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

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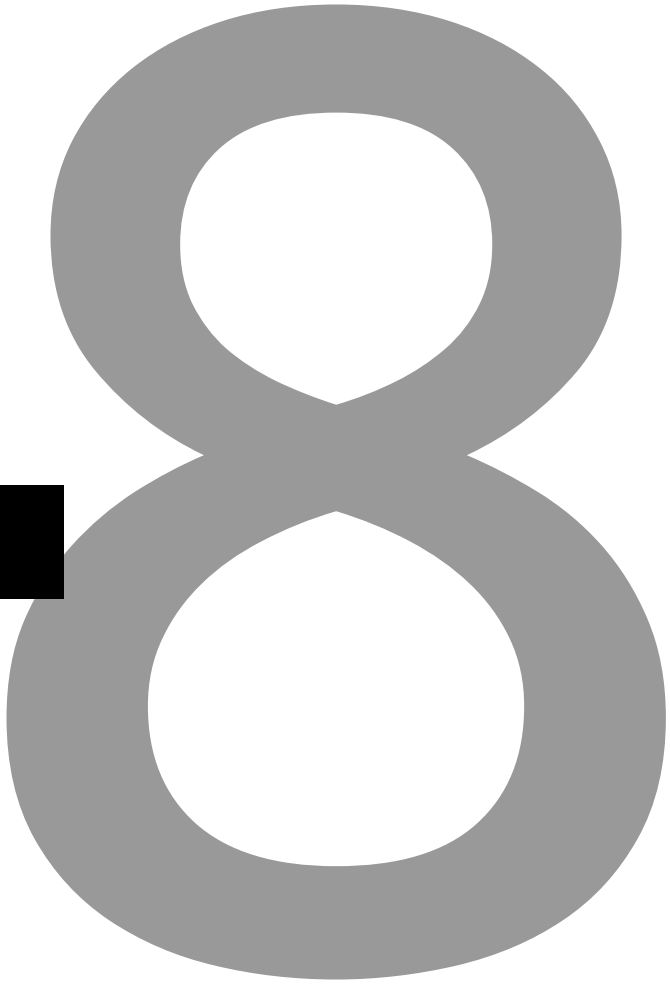
CHAPTER 8



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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