several surgery and anesthesia-related factors increase the risk of an adverse respiratory event (ARE) in the perioperative period. Most importantly, AREs are highly associated with the use of opioid therapy for pain, resulting in opioid-induced respiratory depression (OIRD)(1-4). OIRD is a potentially lethal complication of activation of opioid receptors in brainstem respiratory neuronal networks, associated with bradypnea, apnea, hypercapnia and hypoxia. The number of OIRD events in the postoperative period is not known. A recent multicenter observational study showed the occurrence of an OIRD event in 41% of patients in the first 48 h after surgery under general anesthesia(5, 6). In that study, continuous capnography was used to detect patterns of OIRD. Still, deterioration of the patient from a capnography-related pattern abnormality to a sentinel event requiring an intervention (*e.g.,* administration of opioid antagonist naloxone, reintubation, mechanical ventilation, cardiopulmonary resuscitation, or transfer to the ICU) is much less common and may occur not more than once in every 200-1,000 postoperative patients(2, 5, 7). When respiratory deterioration does occur, however, results can be catastrophic and costs for both the patient and the healthcare system are high(2, 5, 8, 9). Given the availability of effective interventions, these respiratory catastrophes following routine, elective surgery have been termed 'never events' in that they should never be allowed to occur(9).

The challenge is to predict or identify respiratory events and intervene before any further respiratory deterioration. Available scoring systems based on known surgery- and patient-related risk factors predict postoperative AREs poorly(10, 11). Moreover, current standard monitoring practices in postoperative patients do not detect many instances of respiratory compromise(4, 5, 12-14). Sun et al. showed that prolonged episodes of hypoxemia are common in the first 48 hours following non-cardiac surgery and that 90% of these events were missed by routine 4-hourly spot checks in the postoperative wards(15). Similarly, Lee et al. showed that the time between the discovery of respiratory depression and the last nursing assessment was 2 hours in 42% of the cases and a concerning 15 minutes in 13% of the cases(13).

Given all of the above, continuous respiratory monitoring in patients receiving parenteral opioids in the first 24 postoperative hours has been advocated by multiple stakeholders (including the Anesthesia Patient Safety Foundation, the Joint Commission, the American Society for Pain Management Nursing)(16). A systematic review of studies evaluating continuous monitoring *via* pulseoximetry or capnography reported improved detection of oxygen desaturation or OIRD-events compared to routine nursing checks (17). However, impact on clinical outcomes has so far not been demonstrated(12, 17). Furthermore, continuous monitoring, regardless of which parameter it is based on, has its own limitations, with a potential for false positive alarms disrupting nurse workflow and

leading to alarm fatigue(12, 17-20). Recent developments aim to use multiple parameters to detect AREs. Application of smart algorithms that combine individual physiological variables into one index may increase the ability to detect a true adverse respiratory event while avoiding false alarms and limiting alarm fatigue(1). An example of such a multiparameter index is the Integrated Pulmonary Index or IPI™, which integrates oxygen saturation (SpO_2), respiratory rate (RR), end-tidal PCO_2 ($P_{ET}CO_2$) and heart rate (HR) into a single integer value of 1-10 that represents adequacy of respiratory condition of the patient using a fuzzy logic inference mathematical model (20, 21). So far, the IPI has been validated with retrospective data obtained in a variety of clinical settings, but it has not been studied prospectively as a monitor of postoperative AREs(21).

In this randomized controlled trial, the use of the IPI was compared to standard continuous respiratory monitoring in postoperative patients. Our aim was to determine whether the IPI enables early detection of postoperative respiratory events and alters clinical interventions.

Materials and Methods

Initially we performed an observational trial to evaluate the clinical utility of the IPI algorithm in postoperative patients and to determine the incidence of AREs. The results of this study are published elsewhere(22). The data generated by this study were used to design and power the current study.

Ethics and Patients

The protocol was approved by the Investigational Review Board (IRB) (Commissie Medische Ethiek, Leiden University Medical Center, the Netherlands) in August 2015. All study procedures were performed in compliance with the 2013 version of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered at the trial register of the Dutch Cochrane Center under identifier 5231. Patients were recruited between November 2017 and January 2019. Subjects were enrolled for the study and they gave verbal and written informed consent prior to study procedures.

Patients were adult (at least 18 years old), American Society of Anesthesiologists (ASA) class 1-3, scheduled for elective surgery under general anesthesia, expected to receive opioids for treatment of postoperative pain, and requiring an overnight post-anesthesia care unit (PACU) stay following surgery. Exclusion criteria included use of epidural anesthesia, nerve blocks, surgery that would hamper the postoperative application of the IPI sensors, emergency surgery or the inability to give informed consent.

Study Design

The study had a two-arm, parallel, randomized controlled design. Patients were randomized on the day of surgery to an observational arm or an interventional arm using a computer-generated randomization list. Neither patient nor the anesthetic team responsible for clinical care during surgery were informed of the allocation. Due to the nature of the study, patients and PACU nurses were not blinded to the study allocation once data collection commenced. Outcome assessors were blinded to allocation.

Clinical care in both treatment groups. Anesthesia technique (total intravenous anesthesia or volatile anesthesia, opioid use, use of neuromuscular reversal agents) was left to the discretion of the attending anesthesiologist. Once surgery had ended and the patient was extubated and transported to the PACU, the patient was connected to standard monitoring equipment (3-lead ECG, non-invasive blood pressure monitoring using an arm cuff, pulse oximetry *via* a finger probe). Additionally, the standalone Capnostream 20p monitor (Medtronic, Fridley, Minnesota) was connected to the patient. This monitor collects inhaled and expired CO_2 tracings *via* a nose cannula (from which the RR is also calculated) and SpO_2 and HR measurements *via* pulse oximetry using a (second) finger probe connected to the monitor. All patients were admitted to the PACU until 8AM the following morning, when monitoring by Capnostream was discontinued. Any complication or the need for a prolonged PACU stay was noted in the patient electronic health record. Nurses were asked to note instances in which the Capnostream monitor (finger probe or nasal cannula) was disconnected as may have occurred during meals or patient care.

Clinical care in the observational arm. Patients randomized to the observational arm of the study were attached to the Capnostream monitor, but the monitor screen was shielded and Capnostream alarms were silenced. Nurses were instructed to treat their patients according to standard clinical care using standard monitors and clinical experience. The PACU nurses were requested to note every respiratory event such as apnea, hypoxia, respiratory depression or obstructed breathing. For every respiratory event, they were also asked to note the associated intervention to improve respiratory condition such as verbal or tactile patient stimulation, chin lift, administration of supplemental oxygen *via* the nasal cannula, escalation to involve the attending PACU physician, naloxone administration, or reintubation. The decision to intervene and manner of intervention was based on local protocol, which relies on monitoring of SpO_2, respiratory rate and sedation level.

Clinical care in the interventional arm. Patients randomized to the interventional arm of the study were attached to the Capnostream monitor with the screen visible to the nursing staff. The screen displays the capnography trace, HR, RR, SpO_2 and IPI value. Prior to the start of the study, nurses were trained to use the Capnostream monitor

and interpret the IPI values. Initially, alarms were set to be triggered at IPI values ≤ 4, as per the manufacturer's suggestion (see also ref 16). However, when nurses reported an overwhelming number of alarms that were clinically irrelevant, we amended the protocol and changed the alarm threshold to an IPI value of 1. Patients that were included prior to the amendment, were replaced.

Since it is mandatory in our hospital to collect vital signs in the patient's electronic health record, the patient was also attached to standard clinical monitors. However, nurses were requested to guide their assessment of the patient's respiratory condition based on the IPI value. In case of a clinically relevant discrepancy between the monitors, nurses were asked to evaluate the patient and intervene according to their experience and report the discrepancy to the investigators. In case of an alarm at an IPI value of 1, the nurses were instructed to approach the patient, assess the patient's condition (apnea, respiratory depression, hypoxia, but also whether the low IPI event could be considered an artefact) and intervene as required (see above). The occurrence of a low IPI event was noted as well as the assessment of the patient's condition.

Data collection

Data were collected from the Capnostream monitor, the electronic health record database (Healthcare Information X-change (HiX), Chipsoft, the Netherlands) and the case record forms (CRF) containing the notes regarding respiratory events, and interventions. The Capnostream monitor stored data at 0.5 Hz intervals; the HiX database provided information regarding patient history and characteristics, drugs administered during surgery and during PACU stay, vital signs from standard monitors averaged over 1 min intervals. Major complications were recorded in the electronic health record and the CRF, adverse events were collected in the CRF.

Primary and Secondary Study Endpoints. The primary study endpoints were the number of low IPI events and the number and nature of the nurse responses to low IPI values. Secondary endpoints were the duration of IPI events and the main causes of IPI events, as determined by one or more of the 4 individual variables used in the calculation of the IPI value.

