

Isocapnic hyperventilation in anaesthesia practice

Clinical and experimental studies

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“When you gonna wake up, when you gonna wake up
When you gonna wake up and strengthen the things that remain?”

Bob Dylan

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ABSTRACT

Background: Isocapnic hyperventilation (IHV) has been shown to shorten recovery time after volatile anaesthesia by accelerating elimination of inhalational agents by increasing minute ventilation while maintaining normal carbon dioxide (CO₂) levels. It has also been shown that IHV reduces time spent in postoperative care units (PACUs). There are several principally different ways to maintain the CO₂ level during hyperventilation but IHV methods currently in clinical use has unfortunately not reached wider clinical implementation. The original method of directly adding CO₂ to the breathing circuit of the anaesthesia apparatus during hyperventilation was abandoned in the 1980ies, partly due to development of short acting anaesthetic agents and partly due to the risk of hypercapnia associated with this procedure. Thus, this particular IHV-method has not been studied to a great extent since then, although a considerable technical development of anaesthesia delivery systems and methods for monitoring airway gas concentrations have taken place in the last 30 years.

Aims: The aims of the present thesis were: 1) to investigate if a method of adding CO₂ directly into the breathing circuit using standard monitoring equipment and mechanical hyperventilation, provides effective and safe isocapnic hyperventilation, 2) to quantify the amount of delivered CO₂ and to construct a nomogram for CO₂ delivery during isocapnic hyperventilation at various physiological conditions, 3) to assess whether elimination of volatile anaesthetics can be accelerated using this IHV method, 4) to evaluate the clinical feasibility of this IHV method, 5) to compare the perioperative outcome for this IHV method to a routine wake-up method in a two-armed randomized study.

Methods: Studies were performed in a mechanical lung model with simulated metabolism, in an experimental porcine model and in patients undergoing major head and neck surgery. A standard breathing circuit with a 450-ml CO₂-mixing box connected to the inspiratory limb was used. A CO₂ bottle was connected to the mixing box. CO₂ flow was manually regulated by a high precision mechanical flow meter, dosed according to a nomogram during a standardised hyperventilation procedure using mechanical ventilation. The expired (FETCO₂) and inspired (FICO₂) fraction of CO₂ values provided by the standard monitoring equipment, were used to monitor CO₂-levels, also confirmed by arterial blood samples. Electric impedance tomography (EIT) was used in the porcine study for monitoring lung volume changes during hyperventilation. In the clinical studies, the end-points were time to extubation, eye-opening and time to discharge from the operation room (OR) as well as postoperative measurements of pain, nausea and cognition according to the Postoperative Quality of Recovery Scale (PQRS).

Results: In a bench study, we established a nomogram for CO₂ delivery when base-line minute ventilation was doubled, to achieve IHV. In an animal experiment, the method proved to increase the elimination rate of anaesthetic gas without any relevant respiratory or circulatory side-effects. In a clinical pilot study, the nomogram was validated. In all studies a FICO₂ level of about 3 % produced stable isocapnia, provided that the study protocol was followed. In the randomized prospective study, a shortening of time to extubation by 50 %, time to eye-opening by 34 % and time to discharge from OR by 30 %, was noted. We could not find any statistical difference in cognitive ability in the PACU after waking with IHV compared with a "standard" wake up procedure.

Conclusions: The described method for isocapnic hyperventilation is a safe technique when used in the clinical setting with the intention to decrease emergence time from inhalation anaesthesia. It has been shown to present no increased risk to patients.

Keywords: Hypercapnia, Hyperventilation, Hypocapnia, Electric Impedance Tomography, Weaning, Ventilator Weaning, Anesthesia Recovery Period

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SAMMANFATTNING PÅ SVENSKA

Varje år genomgår cirka 650 000 patienter narkos eller bedövning i samband med kirurgiska ingrepp i Sverige. En stor del av dessa patienter sövs med narkosgas, en väl beprövad metod som ger ett lättstyrkt narkosdjup och effektiv smärtstillning. Isokapnisk hyperventilation (IHV) är en metod som används för att påskynda utsköljning av narkosgas, med avsikt att förkorta uppvaknandet efter sövning för kirurgiska ingrepp. Genom att tillföra koldioxid (CO₂) under hyperventilation ökar man utsköljningstakten av narkosgasen men motverkar samtidigt de negativa effekter som annars hyperventilationen orsakar i form av en sänkt koldioxidnivå i blodet. Metoden har använts av narkosläkare sedan 1920-talet men i takt med att mer kortverkande narkosläkemedel utvecklades under slutet av 1900-talet slutade man använda isokapnisk hyperventilation rutinmässigt. En del patienter drabbades också av för hög och skadlig koldioxidnivå då man inte hade samma övervakningsmöjligheter som idag. De narkosapparater som hade metoden inbyggd slutade därför att tillverkas. Detta var förmodligen ett välgrundat beslut vid denna tid. Andra varianter av metoden har dock de senaste 10 åren framgångsrikt prövats i flertalet studier och visat sig halvera tiden till uppvaknande på operation. Metoden förkortar även tiden på uppvakningsavdelning. Trots att man använder moderna narkosmedel kan man alltså avsevärt påskynda uppvakningsprocessen. En effektivisering av uppvaknandet har stor betydelse för hela den perioperativa vårdkedjan och för de patienter som sövs. Tyvärr så har befintliga IHV-metoder som är godkända för kliniskt bruk inte fått någon större spridning eftersom man är tvungen att använda extern, specialtillverkad apparatur.

Avsikten med denna avhandling var att studera och vidareutveckla den ursprungliga metoden som innebär att man ger koldioxid direkt in i narkosapparatens andningsslangar. Metoden är inte studerad i någon större utsträckning i nutid eftersom den slutade användas. Den primära frågeställningen var att undersöka hur mycket koldioxid som behövs tillföras när man dubblar andningsvolymen per minut via narkosapparaten. Med denna metod skulle narkosläkaren kunna styra andningen och övervaka koldioxidnivåerna i andningsluften med hjälp av den vanliga narkosapparaten och dess övervakningsutrustning. Det var också viktigt att studera om metoden var säker.

I de två första studierna visade det sig att runt 3 % CO₂-koncentration i inandningsluften, motsvarande 150–300 ml CO₂/min beroende på kön och vikt, räckte för att upprätthålla en stabil och effektiv isokapnisk hyperventilation utan några hjärt/lung- eller cirkulationsbiverkningar. I de två

påföljande studierna prövades metoden vid väckning av patienter och resultatet blev att tiden till uppvaknande förkortades med 50 % och tiden till att patienterna kom ut från operationssalen med 30 %. Detta stämmer väl överens med resultat från studier av andra IHV-metoder. Efter väckning och vid vård på uppvakningsavdelning utgjorde den studerade IHV-metoden ingen risk för patienterna. Vi såg inga fall av höga koldioxidnivåer, eller ens en tendens till höga koldioxidnivåer i blodet eller utandningsluften. Det fanns en tendens till snabbare kognitiv återhämtning och mindre smärta och illamående i IHV-gruppen, men den var inte statistiskt säkerställd.

Sammanfattningsvis är isokapnisk hyperventilation ett effektivt sätt att påskynda uppvaknandet efter gasnarkos även när moderna kortverkande narkosmedel används. Det är möjligt att utföra detta på ett säkert sätt via den vanliga narkosapparatusens respirator och övervakningsutrustning genom att tillföra en liten mängd koldioxid i inandningsluften i samband med väckning, doserat efter kön och vikt. En bred klinisk implementering av metoden skulle kunna öka effektiviteten i den perioperativa vårdkedjan och potentiellt förbättra vårdkvaliteten för hundratusentals patienter varje år. Fler studier och en mer utbredd klinisk användning behövs för att kunna säkerställa detta.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. **A simple method for isocapnic hyperventilation evaluated in a lungmodell**
Hallén K, Stenqvist O, Ricksten S-E, Lindgren S
Acta Anaesthesiologica Scandinavica 60 (2016) 597–606
- II. **Isocapnic hyperventilation shortens washout time for sevoflurane – an experimental in vivo study**
Hallén K, Stenqvist O, Ricksten S-E, Lindgren S
Acta Anaesthesiologica Scandinavica 60 (2016) 1261–1269
- III. **Evaluation of a method for isocapnic hyperventilation: a clinical pilot trial**
Hallén K, Jildenstål P, Stenqvist O, Ricksten S-E, Lindgren S
Acta Anaesthesiologica Scandinavica 62 (2018) 186-195
- IV. **Isocapnic hyperventilation provides early extubation after major ear-nose-throat surgery: a prospective randomized clinical trial**
Hallén K, Jildenstål P, Oras J, Stenqvist O, Ricksten S-E, Lindgren S
Manuscript

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ABBREVIATIONS

ANOVA	Analysis of variance
BLV	Base-line ventilation
CO ₂	Carbon dioxide
CO	Cardiac output
Crs	Compliance of the respiratory system
CVP	Central venous pressure
DCO ₂	Delivered carbon dioxide
DS	Dead space
EELV	End expiratory lung volume
EELI	End expiratory lung impedance
EIT	Electric impedance tomography
ENT	Ear-nose- and throat
ETCO ₂	End tidal expiratory carbon dioxide
FETCO ₂	End tidal expiratory fraction of carbon dioxide
FICO ₂	Inspiratory fraction of carbon dioxide
FiO ₂	Inspiratory fraction of oxygen
FGF	Fresh gas flow
I: E	Inspiratory-to-expiratory ratio
IHV	Isocapnic hyperventilation
i.v.	Intra-venous
HV	Hyperventilation
HR	Heart rate

MAC _{age}	Minimum alveolar concentration age related
MAP	Mean arterial pressure
MV	Volume per minute
NO	Nitric oxide
NYSAM	Swedish collaboration for sharing key health statistics
OR	Operation room
PACU	Postoperative care unit
PaCO ₂	Arterial carbon dioxide tension
PaO ₂	Arterial oxygen tension
PCV	Pressure controlled ventilation
PEEP	Positive end expiratory pressure
P/F ration	Perfusion ventilation ratio between PaO ₂ and FiO ₂
PONV	Postoperative nausea and vomiting
P _{peak}	Peak tracheal pressure
P _{plateu}	Plateau tracheal pressure
PRVC	Pressure regulated volume controlled ventilation
P _{trach}	Tracheal pressure
PQRS	Postoperative quality of recovery scale
RR	Respiratory rate
SaO ₂	Arterial oxygen saturation
SD	Standard deviation
SpO ₂	Arterial oxygen saturation by pulse-oximetry

