1 Introduction

ANESTHESIA has profound effects on the respiratory control system. It has long been known that anesthesia may diminish pulmonary ventilation, and hypercapnia is commonplace if spontaneous breathing is preserved. Studies looking at the incidence of postoperative respiratory complications show that hypoxemia is a common problem at the emergence of anesthesia in the postanesthesia care unit (PACU).[76,90] During recovery from anesthesia, hypoxia, hypercapnia, and acidosis have several causes: residual anesthetic and analgesic drugs at their effect site, atelectasis, reduced cardiac output, upper airway obstruction, analgesic/sedative medication, pain/stress, and underlying disease. The patient may continue to breathe during a hypoxemic episode, but hypoxia and hypercapnia have further effects. They cause sympathetic nervous system activity, which can lead to tachycardia, hypertension and ischemic ECG changes. Afferent input from the peripheral chemoreceptor is an important stimulus to arousal, the clearing of upper airway obstruction and the subsequent hyperventilatory response to correct any hypoxia, hypercapnia and acidosis. Therefore it is of utmost importance to understand the effect of anesthetics and analgesics on cardiorespiratory control and the mechanism of action of these agents.

Control of Breathing

Breathing results from activity of the respiratory centers in the brainstem and is well adjusted to the metabolic and non-metabolic needs of the body. Optimal adjustments are possible by incorporating information from various sites in the body. With respect to the metabolic control of breathing, the chemical composition of arterial blood primarily regulates breathing through effects on the peripheral and central chemoreceptors. The peripheral chemoreceptors in the carotid bodies are sensitive to changes in arterial pH, PCO_2 and PO_2. The central chemoreceptors on the surface of the ventral medulla are sensitive to changes in brain tissue PCO_2 and pH. To maintain a chemical equilibrium in the body, the metabolic ventilatory control system makes use of two reflex pathways. The peripheral chemoreflex loop consists of the peripheral chemoreceptors, the sinus nerve, sites in the brain stem that receive and process afferent input from the carotid bodies, the brainstem respiratory centers and the neuromechanical link between brainstem and ventilation (phrenic nerve, spinal motorneurons, diaphragm, intercostal nerves and muscles, lungs). The central chemoreflex loop involves the central chemoreceptors, and neuronal connection between these receptors and the brainstem respiratory centers and the above mentioned link between respiratory centers and ventilation (*i.e.*, the pathway common to both chemoreflex loops).[37,169,196]

Pure chemical control of breathing operates only during non-rapid-eye-movement (non-REM) sleep and anesthesia (in spontaneous breathing patients). During wakeful-

ness and REM-sleep, another equally important system, the behavioral control system, will influence breathing and may even temporarily override the chemical system. Behavioral control of breathing allows for adjustment of breathing to specific situations such as speech, singing, reading, eating, diving, *et cetera*.[211] In the postoperative patient various other systems will influence breathing, such as the pain-related control of ventilation and the stress response to surgical stimulation. Clinical and experimental studies show that pain and surgical stimulation act as a chemoreflex-independent respiratory stimulant in the awake, sedated and anesthetized states.[109,163,173]

The aim of this thesis is to increase our insight in the cardiorespiratory control of perioperative patients. Studies were performed in animals, volunteers and patients. They were designed to answer the following questions:

1. What is the role of the carotid body in the control of breathing in man?
2. What is the mechanism of anesthesia-induced depression of the peripheral chemoreflex loop and are we able to develop cheap and effective regimens to prevent depression of this vital chemoreflex?
3. How do intravenous and inhalational anesthetics and opioids, given alone and in combination, affect cardiorespiratory control?
4. Is the depression of anesthetics and analgesics on respiration, counterbalanced by the stimulatory effects of pain and stress?

- In *Chapters 2 and 3*, items 1 and 2 are addressed. In *Chapter 2* respiratory studies were performed in healthy volunteers as well as in unilateral and bilateral carotid body resected patients in order to quantify the influence of the carotid bodies on the control of breathing. Studies performed are multiple steps into and out of hypercapnia according to a multifrequency binary sequence (MFBS) recently developed in Oxford to optimize the study of the peripheral chemoreflex loop.[144]
- In *Chapter 3* hypoxic studies were performed in healthy volunteers in the absence and presence of antioxidants (iv ascorbic acid and oral α-tocopherol) during the inhalation of the potent volatile anesthetic halothane. Halothane, at already subanesthetic concentrations (0.05–0.1 end-tidal %) causes profound depression of the carotid bodies and consequently of the ventilatory response to hypoxia.[47] This protocol was developed to test the ability of antioxidants to prevent halothane-induced depression of the hypoxic ventilatory response. The administration of antioxidants makes sense taking into account the vast literature showing the involvement of free radical species in oxygen sensing at the carotid bodies, and the production of radicals species from halothane due to its reductive metabolism.[95,96]

- In *Chapters 4 and 5*, the influence of the intravenous anesthetic propofol on cardiorespiratory control is discussed. The results of experiments on various cardiorespiratory and EEG parameters such as the acute and sustained hypoxic ventilatory response, dynamic carbon dioxide ventilatory response (MFBS), heart rate and bispectral index of the EEG are reported. Furthermore, the possible site of action of propofol within the chemical ventilatory control system is discussed (item 3).
- In *Chapters 6 and 7*, the effect of combining opioids and anesthetics on the cardiorespiratory control system is described. The nature and magnitude of interaction of an anesthetic-opioid combination on resting ventilation, resting end-tidal carbon dioxide concentration, blood pressure, heart rate and bispectral index of the EEG and the steady-state ventilatory responses to carbon dioxide and acute hypoxia is assessed using the technique of response surface modeling (item 3).
- In *Chapter 8*, the influence of tramadol on ventilatory control in the anesthetized cat is discussed. To examine the involvement of the μ-opioid receptor in tramadol effects on respiration, the ability of naloxone, an opioid-antagonist, to reverse the respiratory effects of tramadol was studied (item 3).
- Finally, in *Chapter 9*, the complex of factors that interact on the cardiorespiratory control system in postoperative patients is examined. Respiratory studies are performed in patients shortly after major abdominal surgery as well as weeks to months later so that these subjects could serve as their own control. Breathing was tested by applying ramp-like increases in end-tidal PCO_2 combined with concomitant ramp-like decreases in end-tidal PO_2. This stimulus was chosen to mimic the changes in arterial gas composition that occur during upper airway obstruction (item 4).

SECTION 1

Physiology