Data selection. We manually checked the data for the presence of artefacts at the end of the study. Low IPI events were considered true and clinically relevant adverse respiratory events if (1) the nurse had not noted the event as an artefact or sensor mispositioning and (2) the recording of vital signs from the electronical medical database corroborated the Capnostream data and (3) in case of hypoxia or obstructed breathing (as noted by the nurses), the event was followed by a sympathetic response such as tachycardia. Once a low IPI event was confirmed to be a true ARE, the nature of the event was examined. An

event was considered to be associated with hypoxia when the SpO2 was ≤ 90%; an event was considered a respiratory depression event when: (1) RR < 6 breaths/min or (2) at least 1 episode of apnea (RR = 0 breath/min for at least 15 s) and (1) end-tidal PCO_2 > 60 mmHg) or (2) end-tidal PCO_2 < 15 mmHg.

Statistical Analysis

We assumed that an intervention would be required in all subjects of the interventional study, and assuming an 'intervention:low IPI event' ratio of 99.9% in the interventional arm and 70% in the observational arm, 35 patients were required per group to assess if IPI based intervention differs from local protocol (alpha = 0.05, 1-beta = 0.9). Because of anticipated drop-outs, we aimed to include 80 patients in the study (40 per group).

The normal distribution of numerical data was visually assessed and groups were subsequently compared using either independent samples t-tests or Mann-Whitney U tests. Categorical data were compared using Pearson's chi-squared test. Results were considered significant with a p-value of <0.05. Statistical analyses were performed using IBM SPSS statistics for Windows v25.0 (IBM Corp., Armonk, NY).

Results

A total of 335 patients were approached for participation. 220 patients either refused participation (n= 61) or were not randomized because their surgery was rescheduled (n = 159). 115 patients were randomized, of which 35 did not complete the study. The reasons for dropout or exclusion are given in the Figure. Eighty patients completed the study, 40 in the observational arm and 40 in the interventional arm. In the observational arm, one patient was excluded from analysis due to an exceptionally high number of artefacts in the Capnostream monitor data. The data of 79 patients were included in the analysis.

Patient characteristics

Patient and peri-operative characteristics are given in Table 1. Both groups were similar in terms of age, ASA classification and risk factors for postoperative respiratory events. A total of 28 patients (35%) had a STOP-BANG of > 3 and were considered at high risk for the presence of obstructive sleep apnea (OSA). Nine other patients had been diagnosed with OSA, of which one used a continuous positive airway pressure device at home. In 38% of patients, there was no pre-operative risk assessment for the presence of OSA. Seventy-six patients (95%) received either morphine or methadone 45 to 60 min before the end of surgery to cover the initial part of postoperative analgesia. During their PACU admission,

Table 1. Patient and peri-operative characteristics.

	Observational arm		Interventional arm		Standardized mean difference
Number of patients	39		40		
Sex (male/female)	24/15		22/18		
Age (years), average (SD)	54.3	(14.6)	59.2	(11.8)	0.37
BMI (kg/m^2), average (SD)	26.7	(4.7)	26.2	(3.7)	0.13
BMI ≥ 30, n (%)	9	(23.1)	6	(15.0)	
ASA Class, n (%)					
I	3	(7.7)	3	(7.5)	
II	17	(43.6)	13	(32.5)	
III	19	(48.7)	24	(60.0)	
Comorbidities, n (%)					
Cardiac	10	(25.6)	11	(27.5)	
Pulmonary	5	(12.8)	4	(10.0)	
Diagnosed with OSA, n (%)	4	(10.3)	5	(12.5)	
Requiring home CPAP, n	0		1		
STOP-BANG scores, n (%)					
Above 3	11	(28.2)	17	(42.5)	
Below or equal to 3	16	(41.0)	14	(35)	
Unknown	12	(30.8)	9	(22.5)	
Type of surgery, n (%)					
General abdominal	23	(59.0)	26	(65.0)	
Vascular	4	(10.3)	6	(15.0)	
Reconstructive	5	(12.8)	5	(12.5)	
Orthopedic	3	(7.7)	0	(0.0)	
Neurosurgical	2	(5.1)	1	(2.5)	
Head and neck	2	(5.1)	2	(5.0)	
Duration of surgery (hours), average (SD)	3.8	(2.1)	3.2	(2.1)	0.29
Intra-operative opioid loading dose (mg), average (SD)	11.3	(3.7)	11.0	(3.1)	0.30
No intra-operative opioid loading dose, n	1		3		
Postoperative opioid analgesia, n (%)					
None	10	(25.6)	17	(42.5)	
Patient-controlled analgesia	12	(30.8)	7	(17.5)	
Capnostream IPI collection time (hours), average (SD)	1.8	(3.3)	16.2	(3.9)	0.11

For continuous variables, the (absolute) standardized mean difference is listed in the right column. Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index; CPAP, continuous positive airway pressure; IPI, integrated pulmonary index; n, number; OSA, obstructive sleep apnea; SD, standard deviation; STOP-BANG, snoring-tired-observed-pressure BMI-age-neck-gender, questionnaire covering several risk factors related to obstructive sleep apnea.

fifty-two (66%) patients required additional intravenous opioids (morphine, methadone or fentanyl); 19 (24%) patients received either morphine or fentanyl by a patient-controlled analgesia (PCA) device. Twenty-seven (34%) patients did not require additional opioids postoperatively. Five of these patients had received an intraoperative continuous sufentanil infusion for more than 6 hours, the remainder had been given either morphine or methadone during surgery.

Adverse respiratory events and artefacts

Incidence. A total of 860 low IPI events were recorded, of which 523 (61%) were considered artefacts and 337 were considered true adverse respiratory events. The proportion of artefacts was similar in both groups (60% in the observational group *versus* 64% in the interventional group, p=0.292). In 37 (47%) patients, one or more true respiratory events were recorded, 21 in the observational group and 16 in the interventional group (p=0.218). The number of respiratory events was almost four times higher in the observational group than in the interventional group (265 *versus* 72 respectively), accounting for 79% of all events.

In patients experiencing at least one ARE, those in the observational group experienced a median of 6 events compared to 2.5 events for those in the interventional group ($p<0.05$). When corrected for length of PACU stay, patients in the observational group experienced 0.4 events/h compared to 0.1 events/h in the interventional group ($p<0.05$). Moreover, the median duration of events was significantly longer in the observational arm than in the interventional arm (75 s *versus* 62 s, respectively, $p<0.001$). The increased incidence and duration of true respiratory events in the observational group is reflected in the total time spent in a state of potential respiratory compromise: 57 s/h of PACU admission time in the observational group compared to 9 s/h of PACU admission time in the interventional group ($p<0.05$). These findings are summarized in Table 2.

Respiratory depression and hypoxia. Only 17.5% (59/337) of all respiratory events were associated with hypoxia. Most events were episodes of respiratory depression with (n=55 total, 16.3%) or without (n=278, 82.4%) hypoxia. The proportion of respiratory events associated with hypoxia was significantly higher in the interventional group than in the observational group. These findings are summarized in Table 2.

Table 2. Characteristics of adverse respiratory events.

	Observational arm		Interventional arm		
Adverse respiratory events, n	660		200		
True event / artefact	265 / 395		72 / 128		p=0.292*
Patients with at least one event, n (%)	21	(53.8)	16	(40.0)	p=0.218*
In patients with ≥ 1 event					
Events per patient (n), median (range)	6	(1-37)	2.5	(1-17)	p<0.05#
Events per hour (n), median (range)	0.4	(0.06-2.53)	0.1	(0.05-1.44)	p<0.05#
Duration of event (sec), median (range)	75	(29-848)	62	(28-424)	p<0.001#
Time spent in true ARE (sec/h), median (range)	57	(2-381)	9	(2-88)	p<0.05#
Characteristics of ARE, n (%)					p<0.001*
Respiratory depression without hypoxia	231	(87.2)	47	(65.3)	
Respiratory depression with hypoxia	34	(12.8)	21	(29.1)	
Hypoxia without respiratory depression	0	(0.0)	4	(5.6)	

An adverse respiratory event (ARE) is defined as an Integrated Pulmonary Index (IPI) of 1 for at least 30 seconds. Events were considered true if the nurse did not annotated the event as an artefact/ sensor mispositioning, if the vital signs recording of the electronic medical record corroborated with the findings, and if the event was followed by a sympathetic response. Respiratory depression was defined as respiratory rate <6 breaths per minute or at least 1 episode of apnea and end-tidal PCO_2 > 60 mmHg, or end-tidal PCO_2 < 15 mmHg. Hypoxia was defined as SpO_2 ≤ 90%. Abbreviations: ARE, adverse respiratory event; h, hour; IPI, integrated pulmonary index; n, number; sec, seconds. *,Pearson's Chi-square or Fisher's Exact test; #, Mann-Whitney U-test or independent t-test, depending on data distribution.