SPOR	Swedish perioperative registry
SV	Stroke volume
SVR	Systemic vascular resistance
VCO ₂	Carbon dioxide production
VCV	Volume controlled ventilation
VO ₂	Oxygen consumption
VT	Tidal volume

1 INTRODUCTION

The most commonly used method for general anaesthesia worldwide is inhalation anaesthesia which constitutes a considerable part of the anaesthetic drug budget in health systems.[1] In Sweden, an approximation of the yearly number of anaesthetic procedures reaches up to 650 000 (NYSAM 2015). [2] In the yearly summary from The Swedish Perioperative Registry (SPOR) 2016, which at this time covered 45% of Sweden's all anesthetic procedures, it is seen that general inhalation anaesthesia is used in 44% of the surgical procedures. The remaining 56% of the surgical cases are performed under intravenous anaesthesia.[3] Sahlgrenska University Hospital was not represented in SPOR 2016. At the Sahlgrenska University Hospital (SU/Sahlgrenska), inhalation anaesthesia represented 75% of the general anaesthetic procedures with a total of 10619 procedures in 2016. (Data from hospital database OPERÄTT) Although the increasing popularity of total intravenous anaesthesia in recent years, prospective randomized studies or systematic reviews have not been able to show an advantage on postoperative recovery compared to inhalation anaesthesia. [4]

There are several good reasons to shorten the awakening time after general anaesthesia. The goal is to have a patient as alert as possible, as quickly as possible, which facilitates extubation, mobilization, postoperative monitoring time, assessment of pain and also affects process measures in the operation room.

Recovery time after inhaled anaesthesia depends on alveolar ventilation, solubility of the drug in blood and tissue, cerebral blood flow, and duration of anaesthesia. We can accelerate this process through hyperventilation, i.e. increase alveolar ventilation. When hyperventilation is used during emergence to quickly decrease the alveolar and arterial concentration of the anesthetic, the rate of carbon dioxide (CO₂) removal from the lungs exceeds its rate of production and hypocapnia occurs. Hypocapnia decreases cerebral blood flow, which, in turn, decreases the rate of clearance of anesthetic from the brain. Isocapnic hyperventilation (IHV) is a method that shortens time to extubation after inhalation anaesthesia by maintaining airway CO₂ during hyperventilation (HV). IHV provides an alternative method for weaning from inhalation anaesthesia which decreases the time to eye-opening, extubation and time spent in the PACU. [5-13]

1.1 Historic background

Carbon dioxide was first used in anaesthesia in 1824 by Henry Hill Hickman, who performed a series of operations on animals.[14] Leak and Waters used 30% CO₂ in oxygen to produce unconsciousness in humans in 1928.[15] Marked ventilatory and circulatory stimulation, rigidity and convulsions rapidly ended its use as an inhalational anaesthetic agent. The first general inhalation anaesthesia was performed by dentist William Morton (successfully) in 1846 at Boston Massachusetts General Hospital. The patient was anaesthetized with ether for thyroid surgery.[16]



Figure 1.1 Fragment of anaesthesia circuit with rotameter and ether vaporizer from 1960. (Photo taken at medical historical display during annual ESA-meeting in Genève 2017, Sophie Lindgren)

Ether and ether derivatives were used until the 1960s. Halogenated and fluorinated hydrocarbons in the form of halothane began to be used in the 50's. Enflurane and isoflurane came on the market in the 70's and 80's. When sevoflurane was introduced in the 90's, it replaced halothane as induction agent.[17] The method of isocapnic hyperventilation after inhalational anaesthesia is well known since at least 60-70 years and involves the maintenance of a stable CO_2 level during hyperventilation, which increases the elimination of anaesthetic gas without producing hypocapnia.



Figure 1.2 CO_2 absorber Carba from the middle of the last century. (Photo taken at medical historical display during annual ESA-meeting in Genève 2017, Sophie Lindgren)

Gas bottle and flowmeter for carbon dioxide distribution to stimulate spontaneous breathing were first adapted to Boyle's anesthesia apparatus in 1927 and a little later to Dräger's apparatus. In the mid-1930s, CO₂ bottles were essentially attached to all anesthesia devices around the world. The opportunity to connect CO₂ bottles remained until the 1960s. [18-20]

Circuit systems with carbon dioxide absorbers became common in Germany in the 1920s and introduced in the United States in 1928. The carbon dioxide absorber used in the anesthetic circular system arose in response to the need for respiratory equipment in coal mines. Furthermore, carbogen, a mixture of 5% carbon dioxide and 95% oxygen, was used as an antidote to the carbon monoxide poisoning in the coal mines. By hyperventilating with carbogen, you could wash out the carbon monoxide faster than with normal oxygen, as hyperventilation with pure oxygen led to hypocapnia.[18, 21-23]. As many industrial and military inventions during the 20th century, it soon reached the hospital operation rooms. The anesthesia agents used in the 1920s were either chloroform, nitrous oxide or ether calibrated in oxygen in spontaneously breathing patients. Henderson, a respiratory physiologist and gas expert at this time, describes how he ordered carbogen for physiological reasons and safety aspects. He also describes how one anaesthetist after another began to use stronger concentrations of CO₂ as they saw improved results on breathing and recovery. The technique gave them perfect control of the respiration.[23, 24] Nitrous oxide became cheap when the Germans during World War II managed to produce it in large quantities to get more impact from the poor engine fuel they had access to. In Sweden during World War II, when the use of producer gas (generatorgas or gengas in Swedish) was very common in vehicles, carbon monoxide poisoning was not uncommon. Carbogen inhalators were therefore easily accessible in the Swedish community at this time. Carbogen can still be obtained from AGA and is presently mostly used for cell cultivation. (Personal communication with Hans Sonander, Oct 2017).

When newer inhalational agents, less soluble in blood and tissues and consequently more short acting, were introduced during the latter part of the 20th century, it was thought that the carbogen did not have the same place in recovery after anaesthesia anymore.[25] In addition, the hospitals had begun to implement post-operative care departments, which reduced the need for patients to be fully awake and perfectly spontaneously breathing when leaving the operation room.[26, 27] Carbogen was replaced with carbon dioxide as the gas used to accelerate weaning after inhalational anesthesia.[20] In 1975, the Nunn's textbook "Applied Respiratory Physiology", it was stated that there is no indication of using carbon dioxide during anaesthesia due to the risks of overdose. Despite this, a survey from 1986, found the use of CO₂ in anaesthetic

practice in the United Kingdom to be widespread and enthusiastically defended. The stimulation of spontaneous ventilation after a period of controlled hyperventilation was the main indication for the use of CO₂ at this time. However, due to reports of fatal hypercapnic incidents, the method of direct adding of CO₂ to the breathing circuit during weaning successively was abandoned.[15, 20] The possibility of connecting a CO₂ bottle to the anaesthesia machines, was consequently phased out by the manufacturers. Limited CO₂ monitoring capacities at this time could be a part of the explanation for the hypercapnic incidents as it probably was difficult to monitor and fine tune the CO₂ delivery during weaning. At present, there are several clinically approved methods for performing IHV in use.[7, 10, 13] However, they are not widely implemented as they require external breathing or monitoring equipment connected to the patient and/or anaesthesia delivery system. Also, the optimal flow or amount of CO₂ needed during IHV,[28] has not been quantified in any of the methods, old or new. Nor has any study, up until now, presented results from blood-gas analysis during isocapnic or hypercapnic hyperventilation. (See Introduction 1.3)



Figure 1.3 Gas monitor from the 1980s manufactured by Datex in Finland. (Photo taken at medical historical display during annual ESA-meeting in Genève 2017, Sophie Lindgren)

1.2 Physiological background

1.2.1 Hyperventilation

It has long been known that hyperventilation increases the elimination of anesthetic gases from the blood but hyperventilation also causes hypocapnia i.e. a low PaCO₂. This provides a post-hyperventilation apnea and a cerebral vasoconstriction that reduces cerebral blood flow. This prolongs the elimination of the anesthetic gases and thus causes a prolonged postoperative recovery. Chemoreceptors on the ventral side of the brain stem is very sensitive to small PaCO₂ -and pH changes in the cerebrospinal fluid and fine tunes the breathing drive with high precision. A low PaCO₂ and a high pH causes a drive to decrease ventilation and vice versa. [28, 29]

1.2.2 Carbon dioxide

Carbon dioxide is the end product of aerobic metabolism, which occurs almost exclusively in mitochondria. CO₂ is carried in the blood in three forms, dissolved, as bicarbonate or in combination with hemoglobin and proteins. In the lung capillaries, PaCO₂ is higher than in the lung alveoli. Therefore, there is a passive diffusion of CO₂ from blood to the lung alveoli. Furthermore, an increase in the concentration of O₂ in blood will displace CO₂ from hemoglobin and vice versa. This phenomenon is referred to as the Haldane effect. CO₂ is also more easily soluble in blood than O₂ and therefore, according to Fick's law, passes more easily through tissue barriers. According to the Bohr effect, changes in PaCO₂ and pH causes a shift in the oxygen-hemoglobin dissociation curve, where a high PaCO₂ and a low pH results in a looser binding of O₂ molecules to the hemoglobin which facilitates release of O₂ in the peripheral tissues. A low PaCO₂ and a high pH results in a tighter binding of O₂ to hemoglobin which facilitates an easier upload of O₂ to the hemoglobin molecules in the lung.[28, 29] Exhalation air from a human contains about 4% carbon dioxide, which in a resting awake male of 70 kg corresponds to a CO₂ production (VCO₂) of about 200 ml/min depending on alveolar ventilation.[30] The constantly shifting metabolism of a living organism with changing demands on oxygenation and CO₂ elimination results in a continuous variation in ventilation. The main cause if this accurate control of ventilation is to regulate the acid-base balance, which is necessary to maintain the function of important proteins. Consequently, in a healthy subject, the CO₂ concentration in exhaled air should be fairly constant in spite of changing CO₂ production/output and shifts in metabolic demand, due to a constant high precision regulation of respiratory rate and lung volume. [29] (See Introduction 1.2.3)

CO₂ is a heavy colorless gas and is readily soluble in water and then forms an aqueous solution containing the weak acid carbonic acid, H₂CO₃. Inhalation at high concentrations causes a sour taste in the mouth and a tingling throat as the gas dissolves in the saliva and forms carbonic acid. The molecule is straight and consists of a carbon atom surrounded by two oxygen atoms. At low temperatures, the gas passes to a solid state, known as carbonic acid or dry ice. At normal pressure, the CO₂ is converted to gaseous form. The CO₂ sublimation point at normal pressure is at -78 ° C.[31]

