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

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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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