Interventions

A total of fifty-two interventions were reported by the nurses, of which 39 occurred in the interventional arm and 13 in the observational arm of the study. Interventions were mostly limited to verbal or tactile stimulation of the patient and/or initiating or increasing supplemental oxygen administration. A list of all interventions is found in Table 3.

Of the 52 interventions, 23 were initiated by the nurses despite the absence of a respiratory event as defined by an IPI of 1 for more than 30 seconds (8 in the observational arm and 15 in the interventional arm). Interventions by nurses for these non-low IPI events were initiated either by hypoxia that was not low enough to trigger an IPI alarm (e.g. increasing oxygen administration when SpO2 was < 94% but > 91%) or by episodes of apnea < 30 seconds. The ratio of respiratory interventions to respiratory events was significantly lower in the observational group (13/265) than the interventional group (39/72) ($p < 0.00001$).

Table 3. Characteristics of respiratory interventions by PACU nurses.

	Observational arm	Interventional arm	Total
Interventions, n	39	13	52
Interventions in the absence of an ARE, n	8	15	23
Intervention, n			
Verbal or tactile stimulation	5	21	26
Increase supplemental O_2	8	8	16
Decrease supplemental O_2	0	2	2
Patient repositioning	0	1	1
Combination of the above	0	2	2
No intervention required*	0	5	5

Respiratory interventions as reported by the PACU nurses. *In 5 respiratory events, no intervention turned out to be required as the patient recovered spontaneously or the Capnostream 'low IPI' alarm sound aroused the patient resulting in improvement of respiration. Abbreviations: ARE, adverse respiratory event; n, number.

Serious adverse respiratory events. Despite the occurrence of respiratory events, there was no need for naloxone administration, airway maneuvers or assisted ventilation in either group. However, two patients had an abnormal postoperative course related to respiratory complications. In one case a pulmonologist was consulted on the day after surgery for persisting hypoxia and high oxygen requirement. This patient had been randomized to the interventional arm of our study, had triggered 17 IPI alarms and had received 9 interventions (tactile stimulation and supplemental oxygen administration). The consultation did not delay discharge from the PACU. The patient was subsequently diagnosed with emphysema and followed-up in an outpatient setting. In a second patient that had been randomized to the observational arm of the study, a routine morning arterial blood gas revealed an acute respiratory acidosis, which was considered to be opioid-induced and for which PACU discharge was delayed by 24 h. In this patient, the IPI monitor had recorded 29 events of respiratory depression with signs of obstructed breathing. However, the nurses had only noted one respiratory event and intervened by increasing the supplemental oxygen administration.

Risk factors for respiratory events

When comparing characteristics for the patients that experienced AREs as opposed to none, only sex was significantly different, with male patients being more likely to experience a respiratory event. Other known risk factors were not significantly different between groups (see Table 4). The average cumulative postoperative opioid dose did not differ significantly between patients with or without adverse respiratory events (6.6 mg *vs.* 5.1 mg, respectively; p=0.31).

Discussion

To our knowledge, this is the first randomized controlled trial that studied the use of a multiparameter monitoring system to track the respiratory status of postoperative patients. We found that compared to continuous monitoring using respiratory rate and pulse oximetry alone, the use of the IPI monitor led to an increase in the number of interventions performed by nurses to improve the respiratory condition of the patient. This did not lead to a reduction in the number of patients that experienced an ARE, but did cause a significant reduction of the number of events per patient combined with a shorter duration of respiratory events.

Our study shows that 47% of patients experienced one or more adverse respiratory events in the first 24 hours following surgery, with an equal distribution among randomization arms. This is consistent with the findings in the PRODIGY trial(5). In that prospective, observational, multicenter trial, patients receiving opioids for postoperative pain relief were monitored with the Capnostream monitor and separate signals (end-tidal CO_2, RR, SpO_2 and HR) were collected and analyzed. Respiratory depression was defined by an end-tidal $PCO_2 \leq 15$ or ≥ 60 mmHg for at least 3 min, RR $\leq$ 5 breaths/min for at least 3 min, apnea lasting more than 30 s, or any opioid-related adverse respiratory event. A respiratory depression event occurred in 41% of 1,496 patients.

The clinical relevance of many of these events remains unknown, as deterioration towards a serious adverse event requiring major interventions was fortunately infrequent in our study. However, both studies suggest that nearly half of our patients spend some of the early postoperative period in an state of potential respiratory compromise.

Aside from male sex, we did not detect any risk factors for the occurrence of a postoperative AREs. Other studies, including the aforementioned PRODIGY trial, detected several predictors of a respiratory event, including age, sleep disorders, opioid naivety or high blood pressure(5). Our relatively small sample size precluded detection of additional risk factors.

Although monitoring of the IPI did not lead to a reduction in the number of patients experiencing a respiratory event, the number and duration of events per patient was decreased. Since we allowed the use of supplemental oxygen, low SpO_2 values triggered the IPI alarm in only 17% of events. In all other cases the events were triggered by the other measured parameters (end-tidal CO_2, HR and/or RR). It is important to realize that supplemental oxygen may mask or may even exacerbate opioid induced respiratory depression when only SpO_2 is monitored(4, 20, 23). Patients on oxygen will have some oxygen reserve causing a delay in the detection of an obstructive or central apneic event.

Additionally, the peripheral respiratory drive is blunted by supplemental oxygen which will cause a further depression of ventilation(23). Our study indicates that it is a challenge for nurses to identify patients experiencing opioid induced respiratory depression in the absence of hypoxia, even with continuous monitoring of respiratory rate in a high care setting with experienced nurses and a low (1:2) nurse to patient ratio. This suggests that continuous monitoring with just SpO_2 is not effective for the identification of opioid-induced respiratory depression. This is especially true on general wards, where nurse:patient ratios are generally lower and the intensity of clinical monitoring is relatively low.

We observed a large number of IPI alarm artefacts. These artefacts were related to the malpositioning of the nasal sensor causing sensing artefacts or the result of minor clinical events. One such frequent alarm that we considered an artefact was related to mildly obstructed breathing during sleep which caused low end-tidal PCO_2 values with low but otherwise normal breathing. Still, while our study suggests that lowering the triggering alarm to an IPI value of 1 can be done safely (no serious respiratory events were missed by the monitor), more than half of the alarms did not represent actual respiratory compromise. For successful implementation of future monitoring systems without disrupting nurse workflow, the issue of false alarms and alarm fatigue needs to be addressed. Interestingly, in case of a true alarm, some of our patients did not require actual interventions because their bedside monitor alarm had aroused them before the nurse had intervened. It is imaginable that future monitoring systems could trigger bedside alarms first and only be transmitted to a nursing pager when the respiratory compromise persists or worsens.

This study has some methodological issues that warrant comment. First, we tested the IPI in the PACU setting. Consequently, extrapolation of our results to the general surgical ward should be done with caution. We chose the current approach in order to have two comparable arms, one arm with intervention based on the IPI monitor, and one arm with intervention based on standard PACU monitors (RR and SpO_2) allowing reliable comparison of event occurrences and interventions. We observed that patients receiving respiratory intervention based on the IPI monitor had less and shorter adverse respiratory events, compared to control patients. We expect the benefit of the IPI monitor to be higher on the general surgical ward, where opioids are given, respiratory events can occur but clinical monitoring is infrequent(24).

Second, we studied the IPI monitor in a population of patients expected to require opioids in the first 24 hours after surgery. Several studies have shown that events are most likely to occur within this timeframe and that the use of opioids is a major risk factor for adverse respiratory events(1-3, 13). However, half of our patients did not experience any respiratory event and not all patients received an opioid postoperatively. It is likely that more benefit

and less harm (*e.g.,* disruptions because of alarm artefacts) could be achieved if the monitor was tested in a population at intrinsically higher risk for postoperative respiratory events (e.g. patients receiving parenteral opioids).

Given all of the above, we suggest that future studies of continuous respiratory monitoring focus on devices using algorithms that rely on multiple parameters and that most benefit is to be expected in general surgical wards in patients that are expected to be at a high risk of AREs.

In conclusion, the use of the IPI monitor in postoperative patients did not result in a reduction of the number of patients experiencing adverse respiratory events, compared to standard clinical care. However, use of the IPI monitor did lead to an increase in the number of nurse interventions and a decrease in the number and duration of respiratory events in patients that experienced postoperative AREs.