Carbon dioxide forms small gas bubbles in pastries. As a preservative, carbon dioxide is designated by E-number E 290. Carbon dioxide is also used in fire extinguishers as it displaces oxygen and cools down the fire and as a fuel for paintball markers and some air guns. In addition, carbon dioxide is used as a protective gas during welding, in most cases mixed with other gases.[32]

Carbon dioxide is a greenhouse gas and is formed upon complete combustion of carbon compounds in oxygen. In combustion of biomass, the amount of carbon dioxide in the atmosphere does not increase as long as the biomass is allowed to grow up again and be reabsorbed in the same amount of carbon dioxide. By means of photosynthesis, the plants bind carbon dioxide and water to sugars, which they use in their own metabolism, partly stored in the cells, often converted to cellulose or starch. The increase in carbon dioxide emissions caused by the large-scale utilization of fossil fuels leads to an increased greenhouse effect and furthermore leads to marine acidification.[33]

1.2.3 Alveolar ventilation and dead-space

The part of the minute volume (V_T) that reaches perfused alveoli and enables gas exchange is called alveolar ventilation. It can be calculated by the formula

$$V_A = RR (V_T - V_D) \text{ or by the formula } V_A = k V_{E\text{CO}_2} / P_{a\text{CO}_2}$$

Where $V_{E\text{CO}_2}$ is exhaled CO₂, $P_{a\text{CO}_2}$ is alveolar partial pressure of CO₂ and k is a constant. The part of the minute volume that stays in the airways underneath each breath without reaching the alveoli is called dead space (V_D). With altered dead space, minute volume or respiratory rate, the alveolar ventilation is affected. In the case of hyperventilation there will be an increase in dead-space ventilation due to an increase of respiratory rate, which does not allow an effective gas exchange.[28, 29, 34, 35]

1.2.4 Gas exchange

Oxygen diffuses from alveoli to pulmonary capillaries and CO₂ diffuses in the opposite direction in a passive process. Diffusion rate is due to partial pressure gradients between alveoli and capillaries, total diffusion surface and diffusion distance, i.e. alveolar epithelium, capillary endothelium and interstitial tissue. Arterial CO₂ levels are more important for respiratory control than oxygen levels. For carbon dioxide-controlled respiratory regulation, central chemoreceptors are more important than peripheral. Hypercapnic respiratory stimulation is significantly enhanced at a PaCO₂ >8 kPa. Unconsciousness occurs at a PaCO₂ >12-16 kPa. At the same time, the hypercapnic respiratory stimulation is gradually attenuated. The chemoreceptors are easily inhibited by anaesthetic drugs and changes in intracranial pressure.[28, 29, 36]

1.2.5 Elimination of anaesthetic gas

At the termination of the delivery of anesthetic agent, washout starts immediately. In just a few minutes, the concentration of alveolar anesthesia agents has been reduced significantly due to the supply of oxygen. Thereafter the curve of the recovery becomes flatter, in analogy with how the anaesthesia gas uptake in the body is dependent on its solubility in blood and tissues. The gas is rapidly absorbed into the blood but the uptake is slower in different organs and tissues depending to their perfusion rate. The slowest uptake is seen in fat and muscle tissue. After a long period of inhalational anesthesia, time to recovery is depending on how easily soluble the anaesthetic agent is in fat and muscle tissue, i.e. their tissue and blood distribution coefficient, total tissue volume, regional blood flow and regional arteriovenous partial pressure differential.[37] Unlike all other anaesthetic agents it is possible to affect the elimination phase of volatile anaesthesia by manipulation of the alveolar ventilation. An increase in ventilation will increase the elimination rate and vice versa.[23] The longer the anaesthesia duration is, the larger reduction in wash-out time is possible to achieve using hyperventilation. Current methods for isocapnic hyperventilation have not been studied in long duration anaesthetic procedures (>3h).

1.3 Methods for isocapnic and hypercapnic hyperventilation

There are several principally different ways to maintain the CO₂ level during hyperventilation, where a number of technical solutions have been studied during the last 10-15 years.[5-13] The clinical use of these methods is however not wide spread. It would be of substantial importance for anaesthesia care if

IHV could be implemented on a daily clinical basis. To achieve IHV you can either passively or actively increase the airway CO₂-level.

1.3.1 Passive rebreathing

One method is to passively raise CO₂ in a rebreathing device using an expandable rebreathing hose, a canister filled with anesthetic adsorbent and two valves to maintain unidirectional flow of gas through the adsorbent. The canister holds medical grade activated charcoal to adsorb anesthetic from the inspired gas as it is rebreathed. In this system, airway CO₂-level during recovery is determined by expanding dead space which leads to an increase in FICO₂. The dead-space device with agent absorber is connected to the breathing circuit between the patient (endotracheal-tube) and Y-piece (anaesthesia machine), during manually assisted or spontaneous ventilation, ANEclear™ (Anecare, South Lake City, USA). This method is approved for clinical use USA and Europe.[6, 7, 12]

1.3.2 Active infusion

One method is performed by disconnection of the patient from the standard breathing circuit and reconnecting to an external breathing device with an isocapnic manifold and self-inflating bag for manual or spontaneous regulation of ventilation with infusion of 6 % CO₂/O₂ mixture via a gas blender, ClearMate™ (Thornhill medical, Toronto, Canada). The FETCO₂ is determined by the O₂ flow, which should not exceed minute ventilation, regulated by a pressure relief valve. The method is approved for clinical use in Canada.[8-11, 13]

Another IHV method using an infusion system, consists of a feedback controller tuned to actively induce and maintain hypercapnia during hyperventilation. The feedback controller introduces CO₂ into the breathing circuit at the optimum rate, dependent on the tidal volume and respiratory rate setting. A computer runs a proportional-integral control algorithm which compares the measured FETCO₂ from the previous breath to the desired target FETCO₂ and determines the amount of CO₂ to be added to the inspired gas in the subsequent breath. This method has only been experimentally tested in pigs. [12]

The method currently approved for clinical use demands disconnection of the patient from the breathing circuit and/or manual/spontaneous ventilation during awakening. This method has proven to be very effective, reducing time to extubation with 50 – 60 % and time to discharge from PACU by 20-30

minutes. [8-11, 13] Unfortunately, this method has not been able to reach a wider clinical implementation.

The method of active infusion of CO₂ presented in this thesis differs from the methods described above. It is performed simply by direct infusion of CO₂ into the inspiratory limb via a mixing box according to a pre-calculated CO₂ dosage nomogram during doubling of minute ventilation. Mechanical hyperventilation and standard monitoring equipment is used to maintain the FICO₂ level around 3 %. The method includes disconnection of the CO₂ absorber. The only extra equipment needed is a mixing box to achieve consistent CO₂ supply throughout the breathing cycle.[38-40]

1.4 Anaesthesia for head and neck surgery

Anaesthesia for ear-nose-throat (ENT) surgery is common and constitutes 4-5 % of all anaesthetic procedures in Sweden. Several ENT surgical procedures are performed as day surgery and are considered relatively uncomplicated. However, in Sahlgrenska University hospital a large proportion of the patients passing the ENT operation ward are subdued to complicated surgical procedures due to head and neck tumors and trauma. These patients often have an increased risk of difficult airway access, due to deviant airway anatomy and bleeding. They also have an increased risk of bronchospasm, postoperative pain and nausea as all surgery that affects mucous membranes is unusually painful and unpleasant. The anaesthesiologists do not have access to the airway during the surgery, not until the surgical dressings are removed. The patients have to be deeply anaesthetized up until then to avoid coughing which can cause bleeding.[17] Consequently, this is a patient population that could have large benefits from an accelerated recovery.

1.5 Perioperative outcome measures

There are several published validated instruments to assess postoperative recovery of various patient groups at different time intervals. Most of these instruments primarily assess postoperative pain and physical function of the patient. There are also specifically developed instruments for evaluating patients after certain procedures. Most perioperative measurement methods concentrate on describing pain, nausea, vital parameters and physical activity. [41, 42] Furthermore, most perioperative measurements use the patient's own experience of recovery which is subjective and with great individual variation. Care staff often describes recovery as the patient's physiological recovery, while patients more often describe recovery as a return to everyday life. Few

instruments assess the cognitive ability of the patient. It can be of great importance to know if the patient recovers cognitively and can absorb information or instructions.[43] The perioperative instrument covering most variables is the Postoperative Quality Recovery Scale (PQRS). It is a comprehensive assessment tool that can be used at several different time points in post-operative recovery.[44] The method assesses recovery after surgery and anaesthesia using a multimodal questionnaire and scoring system. It was developed in 2010 and has been validated in several studies. Physiological, nociceptive, emotive and cognitive variables are measured by using a standardized question protocol. According to the PQRS protocol psychomotor and cognition tests should be performed at the preoperative evaluation and repeated at 20, 40 and 60 min after arrival in the PACU. The changes in postoperative scores are evaluated in relation to the preoperative baseline assessment. Isocapnic and hypercapnic hyperventilation has been shown to decrease time spent in the PACU but the assessment tools used in these studies have not been able to detect the reasons behind this positive effect on postoperative recovery. The PQRS score has not been used to evaluate postoperative recovery after weaning with isocapnic hyperventilation before.

1.6 Main issues

The most commonly used method for general anaesthesia worldwide is inhalation anaesthesia.

Volatile anaesthetics are the only anaesthetic agents whose elimination rate are possible to affect.

Isocapnic hyperventilation is an effective method for reducing recovery time after inhalational anaesthesia.

The wide spread original method for isocapnic hyperventilation was abandoned in the 1970-80s, as the risks were considered higher than the benefits.

The original method has not been used with modern anaesthesia equipment.

Current methods for performing isocapnic hyperventilation has not reached a wide clinical implementation in spite of good evidence of their efficiency.

The methods used for isocapnic hyperventilation have not been studied in long duration anaesthetic procedures such as for major head and neck surgery.