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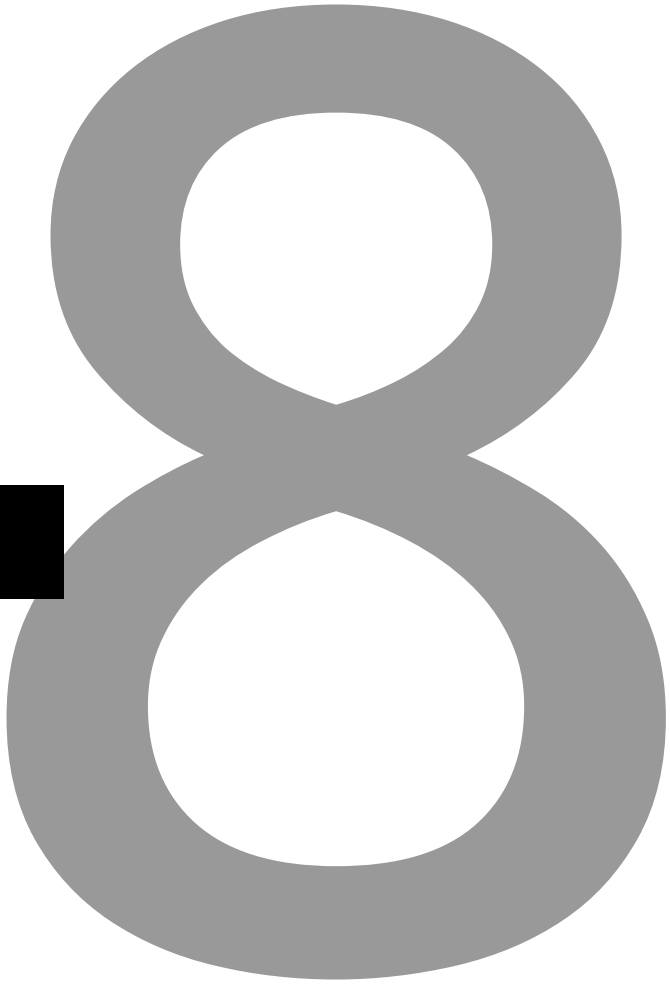
CHAPTER 8



Summary and Conclusions

Summary

In **Section 1**, two new monitors of analgesia were presented. Both rely on parameters that reflect activation of the autonomic nervous system to provide a measure of nociception. Their ability to differentiate between states of nociception and non-nociception was assessed.

Chapter 2 introduced a new method for the detection of nociceptive events by quantifying skin blood flow dynamics using a miniaturized dynamic light scattering (mDLS) sensor. With this technology, light emitted by a laser beam is scattered by moving red blood cells in the skin's microcirculation. From the resultant speckle pattern, a hemodynamic index (HI) can be derived that contains information about the size, pulsatility and blood flow velocity of the cutaneous blood vessels. HI's are directly related to autonomic activity. In order to test the relationship between HI's and nociception, 17 healthy volunteers (10 women/7 men) were subjected to four 30 second electrical and heat pain stimuli with two mDLS sensors positioned on the palmar aspect of each index finger. The nociceptive stimuli were given in random order and calculated to correspond with estimated numerical rating scores (NRS) of 1, 4, 6 and 9. The difference between response and baseline relative HI (a normalized HI) values were calculated. During noxious stimulation, at all stimulus intensities, an increase in relative flow of the smaller non-pulsatile vessels (SVR) and a decrease in relative flow of the larger pulsatile vessels (LVR) was observed, with a rapid return to baseline once the stimulus was terminated. Noxious stimulation at maximum intensity did not lead to a significant change in heart rate from baseline.

These findings indicate that skin blood flow related parameters can be used to detect noxious events and that they may outperform clinically used parameters such as heart rate. The reduction in skin perfusion and redistribution of skin blood flow from pulsatile to non-pulsatile vessels is likely related to vasoconstriction of the arterioles of the skin secondary to autonomous nervous system activation.

The mDLS sensor described in Chapter 2 was tested in an experimental setting using healthy volunteers and without the use of anesthetic agents . In contrast, **Chapter 3** described the validation of a new index of nociception in patients under total intravenous propofol-remifentanil anesthesia and using clinically relevant noxious stimuli. The Nociception Level (NoL) is a multiparameter, nonlinear combination of heart rate (HR); heart rate variability (HRV); amplitude of the finger photoplethysmogram (AP); skin conductance level; fluctuations in skin conductance; and their time derivatives, derived from random forest regression and scaled from 0 to 100 to produce a dimensionless value for the NoL. 72 patients (39 women/33 men) were randomized to one of six possible remifentanil target concentrations (0/1/2/3/4/5 ng/ml). Mean arterial pressure (MAP), HR,

Bispectral Index (BIS) and NoL values before and after three distinct noxious events (non-noxious; moderate/incision; severe/intubation) were measured. ΔNoL outperformed all variables in the ability to discriminate between noxious and non-noxious events (AUC 0.95; CI 0.91 – 0.99. $p = 0.0003$ *vs.* ΔHR; $P < 0.0001$ *vs.* ΔMAP; $p < 0.0001$ *vs.* HR; $p = 0.00004$ *vs.* MAP). A cutoff value of 16 yielded a specificity and sensitivity of 80% and 73%. In the absence of noxious stimuli, NoL was not correlated to remifentanil concentration, whereas MAP and HR decreased significantly with increasing remifentanil concentrations under all conditions.

These findings suggest that the use of multiple signals of autonomic activity for the detection of nociception may yield greater sensitivity and specificity than the use of single parameters.

Section 2 confirmed earlier work on the effect of non-depolarizing neuromuscular blocking drugs on the ventilatory response to hypoxia as mediated by the carotid bodies and addressed the implications of this effect for neuromuscular monitoring and reversal strategies.

In **Chapter 4**, rocuronium, a non-depolarizing aminosteroid neuromuscular blocking drug (NMBD) that acts as an acetylcholinereceptor antagonist at the neuromuscular junction, was given to 40 healthy and awake volunteers, titrated to obtain a Train-of-Four (TOF) ratio of 0.7 at the adductor pollicis muscle. The subjects' ventilatory responses to hypoxia (Acute Hypoxic Response or AHR) and hypercapnia (Hypercapnic Ventilatory Response or HCVR) were then obtained by having the subjects alternately breathe mixtures of hypoxic or hypercarbic air. These measurements were compared to AHR and HCVR values obtained at baseline and following neuromuscular block reversal by either placebo, neostigmine/atropine, or sugammadex in a randomized manner. From this, we derived the carotid body index (F), which represents the effect of neuromuscular blocking agents on the ventilatory response to hypoxia mediated solely by the carotid bodies. At a TOF ratio of 0.7, the iscocapnic hypoxic response was blunted by 42% whereas hypercapnic ventilation was depressed by just 11% ($F = 0.67$). Reversal of the neuromuscular block to a TOF of 1.0, indicating full reversal at the neuromuscular junction, did not result in full return of the AHR to baseline values, irrespective of reversal strategy.

These findings confirm the antagonist activity of non-depolarizing neuromuscular blocking drugs at the acetylcholine receptors in the glomus cells of the carotid bodies at clinically relevant plasma concentrations. Furthermore, these findings suggest that reversal of acetylcholinereceptor antagonism occurs more slowly in the glomus cells than at the neuromuscular junction. Monitoring return of neuromuscular function by TOF ratio

at the adductor pollicis muscle may therefore overestimate a patient's capacity to increase their ventilation in response to hypoxia.

Section 3 introduced two respiratory monitors. These were used in different patient populations to assess the incidence of adverse respiratory events in the postoperative period. Additionally, the effect of the use of a smart algorithm-based respiratory monitor on the incidence of and response to adverse respiratory events in postoperative patients was evaluated.

Chapter 5 described a multicenter observational study in which the Respi8, a continuous respiratory rate (RR) monitor developed to measure RR based on the humidity of exhaled air, was used to quantify the occurrence of postoperative respiratory events. 80 postoperative patients aged 60 years or older were monitored by the Respir8 in the first 6 postoperative hours, both in the post anesthesia care unit (PACU) (mean time of admission 120 min) and on the surgical ward. 78% of patients experienced at least one bradypneic event (defined as a RR of 1-6 breaths/min), with a median of 10 bradypneic events per patient and a median duration of 1.4 minutes. 57% of patients experienced at least one apneic event, defined as an absence of inspiratory air flow at the mouth for at least 1 min, with a median of 3 apneic events per patient and a median duration of 1.6 minutes. None of these events required an intervention. The occurrence of apneic and bradypneic events in the PACU was predictive of events on the ward (r^2=0.4, $p < 0.001$ for bradypnea and r^2= 0.2, $p < 0.001$ for apnea). There was a weak correlation between total morphine dose and number of events occurring in the PACU, but not on the ward (r^2= 0.2, $p <0.05$ for bradypnea and r^2= 0.3, $p <0.05$ for apnea). However, total opioid administration was low, with only 51% of patients receiving any intravenous morphine for pain relief in the PACU (mean dose 9.3 mg) and only 5.9% of patients receiving any opioid on the ward.