2 AIMS

The principal objective of this thesis was to investigate if a method of adding CO₂ directly into the breathing circuit of an anaesthesia machine, during standardized mechanical hyperventilation and using standard monitoring equipment, provides effective and safe isocapnic hyperventilation, with the intention to decrease time to recovery after inhalation anaesthesia

2.1 The main aims were

1. To quantify the amount of delivered CO₂ and construct a nomogram for CO₂ delivery during isocapnic hyperventilation at various physiological conditions.
2. To assess if elimination of volatile anaesthetics can be accelerated using this method for isocapnic hyperventilation.
3. To evaluate the clinical feasibility of this method for isocapnic hyperventilation.
4. To compare the perioperative outcome of this for isocapnic hyperventilation method, to a routine wake-up method in a two-armed randomized study.

...in mechanical lung models, experimental in vivo models and in patients undergoing long-duration inhalational anaesthesia for major head and neck surgery.

3 PATIENTS AND METHODS

3.1 Ethical approval

The Committee for Ethical Review of Animal Experiments in Gothenburg (Study II) and the Gothenburg Regional Ethical Review Board (Study III-IV) approved the protocols for studies II-IV. Study II was performed in accordance with the European Convention for the Protection of Animals used for Experimental Purposes, Council of Europe, 2010/63/EU. In studies III-IV, written informed consent was obtained during preoperative evaluation, before enrolment in the studies. The nature of the studies and the risks involved were presented both orally and in written form. Studies III and IV were registered in the Swedish National Database for Research and Development, project 215601 The prospective randomized study (Study IV) have a ClinicalTrials.gov Identifier: NCT03074110. In study I we used a test lung and the experimental setup did not involve human participants or animals and thus no ethical review board assessment was necessary. See Table 3.1 for summary of animals (II) and patients (III, IV) in studies II, III and IV.

3.2 Lung Model

Into a mechanical lung model, carbon dioxide was added to simulate a CO_2 exhalation (VCO_2) due to metabolism of 175, 200 and 225 ml/min. CO_2 was delivered via a custom-made precision electronic flow controller into the test lung.[45] A Bio-Tek ventilator tester, VT-1 (Bio-Tek Instruments, Winooski, VT, USA), was used as lung model and compliance was set to 50 ml/ cmH_2O . Dead space volume could be set at 44, 92 and 134 ml. The lung model was ventilated with an S/5 Anaesthesia Delivery Unit Carestation® (ADU; Datex-Ohmeda, Helsinki, Finland). From baseline ventilation, hyperventilation was achieved by doubling the minute ventilation and fresh gas flow for each level of VCO_2 , and dead space. To achieve isocapnia during hyperventilation, CO_2 was delivered (DCO_2) by a precision flow meter via a mixing box to the inspiratory limb of the anaesthesia circuit. The CO_2 absorber was disconnected during the hyperventilation procedure. Ventilatory variables were monitored by the S/5 ADU module.[46] Data were continuously collected to a personal computer by dedicated software (S/5 Collect; Datex-Ohmeda, Helsinki, Finland) See Figures 3.1, 3.2 and 3.3.

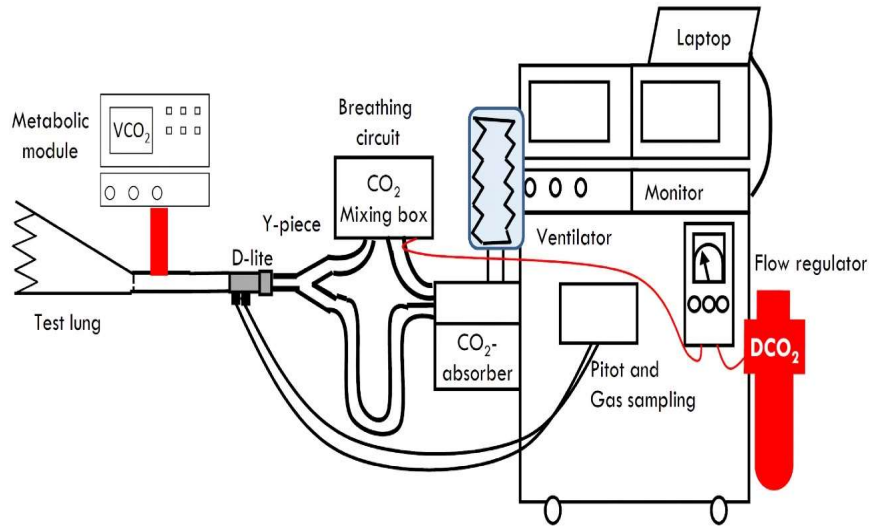


Figure 3.1. Set up of mechanical lung model with metabolic module used in Study I. The same methodological set up was used for animals and patients in Study II-IV. See also Figure 3.2.

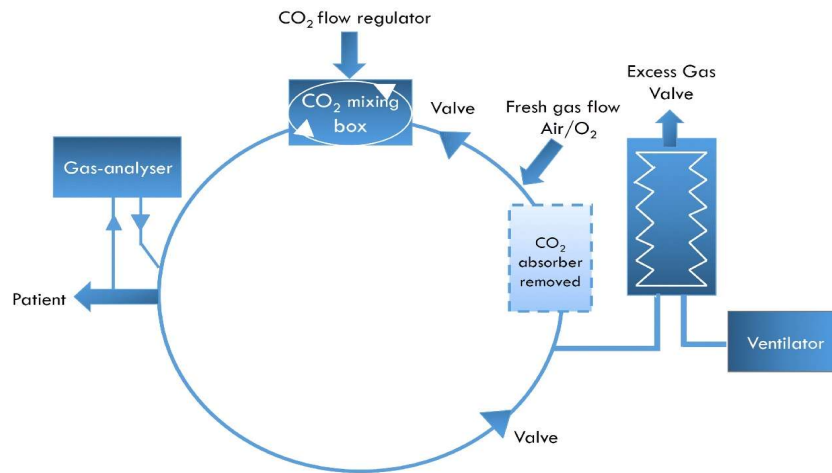


Figure 3.2. Schematic presentation of the anaesthesia circuit used in Study I-IV and its' modifications for performing isocapnic hyperventilation.

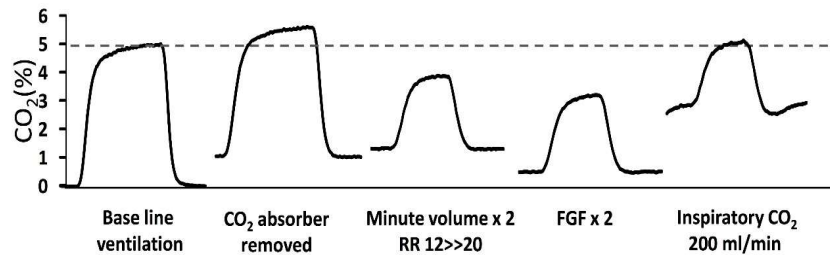


Figure 3.3. Recorded capnometry tracings from Study 1 during gradual introduction of isocapnic hyperventilation in the mechanical lung model, displaying the principle of the IHV method. The end-expiratory CO_2 is lifted as the FICO_2 increases with DCO_2 and the CO_2 mixing box produces an even CO_2 administration throughout the respiratory cycle.

3.2.1 Calculations

Effective alveolar ventilation

We calculated the effective alveolar ventilation for anesthetic gas ($V_{A(\text{AGfunctional})}$) according to Bohr's equation, which includes CO_2 production as well as end-expiratory and inspiratory alveolar concentrations of CO_2 according to the formula:

$$V_{A(\text{AGfunctional})} = V_{\text{CO}_2} / (\text{FETCO}_2 - \text{FICO}_2)$$

The formula gives us the value of the functional alveolar ventilation which accounts only for the elimination of anesthesia gas. Thereafter we modified Bohr's equation to calculate the proportion of alveolar ventilation used for carbon dioxide elimination by removing the inspiratory part of the carbon dioxide in the equation:

$$V_{A(\text{CO}_2)} = V_{\text{CO}_2} / \text{FETCO}_2$$

By this calculation we could separate the effect of the alveolar ventilation used for elimination of the volatile anesthesia agent and CO_2 . When performing isocapnic hyperventilation by doubling minute ventilation, we manipulate the inspiratory carbon dioxide fraction, which means that alveolar ventilation for

carbon dioxide remains unchanged while alveolar ventilation for the volatile anaesthetic is doubled. Thus, we maintain "normal" CO₂ levels in spite of doubling minute ventilation. Elimination of anesthetic gas can therefore be enhanced without producing hypocapnia, acid-base or circulatory side-effects.

Carbon dioxide delivery nomogram

The results from our lung model were used to quantify the amount of CO₂ flow in ml/minute needed to maintain isocapnia during doubling of base-line minute ventilation in the clinical situation. We estimated "normal values" for carbon dioxide supply using Radford's calculations of CO₂ production in relation to body weight and gender.[30] At first, we had to translate the Radford chart from pounds to kilograms. Then we correlated our VCO₂ values to the DCO₂ values at 92 ml dead space. The correlation was used to extrapolate Radford's CO₂ production values into a full table of VCO₂ and DCO₂ according to weight and gender. We also took into account the effect of anaesthesia on metabolism according to Nunn's calculations.[47] The results were summarized in a table or "nomogram". The purpose of the nomogram was to provide an initial target value of CO₂ flow needed to maintain isocapnia during standardized mechanical hyperventilation according to our protocol. See Table 4.1.

Study	Subjects No	Gender M/F	Age Years	Weight kg	ASA I/II/III	Ventilator/ mode	BLV L/min	Sevoflurane MAC-h	Fentanyl µg/kg/h
II	8	0 / 8	NA	28±2	NA	ADU/ VCV	5.2 ± 0.6	1.2±0.2	25
III	15	7 / 8	57±16	76±12	6 / 6 / 3	ADU/ VCV	5.9 ± 0.8	7.1±3.4	2.1±0.7
IV	31	18 / 13	61±17	81±15	9 / 17 / 5	Flowi/ PRVC	7.7 ± 1.5	6.0±1.7	2.4±0.5

M/F = Male/Female, ASA = American Association of Anaesthesiologists physical classification system, ADU = Anaesthesia Delivery Unit (Datex-Ohmeda), Flowi = Anesthesia Delivery System (Maquet), VCV = Volume controlled ventilation, PRVC = Pressure regulated volume controlled ventilation, BLV = Base line ventilation, MAC-h = MAC-hour = average MAC x length of exposure

Table 3.1. Summary of animals (II) and patients (III, IV) in studies II, III and IV

3.3 Porcine Model

It was hypothesized that the IHV-method tested in Study I could be used in vivo for enhancing elimination of an anaesthetic gas. Eight anaesthetized

female pigs weighing 28 ± 2 kg were intubated and mechanically ventilated using the ventilator S/5 Anaesthesia Delivery Unit Carestation® (ADU; Datex-Ohmeda, Helsinki, Finland).