These findings indicate that the frequency of early respiratory events in an older postoperative patient population is high, although the severity of these events was low in this study, possibly because of the minimal use of opioids once patients were discharged to the ward. Additionally, this study indicates that when patients exhibit respiratory events in the PACU, they may be at increased risk of further events after discharge and therefore, continuous respiratory monitoring is advised.

Where the Respi8 monitor described in Chapter 5 is a monitor that measures only a single parameter of respiratory status, **Chapter 6** presented a respiratory monitor that uses an artificially intelligent algorithm that combines the real-time measures of four parameters: end-tidal CO_2 (etCO2), RR, pulse rate (PR) and oxygen saturation (SpO_2). The resultant Integrated Pulmonary Index™ (IPI) represents a patient's respiratory status in a single value on a scale from 1-10. In order to determine the incidence of postoperative

respiratory events, IPI measurements were recorded continuously and blindly in the PACU in 40 postoperative patients for an average of 17 hours per patient (13 -22 hours). 5.8% of measurements were missing (i.e. due to sensor errors). 39 of the 40 patients (97,5%) experienced at least one critical IPI event (defined as an IPI of 1 – 4, which require intervention). In 3 patients, the IPI monitor reported IPI values ≤ 4 in more than 15% of the measurement time. The majority of patients (77.5%) received intravenous opioids for pain relief, however, no correlation between opioid administration and events was found. Due to the observational nature of the study, the number and nature of interventions to improve respiratory status were not recorded. No serious adverse events occurred.

These findings indicate that adverse respiratory events occur in a majority of postoperative patients that receive general anesthesia with opioid analgesia, although again, the severity of these events seems limited.

Chapter 5 and Chapter 6 described two observational studies that used non-invasive respiratory monitors to identify early adverse respiratory events in postoperative patients. Although events occurred frequently, they were not serious . In both chapters, the monitors were used only to identify respiratory events retroactively and not to guide interventions or improve patient respiratory status. Therefore, in **Chapter 7**, the data acquired from Chapter 6 were used to design an interventional study, to assess the effect of IPI monitoring on the incidence of and response to respiratory events.

In this study, 80 postoperative PACU patients were randomized to standard care (which consisted of continuous respiratory rate and pulse oximetry monitoring) or respiratory monitoring via continuous IPI measurements. In the IPI group, nurses performed interventions to improve respiratory condition when IPI was 1 for a minimum of 30 seconds. The standard care group received interventions based on RR or SpO_2, as per usual. All patients were monitored until 8 am on the first postoperative day. Adverse respiratory events (ARE's) were defined as an IPI of 1 for greater than 30 seconds due either to hypoxia or due to bradypnea or apnea and with associated signs of sympathetic activity (increased PR) or hypoxia. ARE's occurred in 47% of all patients (40% in the IPI group vs. 53% in the standard care group, $p = 0.218$). Overall, use of the IPI monitor led to an increase in the number of respiratory interventions (13 interventions for 265 events in the standard care group versus 39 interventions for 72 events in the IPI group, $p < 0.00001$). Although this did not lead to a reduction in the number of patients that experienced an ARE, it did cause a significant reduction in the number and duration of events per patient. In the standard care group, nurses did not succeed in identifying patients experiencing respiratory depression in the presence of supplemental oxygen. Importantly, 61% of IPI alarms consisted of artefacts, which caused considerable alarm fatigue.

These findings show that use of a respiratory monitor in the early postoperative period can lead to altered decision-making by nurses, hereby reducing the amount of time patients spend in a state of potential respiratory compromise. However, when the number of false positive alarms is high, it can significantly affect implementation into clinical practice.

Implications for clinical practice and future research

The studies described in Section 1 indicate that there is a wide range of parameters that reflect activation of the autonomic nervous system that can be used to differentiate between noxious and non-noxious events. Monitoring modalities that combine a variety of these parameters are more likely to have increased specificity and sensitivity compared to classically used single parameters such as heart rate and blood pressure. Multiparameter indices, like the NoL, may also be less likely to be influenced by the hemodynamic effects of anesthetic agents and vasoactive drugs.

The question remains whether the use of monitors of nociception leads to changes in intraoperative opioid administration and, via optimized opioid titration, to improved clinical outcomes. A recent systematic review(1) of randomized controlled trials that compared nociception-guided anesthesia to standard practice was inconclusive, mostly because of the paucity of data. The nociception monitor that was most investigated was the surgical plethysmographic index (SPI), a multiparameter index based on the photoplethysmographic analysis of the pulse wave and the heart beat interval. Pooled analysis of these studies showed an 8% reduction in intraoperative opioid consumption. Another study(2) found that using the NoL to guide intraoperative opioid administration resulted in a 28% reduction of remifentanil consumption and a trend towards improved hemodynamic stability. It seems likely that monitors of nociception do not lead to a reduction of intraoperative opioid consumption *per se*, but rather, that they enable the administration of the right amount of opioid at the right time. Further and larger studies are needed to assess any effect this may have on relevant postoperative outcomes, such as pain, adverse respiratory events, acute kidney injury and or myocardial injury.

The study described in **Section 2** is the first to show that reversal of NMBD effect at the peripheral chemoceptors seems to occur more slowly than at the neuromuscular junction. Although the reason for this is unknown, a possible explanation can be found in different dose-response relationships for neuronal or muscle-type nicotinic acetylcholine receptors . Where the muscle type receptors of the neuromuscular junction require up to 75% occupancy for a detectable reduction in twitch tension, neuronal receptors are blocked in a dose-dependent manner(3). In clinical practice, NMBD effect is monitored by measuring TOF, which represents the activity of NMBD's at the neuromuscular junction.

Current monitoring practices may therefore overestimate a patient's capacity to increase their ventilation in response to hypoxia, even when resting ventilation appears adequate. The depression of hypoxic ventilatory drive may be exacerbated by the residual effects of other anesthetics such as opioids, volatile or intravenous anesthetics, which have all been shown to depress chemoreflex function(4). Full recovery of neuromuscular function, defined as a TOF ratio of 1.0, must be considered a '*sine qua non*—an absolutely necessity, but not of itself a sufficient criterion—'(5) for termination of anesthesia. Future studies should aim to determine the temporal profile of reversal of NMBD effect at the carotid bodies, as well as the magnitude of possible interactions with other anesthetic agents. Development of new neuromuscular blocking drugs should focus on antagonists that have a specific affinity for muscle type nicotinic acetylcholine receptors.

We have shown in **Section 3** that disturbances in ventilation and oxygenation that can be identified by a non-invasive respiratory monitor occur frequently in postoperative patients. The clinical relevance of these events remains questionable. Although signs of respiratory depression were common, no patient experienced serious harm. We know from the literature however, that in some patients, the presence of respiratory depression can lead to a cascade of events ending in severe brain injury and death(6). The risk factors for this are numerous and not present in all patients that go on to develop serious injury. Conversely, some patients in which multiple risk factors are present do not experience respiratory events at all. This is confirmed by the studies in Section 3, in which roughly half the patient population did not experience any events, irrespective of the presence of risk factors or the use of opioids. Once patients did experience an event however, they were more likely to experience several. An explanation for this may be that there is considerable variability in ventilatory chemoreflexes between individuals. The genetic basis for this has not yet been elucidated(7). We must therefore accept that predicting which patients are at risk of ARE's *prior* to surgery and admitting them to a high care facility for the first 24 postoperative hours, as is now common practice, is not a helpful strategy. It diverts finite resources to patients who may not end up requiring them, while at the same time running the risk of missing the patients that will go on to develop serious injury. A more pragmatic approach would be to identify patients that experience ARE's once they are in the PACU. These may then be transferred to a high care facility or, more ideally, they may be sent to the surgical ward with some form of continuous respiratory monitoring. From our research, we would suggest a monitoring modality which uses multiple parameters, and urge against relying solely on pulse oximetry, especially in the presence of supplemental oxygen administration. We've seen however, that even multiparameter algorithms are currently prone to produce an unacceptably high rate of false positive alarms. With further technological development, artificially intelligent systems may be designed that recognize ventilatory patterns that are more likely to lead to serious injury over time. Alternatively,

closed loop systems may be able to intervene without nurse involvement. Future research should evaluate the safety and cost-effectiveness of such monitoring strategies.

Conclusions

From the data presented in this thesis, the following conclusions may be drawn:

1) Skin blood flow related parameters can be used to detect noxious events and may outperform clinically used parameters such as heart rate.
2) The use of multiple signals of autonomic activity for the detection of nociception yields greater sensitivity and specificity than the use of single parameters and may be less affected by the hemodynamic effects of anesthetic agents.
3) Rocuronium exhibits antagonist activity at the acetylcholine receptors in the glomus cells of the carotid bodies at clinically relevant plasma concentrations.
4) Reversal of rocuronium- induced neuromuscular block by placebo, neostigmine or sugammadex occurs more slowly in the glomus cell than at the neuromuscular junction.
5) Monitoring return of neuromuscular function by train-of-four ratio at the m. adductor pollicis can overestimate a patient's capacity to increase ventilation in response to hypoxia.
6) Disturbances in ventilation and/or oxygenation that can be identified by a non-invasive respiratory monitor occur frequently in postoperative patients.
7) The use of a non-invasive respiratory monitor in postoperative patients can lead to altered decision-making by ward nurses, which in turn can affect the frequency and duration of these respiratory disturbances.

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CHAPTER 9

9

Samenvatting en Conclusies

Samenvatting

In **Deel 1** werden twee nieuwe nociceptie monitors gepresenteerd. Beide gebruiken parameters die activatie van het autonome zenuwstelsel weergeven om tot een maat voor nociceptie te komen. Het vermogen van deze monitors om onderscheid te maken tussen momenten van nociceptie en niet-nociceptie werd beoordeeld.

Hoofdstuk 2 introduceerde een nieuwe methode voor de detectie van nociceptie door fluctuaties in de bloeddoorstroming van de huid te kwantificeren met behulp van een geminiaturiseerde 'dynamic light scattering' (mDLS) sensor. Bij deze technologie wordt het licht van een laserstraal verstrooit door passerende rode bloedcellen in de microcirculatie van de huid. Uit het resulterende 'speckle' patroon kan een hemodynamische index (HI) worden afgeleid die informatie bevat over de grootte, de pulsatiliteit en de stroomsnelheid van het bloed in deze vaten. HI's zijn direct gerelateerd aan autonome activiteit. Om de relatie tussen HI's en nociceptie te testen, werden 17 gezonde vrijwilligers (10 vrouwen/7 mannen) onderworpen aan vier elektrische en warmte pijnprikkels van 30 seconden, met twee mDLS sensoren gepositioneerd op de palmaire zijde van elke wijsvinger. De pijnprikkels werden in willekeurige volgorde gegeven en berekend om te corresponderen met geschatte 'numerical rating scores' (NRS) van 1, 4, 6 en 9. Het verschil tussen respons en uitgangs-HI waarden werd berekend. Bij alle stimulus intensiteiten werd tijdens de pijnprikkel een toename gezien van de relatieve doorstroming van de kleinere niet-pulsatiele bloedvaten (SVR) en een afname van de relatieve doorstroming van de grotere pulsatiele bloedvaten(LVR), met een snelle terugkeer naar de uitgangssituatie zodra de stimulus eindigde. Pijnprikkels van een maximale intensiteit leidden niet tot een significante verandering in de hartfrequentie.

Deze bevindingen geven aan dat aan de doorbloeding van de huid gerelateerde parameters kunnen worden gebruikt om nociceptieve gebeurtenissen te detecteren. Ook lijken er aanwijzingen te bestaan dat deze parameters beter presteren dan klinisch gebruikte parameters zoals hartslag. De afname van de huidperfusie en herverdeling van de bloedstroom van pulsatiele naar niet-pulsatiele bloedvaten is waarschijnlijk gerelateerd aan vasoconstrictie van de arteriolen van de huid secundair aan autonome activatie van het zenuwstelsel.

De mDLS-sensor beschreven in hoofdstuk 2 werd getest in een experimentele omgeving met behulp van gezonde vrijwilligers en zonder het gebruik van anesthetica. **Hoofdstuk 3**, daarentegen, beschreef de validatie van een nieuwe nociceptieve index bij patiënten die totale intraveneuze propofol-remifentanil anesthesie ondergingen en met het gebruik van klinisch relevante pijnprikkels. De Nociception Level (NoL) is een multiparameter, niet-lineaire combinatie van hartslag (HR); hartslagvariabiliteit (HRV); amplitude van het vinger

photoplethysmogram (AP); mate van huidgeleiding; schommelingen in huidgeleiding; en de tijdderivaten van deze parameters, afgeleid door middel van random forest regressie analyse en geschaald van 0 tot 100 om een dimensieloze waarde te produceren. 72 patiënten (39 vrouwen/33 mannen) werden gerandomiseerd naar één van zde es mogelijke remifentanil-targetconcentraties (0/1/2/3/4/5 ng/ml). Gemiddelde arteriële bloeddruk (MAP), HR, Bispectral Index (BIS) en NoL waarden werden gemeten voor en na drie verschillende pijnlijkprikkels (niet-pijnlijk; matig/incisie; ernstig/intubatie). ΔNoL presteerde beter dan alle andere variabelen wat betreft het vermogen onderscheid te maken tussen nociceptieve en niet-nociceptieve gebeurtenissen (AUC 0,95; 0,91 – 0,99. p = 0,0003 vs. ΔHR; P < 0,0001 vs. ΔMAP; p < 0,0001 vs. HR; p = 0,00004 vs. MAP). Een afkapwaarde van 16 leverde een specificiteit en sensitiviteit van 80% en 73%. Bij afwezigheid van pijnlijke stimuli was NoL niet gecorreleerd aan de remifentanil concentratie, terwijl MAP en HR significant daalden bij toenemende remifentanil concentraties onder alle omstandigheden.

Deze bevindingen suggereren dat het gebruik van meerdere signalen van autonome activiteit voor de detectie van nociceptie een grotere sensitiviteit en specificiteit kan opleveren dan het gebruik van afzonderlijke parameters. Indices gebaseerd op meerdere parameters lijken ook minder te worden beïnvloed door de hemodynamische effecten van anesthetica.

Deel 2 bevestigde eerder werk naar het effect van niet-depolariserende spierverslappers op de door de carotis lichaampjes gemedieerde ventilatoire respons op hypoxie en ging in op de implicaties van dit effect voor neuromusculaire monitoring en antagoneer strategieën.

In **Hoofdstuk 4** werd rocuronium, een niet-depolariserende spierverslapper (NMBD) die fungeert als een acetylcholinereceptor antagonist op de neuromusculaire overgang, toegediend aan 40 gezonde en wakkere vrijwilligers en getitreerd om een Train-of-Four (TOF) ratio van 0.7 aan de m. adductor pollicis te verkrijgen. De ventilatoire respons op hypoxie (Acute Hypoxic Response of AHR) en hypercapnie (Hypercapnic Ventilatory Response of HCVR) werd vervolgens verkregen door de proefpersonen afwisselend hypoxische of hypercapnisch gasmengsels te laten inademen. Deze metingen werden op gerandomiseerde wijze vergeleken met de uitgangs- AHR en HCVR en na omkering van het neuromusculaire blok door placebo, neostigmine / atropine of sugammadex. Hieruit hebben we de carotid body index (F) afgeleid. Deze vertegenwoordigt het effect van NMBD's op de ventilatoire respons op hypoxie die uitsluitend door de carotis lichaampjes wordt gemedieerd. Bij een TOF-ratio van 0.7 was de iscocapische hypoxische respons met 42% verminderd, terwijl hypercapische ventilatie met slechts 11% verminderde (F = 0.67). Omkering van het neuromusculaire blok naar een TOF van 1.0, wat duidt op volledig antagonisme van het NMBD effect

op het niveau van de neuromusculaire overgang, resulteerde niet in een volledige terugkeer van de AHR naar de uitgangswaarden, ongeacht de omkeringsstrategie.

Deze bevindingen bevestigen het antagonerend effect van niet-depolariserende spierverslappers op de acetylcholinereceptoren in de glomuscellen van de carotis lichaampjes bij klinisch relevante plasmaconcentraties. Bovendien suggereren deze bevindingen dat het opheffen van de activiteit van niet-depolariserende spierverslappers op acetylcholinereceptoren langzamer verloopt in de glomus cellen dan bij de neuromusculaire overgang. Monitoring van het herstel van de neuromusculaire functie door middel van het meten van de TOF ratio aan de m. adductor pollicis kan daarom het vermogen van een patiënt om de ventilatie in hypoxische omstandigheden te verhogen overschatten.