To determine the individual DCO_2 during IHV in each animal, a DCO_2 titration procedure was performed before the administration of sevoflurane. After this, sevoflurane was administered for 55 min. Washout of sevoflurane during normoventilation was performed simply by maintaining the baseline ventilation settings when turning off the vaporizer. All animals were subjected both to IHV and normo-ventilation, during the washout procedures, which were performed in random order. The animals were anaesthetized by pentobarbital infusion, which was discontinued during the sevoflurane anaesthesia and reinstated during the washout procedures. Fentanyl was continuously administered throughout the whole experimental procedure.

3.3.1 Experimental protocol in the animal study (Study II)

From a baseline ventilation of 5 l/min, HV was achieved by doubling minute volume and fresh gas flow. Respiratory rate was increased from 15 to 22/min. The CO_2 absorber was disconnected and CO_2 was delivered (DCO_2) to the inspiratory limb of a standard breathing circuit via a mixing box. The delivered amount of CO_2 was manually regulated via a high precision mechanical flow meter originally used for NO distribution and recalibrated for CO_2 . [48, 49] See Table 3.2 for detailed description of the protocol. Isocapnia was defined as a return to baseline FETCO_2 value. After sevoflurane had been administered for $55 \text{ min} \pm 13$ minutes. FISEvo and FETSevo were almost identical, 2.8 ± 0.1 vs. $2.7 \pm 0.1\%$. Sevoflurane administration was then abruptly discontinued and the time required for end-tidal sevoflurane to decrease from $2.7 \pm 0.1\%$ to $0.2 \pm 0.0\%$ was measured. Time required to decrease end-tidal sevoflurane concentration from 2.7% to 0.2% was defined as washout time.

3.4 Patients

It was hypothesized that the experimentally evaluated method for IHV (Study I-II) was feasible also in the clinical setting to reduce emergence time after long duration inhalational anaesthesia.

3.4.1 Patients and anaesthesia

Adult, ASA grade I-III patients scheduled for major head and neck surgery at the Sahlgrenska University Hospital, Gothenburg were included in Studies III-

IV. Patients with severe pulmonary or cardiovascular disorders, ASA>III, BMI>35, anaesthesia duration<3 hours or communication difficulties were excluded. The indication for surgery was different types of head and neck tumors. See patient flow charts in Results section (Figure 4.6).[50]

General anaesthesia was induced with propofol and fentanyl. Muscle relaxation was achieved by rocuronium. The patients were intubated and ventilated with a target FE_{CO₂} of 5%. Maintenance of anaesthesia was performed with sevoflurane 1.3 ± 0.1 MAC_{age} and iterated i.v. bolus doses of fentanyl. Before weaning from anaesthesia, parecoxib 40 mg i.v. and droperidol, 0.5 mg was administered i.v. Normovolemia was maintained by continuous infusion of Ringer's acetate at a rate of 2-3 ml/kg/h. Infusion of dopamine or phenylephrine was used to maintain a MAP above 65 mmHg at the discretion of the attending anaesthesiologist. Arterial blood pressure was monitored by a radial artery catheter according to clinical standard procedures. See Table 3.1 for intraoperative medication used in Studies III and IV.

3.4.2 Experimental protocol

In Study III all included patients (n=15) were allocated to IHV intervention in a one-armed clinical feasibility trial. In Study IV 34 patients were included and randomized to either IHV or standard weaning procedure by stratification according to age (>75 or <75 years) and gender (male/female) in a 1:1 ratio. Randomization was performed before induction of anaesthesia and for patients randomized to the IHV group, the CO₂ bottle and mixing box was connected to the inspiratory limb of the breathing circuit before pre-oxygenation. After the end of surgery when the surgical dressings were removed from the patients' head and neck region the sevoflurane vaporizer was turned off. In the IHV groups of study III and IV, hyperventilation was started from a base-line tidal ventilation of 7 ± 1 ml/kg, a respiratory rate (RR) of 12/min, and low flow anaesthesia, with a fresh gas flow (FGF) of 1.5 ± 0.4 L/min by doubling the minute volume (MV) and increasing FGF to 10 L/min to avoid rebreathing of the anaesthetic agent. The RR was increased from 12 to 20 /min to keep the VT moderately increased ($\approx 33\%$). The inspiratory/expiratory relationship (I: E) was set to 1:2. To limit the flow of delivered CO₂ needed to maintain isocapnia during hyperventilation, the CO₂ absorber of the anaesthesia circuit was disconnected and CO₂ was added to the inspiratory limb of the anaesthesia circle via a mixing box. A 450-mL rigid plastic box with an inlet for CO₂ and upstream and downstream ports for standard 22 mm tubing of the anaesthesia circuit was used. See figure 3.4. The delivered CO₂ flow (DCO₂) was manually regulated through a high precision mechanical flow meter (1-1000 ml/min) originally used for NO distribution. See figure 3.5. The DCO₂ was initially set

to a dose according to gender and weight, based on a nomogram calculated from our previous mechanical lung model study (Study I) to achieve isocapnia. See Table 4.1 in result section. Isocapnia during IHV was defined as the FETCO₂ level that was obtained before IHV. In Study IV patients randomized to the control group continued on baseline tidal ventilation of 7±1 ml/kg, respiratory rate of 12/min and fresh gas flow was increased to 5 L/minute. After the end of surgery, sevoflurane administration was abruptly discontinued and the time to extubation and eye-opening were measured. Arterial blood-gas samples were drawn before the vaporizer was turned off, before and directly after extubation and on arrival in the PACU. In PACU postoperative cognition, pain and nausea was measured at 20, 40 and 60 minutes after arrival as well as blood gases and ETCO₂.

Steps	Intervention
1	Connect the box for CO ₂ delivery Before starting hyperventilation: Check patient monitor. Normo-ventilation should maintain a stable FETCO ₂ at 5.0 %.
2	Turn off the vaporizer/inhalation agent.
3	Disconnect the CO ₂ absorber.
4	Start CO ₂ delivery according to nomogram.
5	Start mechanical hyperventilation by: <ul style="list-style-type: none"> a) doubling minute volume b) increasing FGF to 10 L/min c) increasing RF to 20 breaths/min
6	Check patient monitor. Aim for a FETCO ₂ around 5.0 % and FICO ₂ around 3.0 %.
7	Extubation: a) Maintain mechanical hyperventilation until extubation. b) Turn of CO ₂ at extubation.

*Steps 7 a-b were not performed in Study I-II

Table 3.2 Description of the IHV method protocol used in Study I-IV. *

3.5 Monitoring and measurements

3.5.1 Hemodynamic measurements

Study II. Arterial and central venous lines were placed by surgical cut-downs. Mean arterial pressure (MAP), central venous pressure (CVP), cardiac output (CO), stroke volume (SV) and systemic vascular resistance (SVR) were measured/calculated via an arterial pulse contour analysis catheter in the right femoral artery (PiCCO₂ Monitoring Platform, Pulsion Medical Systems AG, Germany).[51] We used a blood gas analyzer calibrated for porcine blood (Radiometer ABL 825, Radiometer Medical Aps., Denmark). MAP, CVP and heart rate (HR) was monitored by the AS/3 multimonitor. (Datex-Ohmeda, Helsinki, Finland)

Study III – IV. Radial arterial blood samples for analysis of arterial partial pressures of oxygen (PaO₂), carbon dioxide (PaCO₂) and pH used RAPIDPoint®500 (Siemens, Germany). Body temperature was monitored by a urinary probe (Foley Catheter Temperature Sensor®, Smiths Medical, U.S.). Bispectral index (BIS), HR and MAP was measured by standard monitoring equipment, the AS/3 multimonitor in Study III and the Philips IntelliVue® MX550, IntelliBrigde® in Study IV.

3.5.2 Respiratory measurements

Study II. Electrical impedance tomography (EIT) registration of the lung was used to record tidal and end-expiratory lung volume changes (Δ EELV) during the different ventilation modes. Sixteen electrodes were placed around the chest wall at the level of the fifth intercostal space and connected to the EIT device (Dräger/Pulmo vista 2000, Germany). EIT data were generated by injection of currents (5 mA, 50 Hz) with measurements of differences between adjacent electrodes in a rotating process.[52-54]

Study II and III. Minute volume (MV), tidal volume (VT), total respiratory compliance (CRS), plateau and peak airway pressures (P_{plateau}/P_{peak}) and respiratory rate (RR) were measured using side-stream spirometry. Inspiratory and end-tidal expiratory fractions of oxygen (FI/FETO₂) and carbon dioxide (FI/FETCO₂) were determined by paramagnetic and infrared technology using an AS/3 multimonitor respectively. Measurements of oxygen consumption (VO₂) and CO₂ production (VCO₂) were provided by the monitor (COVX Module, GE Health Care, Finland).[55, 56]

Study IV. Oxygen saturation (SpO₂), MV, FGF, tidal volume (VT), RR, inspiratory and end-tidal expiratory fractions of oxygen (FI/FETO₂) as well as

carbon dioxide (FI/FETCO₂) were continuously monitored via the FLOWi® Anesthesia Delivery System (Maquet, Sweden) and the standard patient monitors (IntelliVue® MX550, IntelliBrigde®, Philips, Netherland).

Study III and IV. Postoperative ECO₂ was measured via a nasal catheter (Smart CapnoLine Plus O₂®, Philips, Netherland) and recorded visually from the patient monitor directly after arrival in the PACU and repeated at 20, 40 and 60 min after arrival together with arterial blood samples, sedation and PONV scores.