Deel 3 introduceerde twee non-invasieve ademhalingsmonitors. Deze werden gebruikt in verschillende patiëntpopulaties om de incidentie van respiratoire events (adverse respiratory events (ARE)) in de postoperatieve periode te beoordelen. Daarnaast werd het effect van het gebruik van een op een kunstmatig intelligent algoritme gebaseerde ademhalingsmonitor op de incidentie van en de respons op respiratoire events bij postoperatieve patiënten geëvalueerd. **Hoofdstuk 5** beschreef een multicenter observationele studie waarbij de Respi8, een continue respiratoire monitor ontwikkeld om ademhalingsfrequentie (RR) te meten op basis van de vochtigheid van de uitgeademde lucht, werd gebruikt om het optreden van postoperatieve respiratoire events te kwantificeren. Bij 80 postoperatieve patiënten van 60 jaar of ouder werd in de eerste 6 postoperatieve uren de Respir8 aangesloten, zowel op de verkoever (Post Anesthesia Care Unit of PACU) (gemiddelde opnametijd van 120 min) als op de chirurgische afdeling. 78% van de patiënten maakte op zijn minst een episode van bradypnoe mee (gedefinieerd als een RR van 1-6 ademhalingen/min), met een mediaan van 10 bradypneu's per patiënt en een mediane duur van 1,4 minuten. Bij 57% van de patiënten werd ten minste één apneu, gedefinieerd als een afwezigheid van een inspiratoire luchtstroom bij de mond gedurende ten minste 1 minuut, met een mediaan van 3 apneu's per patiënt en een mediane duur per apneu van 1,6 minuten. Geen van deze events vereiste een interventie. Het optreden van apneu's en bradypneu's op de PACU was voorspellend voor respiratoire events op de afdeling ($r2=0,4$, $p < 0,001$ voor bradypneu's en $r2= 0,2$, $p < 0,001$ voor apneu's). Er was een zwakke correlatie tussen de totale morfinedosis en het aantal events op de PACU, maar niet op de afdeling ($r2= 0,2$, $p <0,05$ voor bradypnea en $r2= 0,3$, $p <0,05$ voor apneu). De totale toediening van opioïden was echter laag, waarbij slechts 51% van de patiënten intraveneuze morfine kregen voor pijnbestrijding op de PACU (gemiddelde dosis 9,3 mg) en slechts 5,9% van de patiënten op de afdeling opioïden toegediend kregen.

Deze bevindingen geven aan dat vroege respiratoire events bij een oudere postoperatieve patiëntpopulatie frequent voorkomen, hoewel de ernst van de voorvallen meeviel in deze studie, mogelijk vanwege het minimale gebruik van opioïden bij patiënten op de afdeling. Bovendien geeft deze studie aan dat wanneer patiënten respiratoire problemen in de PACU vertonen, ze na ontslag een verhoogd risico op verdere events kunnen hebben, waarvoor verdere bewaking raadzaam lijkt.

Waar de in Hoofdstuk 5 beschreven Respi8-monitor een monitor is die slechts één aan de ademhaling gerelateerde parameter meet, presenteerde **Hoofdstuk 6** een ademhalingsmonitor die gebruik maakt van een kunstmatig intelligent algoritme op basis van real-time metingen van vier parameters: end-tidal CO2 (etCO2), RR, pols frequentie (PR) en arteriële zuurstofsaturatie (SpO_2). De resulterende Integrated Pulmonary Index™ (IPI) vertaalt de ademhalingstoestand van een patiënt naar één waarde op een schaal van 1 tot 10. Om de incidentie van postoperatieve respiratoire events te bepalen, werden IPI-metingen in de PACU continu en blind geregistreerd bij 40 postoperatieve patiënten gedurende een opname van gemiddeld 17 uur per patiënt (13 -22 uur). 5,8% van de metingen ontbrak (als gevolg van foutmetingen). Bij 39 van de 40 patiënten (97,5%) werd ten minste één kritieke IPI-gebeurtenis (gedefinieerd als een IPI van 1 – 4, waarvoor interventie nodig is) geregistreerd. Bij 3 patiënten rapporteerde de IPI-monitor IPI-waarden ≤ 4 gedurende meer dan 15% van de meet tijd. Een meerderheid van de patiënten (77,5%) ontving intraveneuze opioïden voor pijnbestrijding, er werd echter geen correlatie gevonden tussen opiaattoediening en het optreden van respiratoire events. Vanwege het observationele karakter van de studie werden het aantal en de aard van de interventies om de respiratoire conditie te verbeteren niet geregistreerd. Er deden zich geen ernstige complicaties voor.

Deze bevindingen geven aan dat respiratoire events optreden bij een meerderheid van de postoperatieve patiënten die algemene anesthesie met opioïde analgesie ontvangen, hoewel ook nu weer de ernst van deze voorvallen beperkt bleef.

Hoofdstuk 5 en Hoofdstuk 6 beschreven twee observationele studies die niet-invasieve ademhalingsmonitoren gebruikten om vroege respiratoire events bij postoperatieve patiënten te identificeren. Hoewel respiratoire events vaak voorkwamen, waren ze niet ernstig van aard. In beide hoofdstukken werden de monitors alleen gebruikt om respiratoire events met terugwerkende kracht te identificeren en niet om interventies ter verbetering van de respiratoire conditie van de patiënt te initiëren. Daarom werden in **Hoofdstuk 7** de in Hoofdstuk 6 vergaarde data gebruikt voor het ontwerp van een interventionele studie, waarbij het effect van IPI-monitoring op de incidentie van en de reactie op respiratoire events te evalueren. In deze studie werden 80 postoperatieve PACU-patiënten gerandomiseerd naar standaardzorg (die bestond uit continue monitoring van

de ademhalingsfrequentie en de zuurstofsaturatie) versus respiratoire bewaking door middel van continue IPI-metingen. In de IPI-groep voerden verpleegkundigen interventies uit om de respiratoire conditie te verbeteren wanneer de IPI minimaal 30 seconden 1 was. De standaard zorg groep kreeg, zoals gebruikelijk, interventies op basis van RR en SpO_2. Alle patiënten werden bewaakt tot 08.00 uur op de eerste postoperatieve dag. Respiratoire events (ARE's) werden gedefinieerd als een IPI van 1 gedurende meer dan 30 seconden als gevolg van 1) hypoxie of 2) bradypneu of apneu en met bijbehorende tekenen van sympathische activiteit (verhoogde PR) of hypoxie. ARE's traden op bij 47% van alle patiënten (40% in de IPI-groep vs. 53% in de standaard zorggroep, $p = 0,218$). Over het geheel genomen leidde het gebruik van de IPI-monitor tot een toename van het aantal respiratoire interventies (13 interventies per 265 events in de standaardzorggroep versus 39 interventies per 72 events in de IPI-groep, $p < 0,00001$). Hoewel dit niet leidde tot een vermindering van het aantal patiënten bij wie een ARE optrad, leidde dit wel tot een significante vermindering van het aantal en de duur van de events per patiënt. In de standaard zorggroep slaagden verpleegkundigen er niet goed in om patiënten met tekenen van ademhalingsdepressie te identificeren wanneer de patiënten zuurstof kregen toegediend. Opmerkelijk was dat 61% van de IPI-alarmen bestond uit artefacten, wat onder verpleegkundigen een aanzienlijke alarmmoeheid veroorzaakte.

Deze bevindingen tonen aan dat het gebruik van een respiratoire monitor in de vroege postoperatieve periode kan leiden tot gewijzigde besluitvorming door verpleegkundigen, waardoor de tijd die patiënten doorbrengen in een potentieel respiratoir bedreigde toestand verminderd is. Echter, wanneer het aantal vals-positieve alarmen hoog is, kan dit de implementatie in de klinische praktijk aanzienlijk beïnvloeden.

Implicaties voor de klinische praktijk en toekomstig onderzoek

De in **Deel 1** beschreven studies laten zien dat er een breed scala aan parameters bestaat die activatie van het autonome zenuwstelsel reflecteren en die kunnen worden gebruikt om onderscheid te maken tussen nociceptieve en niet-nociceptieve momenten. Monitoringsmodaliteiten die meerdere van deze parameters combineren hebben een grotere sensitiviteit en specificiteit in vergelijking met klassiek gebruikte afzonderlijke parameters zoals hartfrequentie en bloeddruk. Multiparameter indices, zoals de NoL, worden mogelijk ook minder beïnvloed door de hemodynamische effecten van anesthetica en vasoactieve middelen.

Het blijft de vraag of het gebruik van nociceptie monitors leidt tot veranderingen in het intra-operatief gebruik van opioïden en, via geoptimaliseerde opioïd titratie, tot een verbetering van klinische uitkomsten. Een recente systematische review(1) van gerandomiseerde en gecontroleerde studies waarin nociceptie-geleide anesthesie werd vergeleken met de standaard praktijk was niet conclusief, met name vanwege de schaarste

aan data. De meest onderzochte nociceptie monitor was de 'surgical plethysmographic index' (SPI), een multiparameter index gebaseerd op de photoplethysmografische analyse van de polsgolf en het hartslaginterval. Een analyse van samengevoegde data van deze studies toonde een afname van 8% van het intra-operatief opioïd gebruik. Een andere studie(2) wees uit dat het gebruik van de NoL voor nociceptie-gestuurde opioïdtoediening resulteerde in een vermindering van 28% van de remifentanil consumptie en een trend naar meer hemodynamische stabiliteit. Het lijkt waarschijnlijk dat nociceptie monitors niet leiden naar een afname van de intra-operatieve opioïd consumptie op zich, maar dat ze de toediening van de juiste hoeveelheid opioïd op het juiste moment faciliteren. Toekomstige, grotere studies zijn nodig om iets te kunnen concluderen over de eventuele effecten op relevante postoperatieve uitkomsten, zoals pijn, respiratoire events, het optreden van 'acute kidney injury' (AKI) of het optreden van mycocardiale schade.