3.5.3 Postoperative recovery

In Study III and IV we performed psychomotor and cognition tests according to The Postoperative Quality Recovery Scale (PQRS) protocol at the preoperative evaluation (baseline) and at 20, 40 and 60 min after arrival in the PACU.[44] It assesses recovery after surgery and anaesthesia using a multimodal questionnaire and scoring system. Changes in physiological, nociceptive, emotive and cognitive variables are evaluated in relation to a preoperative base line assessment. In these studies (III, IV) we used the cognitive, nociceptive, PONV and emotional domains of the PQRS protocol in order to evaluate the early postoperative period. The PQRS cognitive score was followed up by a telephone survey approximately 2-3 days after surgery on all patients. We used a validated Swedish translation of the PQRS questionnaire, originally published by Royse et al in 2010.[57] An example of the Swedish version was published by Lindqvist et al in 2014.[58] The PQRS-test is well documented and has previously been used in randomized trials [58, 59] evaluating short and long time postoperative recovery, as well as different types of surgery technics, anaesthetics methods and their impact on postoperative recovery.[58, 60, 61] The PQRS-method is sensitive of detecting early postoperative recovery differences compared with baseline.[59-61]

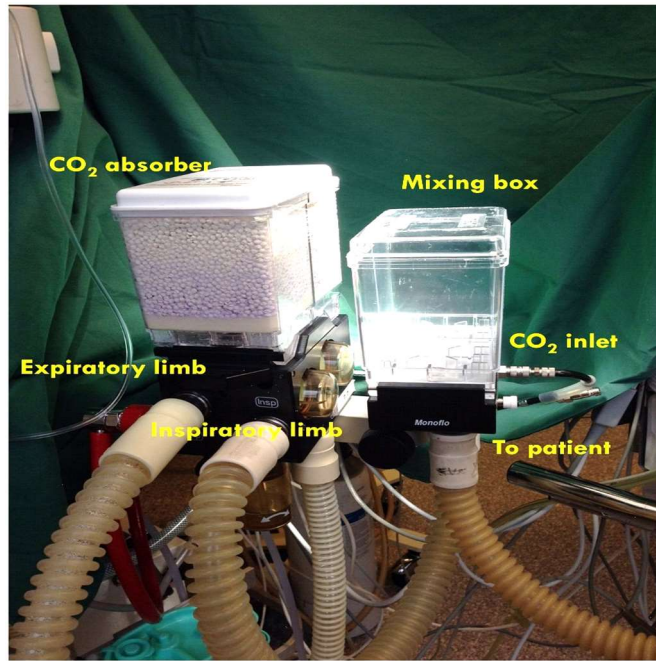


Figure 3.4. Photo of a prototype mixing box and its' connections used in Study I-III

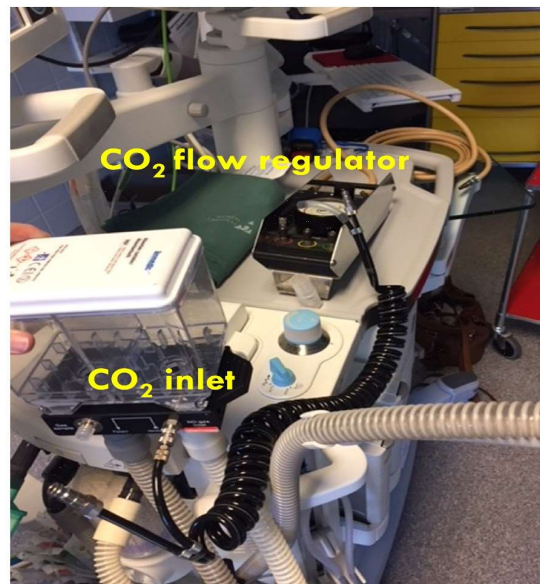


Figure 3.5. Photo of CO₂ regulator (Nomius M) used in Study I-IV and the set up in Operation Unit 7 (OP 7) for Study IV.

3.6 Data collection

In study I – III patient data were collected at 25 Hz to a dedicated software program (S/5 Collect 4, GE Healthcare, Helsinki, Finland)

In study II we used the EIT device (Dräger/Pulmo vista 2000, Germany). EIT data were collected at 5 mA, 50 Hz and downloaded to a USB-memory stick. PiCCO data was collected and downloaded to a USB-stick inserted into the PiCCO-monitor.

In study III and IV perioperative physiological data and postoperative scores were visually and manually recorded in the patient study protocol. The time event intervals for extubation, eye-opening and discharge from OR were relative to the time when the vaporizer was turned off. The post-operative time-intervals were relative to arrival in the PACU.

3.7 Statistical analysis

In Study I non-parametric one-way analysis of variance (Kruskal–Wallis) and Mann–Whitney U-test was used for non-parametric data.

In Study II ANOVA for repeated measurements was used.

In Study II-IV Student's-test was used for continues parametric data.

In Study IV Mann-Whitney U tests were used for non-parametric data and chi-2 tests for categorical data.

In all studies a p-value < 0.05 was considered significant except in paper IV where a p-value < 0.01 was considered significant as Bonferroni's correction was used. Values in tables, figures and text are presented as mean \pm SD as well as median and range when applicable. Descriptive statistics and tests were calculated with software Microsoft Excel® 14.0 (©Microsoft Corp. 2010) and Statview 5.0.1® (©SAS Institute Inc. 1998) and where used in all papers.

In a small pilot study preceding the randomized trial, isocapnic hyperventilation reduced the time to discharge from OR by 44 % (non-published data). For our primary end-points i.e. time to extubation and time to discharge from OR, we calculated that with power set to 0.8 and alfa-value to 0.05, the minimum number of subjects in each group sufficient to test this hypothesis was 10.

4 RESULTS

4.1 Lung Model (Study I)

4.1.1 Effective alveolar ventilation during IHV

In Figure 4.1 we demonstrate the effective alveolar ventilation for anaesthetic gas ($V_{A(AGfunctional)}$) during gradual introduction of isocapnic hyperventilation (IHV) from 1) base line ventilation (BLV) to 2) removal of the CO_2 absorber, 3) increase of minute ventilation (HV1), 4) increase of fresh gas flow (HV2) and 5) infusion of CO_2 into the inspiratory limb. At a dead space of 92 ml and CO_2 production of 200 ml/min the $V_{A(AGfunctional)}$ was 8,7 L/min and $FETCO_2$ was 5,0% during IHV. Simultaneously, selective alveolar ventilation for CO_2 ($V_{A(CO_2)}$) increased from base line ventilation by approximately 50% at hyperventilation (HV2) and remained unchanged at IHV by manipulation of $FETCO_2$, while the functional alveolar ventilation for anaesthetic gas increased with about 100% ($p < 0.001$). The $V_{A(AGfunctional)}$ increased with $113 \pm 6\%$ at all VD and VCO_2 levels during hyperventilation. Correspondingly $V_{A(CO_2)}$ increased with $55 \pm 12\%$ during HV2 but returned to base line value at IHV.

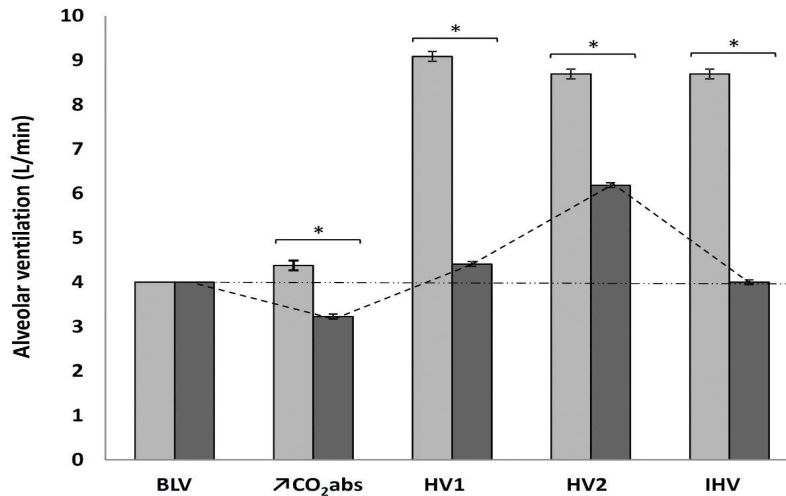


Figure 4.1. In a mechanical lung model (Study I) the alveolar ventilation for CO_2 (dark grey columns) returns to base line (dotted lines) during IHV but the effective alveolar ventilation for anaesthetic gas is doubled (light grey columns). A result of the increase of inspiratory CO_2 level. Note the effect of removal of the CO_2 absorber ($\uparrow CO_2$ abs). * $p < 0.01$

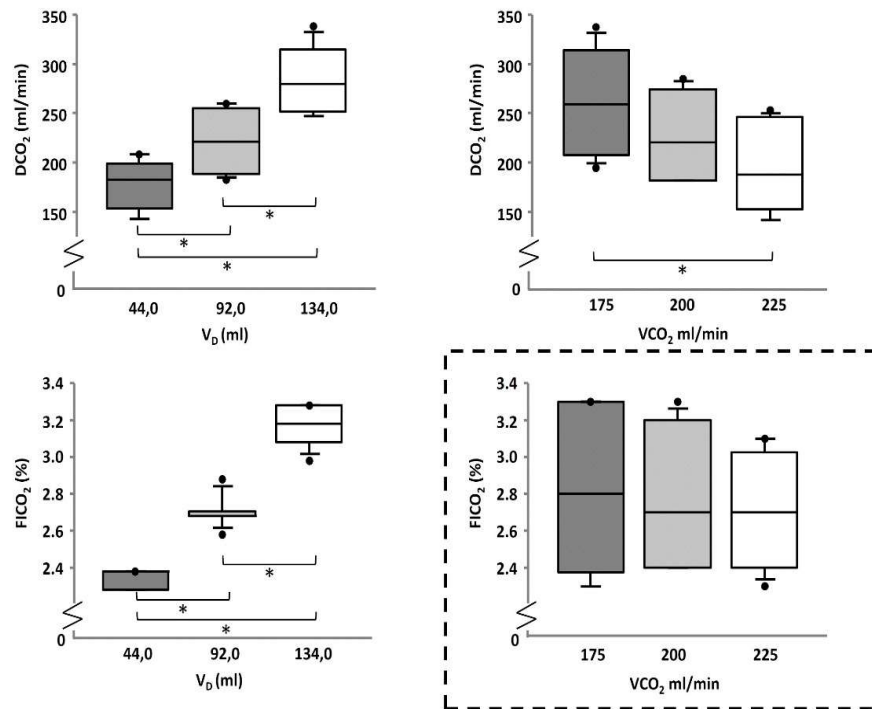
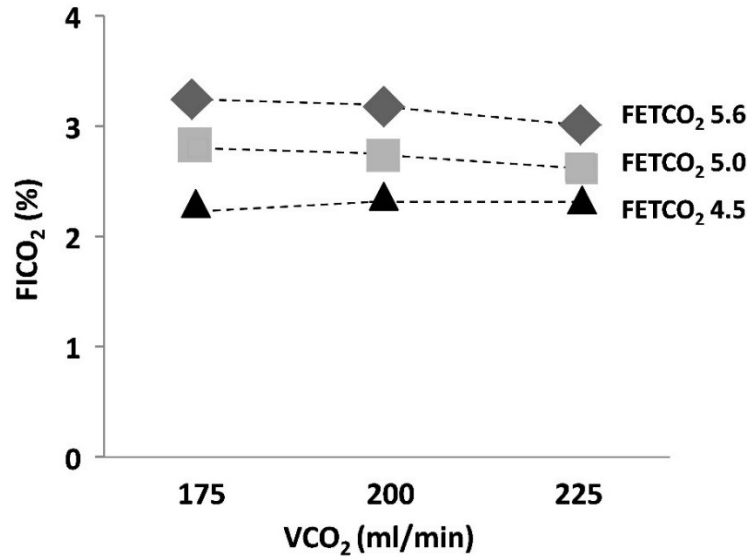


Figure 4.2. In the mechanical lung model (Study I) it was found that the FICO₂ level needed to keep isocapnia was independent of VCO₂ level. Probably a result of rebreathing of CO₂ during hyperventilation at the higher VCO₂ levels. See also Figure 4.3.

4.1.2 The effect of dead space and metabolism on delivered CO₂ during IHV

In study I it was shown that a low CO₂-production (metabolism) and a large dead space resulted in a need for a higher CO₂ flow into the breathing circuit during hyperventilation to maintain isocapnia. See fig 4.2. The amount of DCO₂ varied between 148 and 338 ml/min depending on dead space (44, 92, 134 ml) and metabolic level (175, 200 or 225 ml CO₂/min). We had to elevate the DCO₂ by 14-72 % when increasing dead space from 44–134 ml depending on metabolic level. Elevation of CO₂ production from 175–225 ml/min resulted in a lowered DCO₂ by 7-31 % depending on dead space (DCO₂ vs VD level, $p < 0.001$; DCO₂ vs VCO₂ level, $p < 0.05$). The inspiratory

CO₂ fraction varied slightly between 2.3 and 3.3% at different levels of dead space. In addition, the FICO₂ was not dependent on VCO₂ level at a certain dead space volume as shown in figure 4.3



. **Figure 4.3** The inspiratory CO₂ level during isocapnia (FICO₂) was plotted against different metabolic (VCO₂) levels at three end expiratory CO₂ levels (FETCO₂) in the mechanical lung model (Study I) and it was found that a stable FETCO₂ of 5 % was maintained at all three levels by a FICO₂ of about 3 %.

4.1.3 Quantification of delivered CO₂ during IHV

We used the data of DCO₂ at the dead space volume of 92 ml and correlated them to the different VCO₂ levels. The correlation was combined with the relationship between body weight, gender and VCO₂ in human subjects investigated by Radford.[30] We calculated that DCO₂ varied accordingly with body weight and gender and a nomogram was thereby established, see Table 4.1. We also took into account the metabolic effect of anaesthesia by using Nunn's estimation of a reduced O₂ demand of about 10-20 % in anaesthetized human subjects and extrapolated it to a similar reduction in CO₂ production.[30, 47] The nomogram can be used to perform isocapnic

hyperventilation, provided that the standard mechanical hyperventilation procedure described above (steps 1-5) is followed strictly. See Table 4.1

Body weight (kg)	Female			Male		
	VCO ₂ awake (ml/min)	VCO ₂ anaesthesia (ml/min)	DCO ₂ (ml/min)	VCO ₂ awake (ml/min)	VCO ₂ anaesthesia (ml/min)	DCO ₂ (ml/min)
40	135	115	377	147	125	354
50	145	123	358	165	140	322
60	155	132	340	188	160	285
70	165	140	322	205	174	259
80	175	149	305	222	189	236
90	185	157	289	240	204	213
100	195	166	274	260	221	191
110	205	174	259	280	238	171
120	215	183	245	300	255	154
130	225	191	232	320	272	140

Table 4.1 Gender and weight nomogram (Study I) for predicted CO₂ delivery, DCO₂ (ml/min) with the correlated VCO₂ values “awake” and corrected for “anaesthesia” effect on CO₂ output.

4.2 Porcine Model (Study II)

4.2.1 Elimination of anaesthetic inhalational agent

The washout time of sevoflurane after 55 min of inhalation anaesthesia, was markedly shorter during isocapnic hyperventilation than during normoventilation, 433 ± 135 s vs. 1387 ± 204 s ($P < 0.001$). The whole washout procedure lasted about one-third of the time using isocapnic hyperventilation, compared to normoventilation. FISevo and FETSevo were almost identical, 2.8 ± 0.1 vs. $2.7 \pm 0.1\%$ at the beginning of the washout procedure. In figure 4.4 the difference between normoventilation and IHV regarding sevoflurane washout is graphically described.

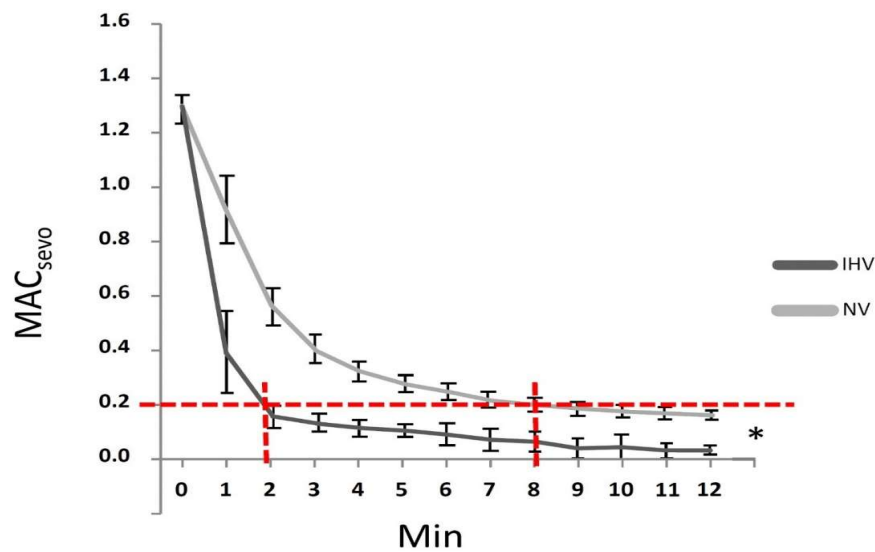


Figure 4.4 Washout of sevoflurane after 55 ± 13 minutes of inhalational anaesthesia in the porcine model of Study II. With isocapnic hyperventilation, MAC of 0.2 is reached about 6 minutes earlier than with normo-ventilation. * $p < 0.01$.

4.2.2 Effect on respiratory and circulatory variables

The anaesthetized and mechanically ventilated pigs had a physiological dead space of 144 ± 14 ml corresponding to the physiological dead space of a 70-kg male. During isocapnic hyperventilation the minute ventilation was 11.5 ± 0.9

L/min. compared to baseline ventilation 5.2 ± 0.6 L/min. The amount of CO_2 needed to maintain isocapnia during the hyperventilation procedure was regulated by monitoring FICO_2 and FETCO_2 values. By administering CO_2 of 261 ± 9 ml/min the FICO_2 varied around $3.1 \pm 0.3\%$ which kept the FETCO_2 value at $5.7 \pm 0.3\%$. Thus, the variability of the delivered CO_2 and the resulting inspiratory CO_2 fraction required to maintain isocapnia was low. During IHV and rapid washout of sevoflurane, MAP and SVR increased slightly, while CO decreased with 0.5 L/min. ($P < 0.01$). During the slower washout of sevoflurane at normoventilation, hemodynamics were not affected. The increase in tidal volume from BLV to HV (ΔVT) was only 124 ± 18 ml as a consequence of the increase in respiratory rate from 15 to 22/min. If the RR had been kept at 12/min, the VT during IHV would have been in mean 960 ml. Minor changes in respiratory system compliance (Cr_s) were registered during the study protocol, comparing BLV to NV, 28 ± 6 and 26 ± 5 ml/cmH₂O respectively (ns). P_{peak} at BLV and during HV was 18 ± 2 and 26 ± 3 cmH₂O respectively. The end-inspiratory airway plateau pressure was 18 ± 2 and 25 ± 3 cmH₂O during BLV and HV respectively. The highest end-inspiratory airway plateau pressure observed was 30 cm H₂O.

Effect of IHV on gas exchange and end-expiratory lung volume (EELV)

Arterial blood gas analyses during the experimental protocol showed that PaCO_2 varied concordantly with FETCO_2 at baseline and isocapnic hyperventilation 5.3 ± 0.5 kPa vs. $5.3 \pm 0.5\%$ and 5.2 ± 0.4 kPa vs. $5.6 \pm 0.4\%$ respectively. Furthermore, PaCO_2 was stable during the washout procedure with IHV compared to baseline ventilation, 5.1 ± 0.3 vs. 5.2 ± 0.5 kPa. The corresponding FETCO_2 values were 5.6 ± 0.4 vs. $5.7 \pm 0.3\%$. Oxygen tension and saturation were stable within normal limits during the whole experimental protocol with no differences between normoventilation or isocapnic hyperventilation and at an inspiratory fraction of oxygen at $35 \pm 2\%$. Consequently, pH values were within normal limits and varied between 7.45 ± 0.02 at baseline and 7.48 ± 0.04 at IHV (ns). The EIT measurements indicated recruitment of lung tissue after start of hyperventilation where the end-expiratory lung impedance (EELI) level increased as an expression of end-expiratory lung volume increase. The change in EELI corresponded to an end-expiratory lung volume increase of 125 ± 53 ml when shifting from BLV to HV by (ΔEELV). Tidal volume increased from BLV to HV (ΔVT) by 124 ± 18 ml. In figure 4.5, an EIT registration from one animal during one minute is describing the course of the hyperventilation procedure.