Het in **Deel 2** beschreven onderzoek is het eerste dat aantoont dat antagonisme van het effect van NMBD's op de perifere chemoceptoren langzamer verloopt dan antagonisme van het effect op de neuromusculaire overgang. Hoewel de reden hiervoor onbekend is, kan een mogelijke verklaring worden gevonden in de verschillende dosis-responsrelaties voor neuronale of spier-type nicotinerge acetylcholinereceptoren. Waar de spiertype receptoren van de neuromusculaire overgang tot 75% bezetting vereisen voor een waarneembare vermindering van spiertrekkingen, worden neuronale receptoren op een dosisafhankelijke wijze geblokkeerd(3). In de klinische praktijk wordt het effect van NMBD-effect gemonitord door de TOF te meten, hetgeen alleen het effect van NMBD's op de neuromusculaire overgang vertegenwoordigt. De huidige monitoringsstrategieën kunnen daarom het vermogen van een patiënt overschatten om zijn ventilatie te doen toenemen in reactie op hypoxie, zelfs als de ventilatie onder normale omstandigheden adequaat lijkt. Onderdrukking van de hypoxische ventilatoire respons kan verder worden verergerd door de resterende effecten van andere intra-operatief toegediende middelen waarvan is aangetoond dat zij allen de perifere chemoreflex kunnen onderdrukken, zoals opioïden, dampvormige of intraveneuze anesthetica(4). Volledig herstel van de neuromusculaire functie, gedefinieerd als een TOF-ratio van 1.0, moet worden beschouwd als een ' *sine qua non* - een absolute noodzaak, maar op zichzelf niet een toereikend criterium'(5) voor het beëindigen van de anesthesie. Toekomstige studies moeten gericht zijn op het bepalen van het tijdsbeloop van antagonisme van het NMBD-effect op de perifere chemoceptoren, evenals op de mate van mogelijke interacties met andere anesthetica. De ontwikkeling van nieuwe spierverslappers moet gericht zijn op antagonisten die een specifieke affiniteit hebben voor spier-type nicotinerge acetylcholinereceptoren.

In **Deel 3** werd aangetoond dat verstoringen in ventilatie en oxygenatie die kunnen worden gedetecteerd door een niet-invasieve respiratoire monitor vaak voorkomen bij postoperatieve patiënten. De klinische relevantie van deze gebeurtenissen blijft

twijfelachtig. Hoewel er vaak aanwijzingen waren voor het optreden van ventilatoire depressie, ondervond geen enkele patiënt ernstige schade. We weten echter uit de literatuur dat bij sommige patiënten de aanwezigheid van ventilatoire depressie kan leiden tot een cascade van gebeurtenissen met ernstig hersenletsel en overlijden tot gevolg(6). De risicofactoren hiervoor zijn talrijk en niet altijd aanwezig bij patiënten met een slechte uitkomst. Omgekeerd maken sommige patiënten met meerdere risicofactoren helemaal geen respiratoire events door. Dit zien we ook in de studies in sectie 3, waarin bij grofweg de helft van de patiëntenpopulatie geen respiratoire verstoringen optrad, ongeacht de aanwezigheid van risicofactoren of het gebruik van opioïden. Zodra er bij een patiënt echter sprake is van een respiratoir event, lijkt de kans op een volgend event toe te nemen. Een verklaring hiervoor kan mogelijk gevonden worden in de aanzienlijke interindividuele variabiliteit van de perifere chemoreflex. De genetische basis hiervoor is nog niet opgehelderd(7).

We moeten daarom accepteren dat het identificeren van patiënten die risico lopen op respiratoire events *voorafgaand* aan een operatie, om hen de eerste 24 postoperatieve uren, zoals nu gebruikelijk is, op een bewaakte afdeling op te nemen, geen nuttige strategie is. Het leidt tot de inzet van schaarse middelen bij patiënten die ze misschien niet nodig hebben, terwijl tegelijkertijd het risico wordt gelopen patiënten te missen die ernstig letsel kunnen oplopen. Een meer pragmatische benadering zou zijn om patiënten bij wie respiratoire events optreden postoperatief te identificeren wanneer ze op de verkoeverkamer zijn. Deze patiënten kunnen vervolgens worden overgeplaatst naar een bewaakte afdeling of, idealiter, naar de chirurgische verpleegafdeling met een vorm van continue respiratoire monitoring. Op basis van onze ervaringen bij het uitvoeren van de studies in sectie 3 zouden we een monitoringmodaliteit voorstellen die gebruik maakt van meerdere parameters. Ook raden we aan om niet uitsluitend te vertrouwen op het monitoring middels een polsoximeter , vooral bij patiënten die zuurstof toegediend krijgen. We hebben echter gezien dat zelfs algoritmen met meerdere parameters momenteel geneigd zijn om een onaanvaardbaar hoog aantal valse positieve alarmen te produceren. Met verdere technologische ontwikkelingen zouden kunstmatig intelligente systemen kunnen worden ontworpen, die ademhalingspatron*en* herkennen die na verloop van tijd kunnen ontaarden in ernstig letsel. Als alternatief kunnen 'closed loop' monitors ontworpen worden die ingrijpen zonder tussenkomst van een verpleegkundige. Toekomstig onderzoek moet de veiligheid en kosteneffectiviteit van dergelijke monitoringstrategieën evalueren.

Conclusies

Uit de gegevens die in dit proefschrift gepresenteerd worden kunnen de volgende conclusies worden getrokken:

1. Parameters gerelateerd aan de bloedflow in de huid kunnen worden gebruikt om nociceptieve events te detecteren en presteren mogelijk beter dan klinisch gebruikte parameters zoals hartslag.
2. Het gebruik van multipele signalen van autonome activiteit voor de detectie van nociceptie levert een grotere sensitiviteit en specificiteit op dan het gebruik van een enkele parameter en wordt mogelijk minder beïnvloed door de hemodynamische effecten van anesthetica.
3. Rocuronium vertoont antagonistische activiteit ter plaatse van de acetylcholinereceptoren in de glomuscellen van de carotislichaampjes bij klinisch relevante plasmaconcentraties.
4. Antagonisme van het door rocuronium geïnduceerde neuromusculaire blok door placebo, neostigmine of sugammadex verloopt langzamer in de glomuscel dan aan de neuromusculaire overgang.
5. Het monitoren van de terugkeer van de neuromusculaire functie door een 'train-of-four' ratio te meten aan de m. adductor pollicis kan leiden tot een overschatting van het vermogen van een patiënt om de ventilatie te doen toenemen in respons op hypoxie.
6. Verstoringen van de ventilatie en / of oxygenatie die kunnen worden geïdentificeerd door een non-invasieve respiratoire monitor komen frequent voor bij postoperatieve patiënten.
7. Het gebruik van een non-invasieve respiratoire monitor bij postoperatieve patiënten kan leiden tot veranderde besluitvorming door verpleegkundigen, wat vervolgens de frequentie en duur van deze respiratoire verstoringen kan beïnvloeden.

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ADDENDA

A

Curriculum Vitae
List of Publications

Curriculum Vitae

Suzanne Broens was born on the 18th of July 1986 in Bayonne, France, daughter to a French mother and a Dutch father. In 1988 the family moved to the Netherlands and in 2001 they moved to Belgium, where she obtained her European Baccalaureate at the European School in Brussels in 2004. She then started to study Medicine at the University of Utrecht and obtained her degree as a Medical Doctor in 2011. Following her first clinical jobs at the Intensive Care Unit of 'Medisch Centrum Alkmaar' in Alkmaar and in the Emergency Department of the 'Hagaziekenhuis' in the Hague, she started her position as an Anesthesiology Trainee under supervision of prof. dr. L.P.H.J. Aarts at 'Leiden Universitair Medisch Centrum' in 2011. In the course of her traineeship, Suzanne became involved in several research projects that culminated in a PhD trajectory under supervision of prof. dr. A. Dahan. Her research was briefly interrupted when she moved to Australia to work in the Intensive Care Unit of Liverpool Hospital in Sydney, Australia in 2017. After her return from Sydney, she concluded her traineeship in 2018. She is currently working as an anesthesiologist at the Antoni van Leeuwenhoek Ziekenhuis in Amsterdam.

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