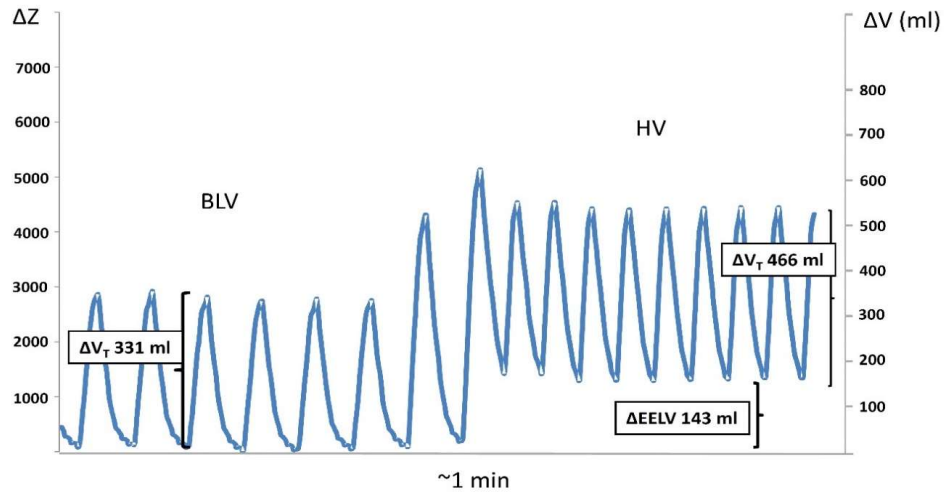


Figure 4.5 In Study II the animals were ventilated with a tidal volume (V_T) of 18 ± 2 ml/kg during isocapnic hyperventilation (bodyweight 28 ± 2 kg). This is an example of an EIT tracing (ΔZ) from one pig during hyperventilation where the ΔV_T is increased by 135 ml and consequently the end expiratory lung volume (EELV) by 143 ml ($\Delta EELV$) as a result of lung recruitment.

Effect of IHV on systemic hemodynamics and metabolism

Compared to normoventilation MAP was increased from 75 ± 8 mmHg to 93 ± 14 mmHg during IHV ($p < 0.01$). CVP was increased from 8.5 ± 3 mmHg to 9.1 ± 3 mmHg. Stroke volume and heart rate were not affected during the hyperventilation procedure. However, cardiac output was lowered during IHV from 3.0 ± 0.5 to 2.5 ± 0.3 L/min ($p < 0.01$) and the systemic vascular resistance was increased from 1871 ± 234 to 2675 ± 586 (dynes*s/cm⁵). During sevoflurane washout, using IHV both the VCO_2 and VO_2 remained stable, 176 ± 22 ml/min vs. 173 ± 23 ml/min and 205 ± 22 ml/min vs. 207 ± 29 ml/min respectively (BL vs. end of washout). However, during the normal ventilation procedure, both the VCO_2 and the VO_2 increased at the end of washout compared to BL, 170 ± 21 ml/min vs. 188 ± 21 ml/min and 203 ± 22 ml/min vs. 224 ± 32 ml/min respectively (BL vs. end of washout, $p < 0.01$).

4.3 Patients (Study III-IV)

Patients scheduled for major head and neck surgery at the Sahlgrenska University Hospital, Gothenburg were enrolled in the preoperative evaluation center. In study III, 15 adult patients, 8 females and 7 males, 57±16 years of ASA grade I-III were included. In study IV, 34 adult ASA I-III patients were included in the study and randomized to IHV or control. Thirty-one patients finalized the study protocol, 16 in the IHV group and 15 patients in the control group. Patients with severe pulmonary and vascular disease, ASA>III, BMI >35, anaesthesia duration<3 hours or communication difficulties were excluded. The indication for surgery was head and neck tumors. See figure 4.6 for patient flow charts and Table 4.2 for summary of patients in study III and IV.

Study	Intervention IHV/NV	ΔT (%)	HV L/min	DCO ₂ ml/min	FICO ₂ %	FETCO ₂ %	PaCO ₂ kPa	VCO ₂ ml/min	P _{plateau} cmH ₂ O
I	3 / 3	NA	10±0	258±4	2.8±0.1	5.0±0.1	NA	175	17±1
II	8 / 8	-67	12±1	261±19	3.0±0.2	5.2±0.2	5.1±0.3	173±23	25±3
III	15 / 0	NA	14±4	285±45	3.0±0.3	5.3±0.3	NA	176±32	19±3
IV	16 / 15	-50	14±4	280±59	3.4±0.3	5.6±0.5	5.3±0.7	NA	NA

IHV = Isocapnic Hyperventilation, NV = Normo-ventilation, HV = Hyperventilation, CO₂ = carbon dioxide, DCO₂ = delivered CO₂ during IHV, FICO₂ = Inspiratory CO₂ fraction during IHV, FETCO₂ = End tidal CO₂ fraction during IHV, PaCO₂ = Arterial CO₂ tension, VCO₂ = CO₂ production, P_{plateau} = plateau airway pressure, ΔT = change/reduction of washout time (II) and time to extubation (IV) using IHV.

Table 4.2. Summary of interventions and CO₂ data at isocapnic hyperventilation in studies I-IV

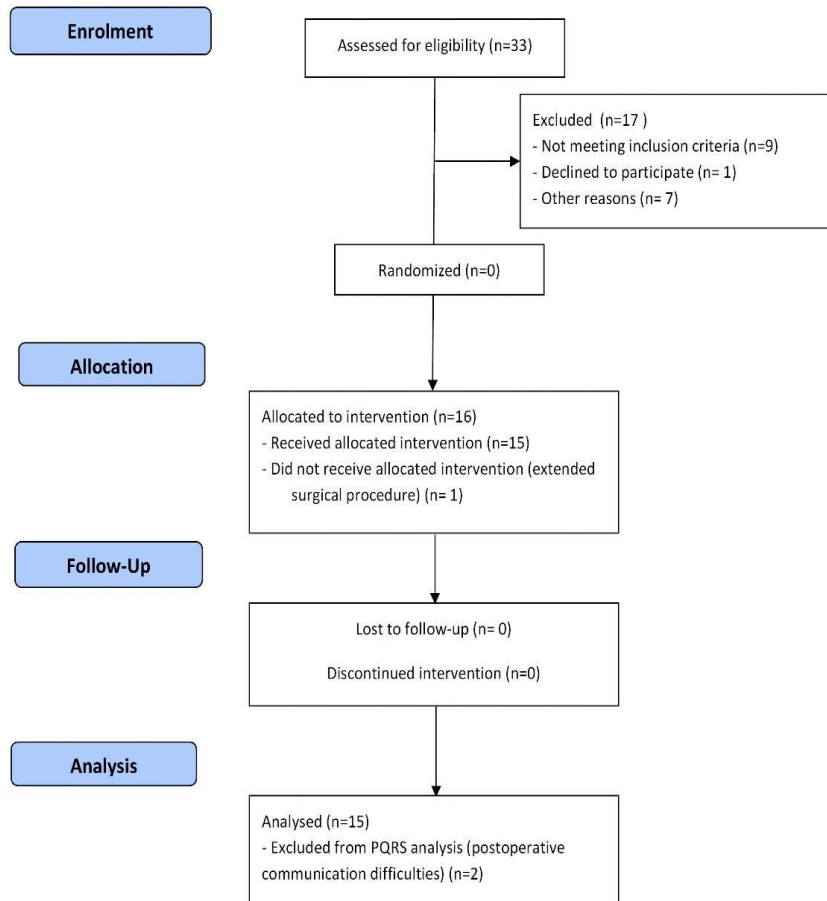
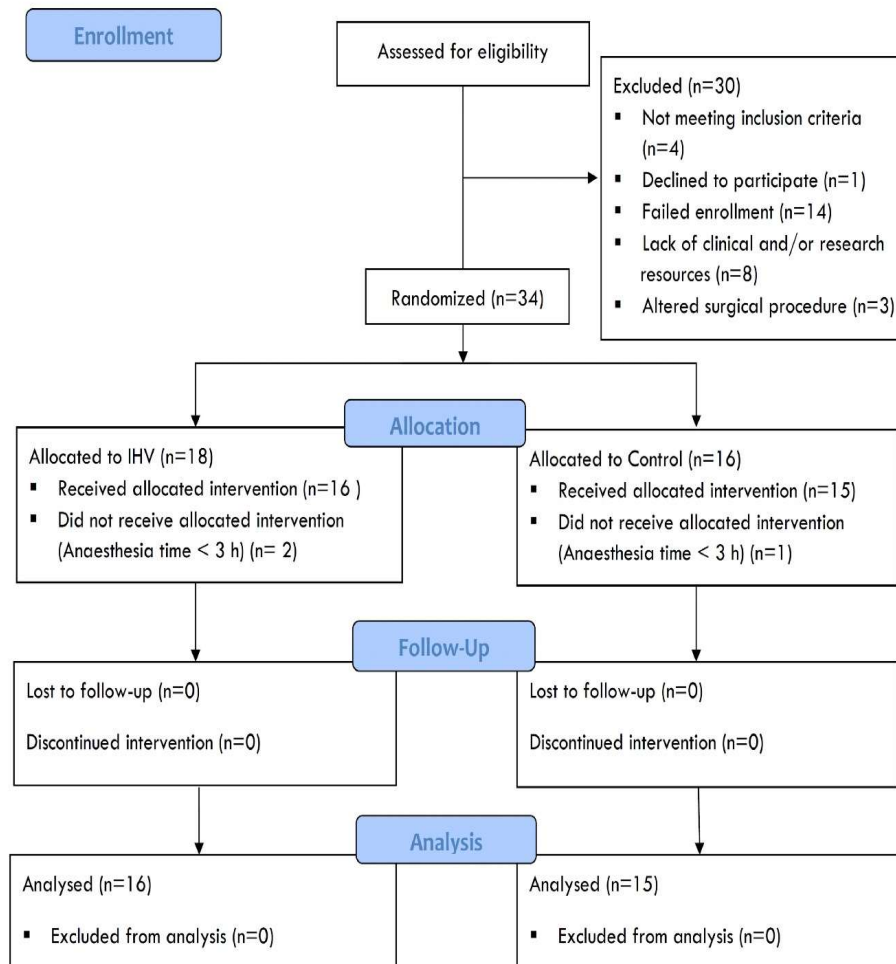


Figure 4.6 a + b. Patient flow charts of the one armed (a; IHV only) and two armed (b; IHV vs. control) randomized clinical trials of Study III and IV



4.3.1 Clinical applicability of method

In the clinical pilot study (Study III), we found that the nomogram was applicable in a clinical setting. We used the gender and weight nomogram for targeting the individual CO₂ flow dosage during the standardized HV protocol in the cohort of 15 patients. A DCO₂ of 285 ml/min (213–348 ml/min) according to the nomogram provided stable isocapnia at a MV of 13.5±4 l/min, without need for adjustment of CO₂ flow. In the prospective randomized study (Study IV) the IHV group of 16 patients received a DCO₂ of 280±159 ml/min, according to the nomogram during a minute ventilation of 14±4 L/min, which produced a stable isocapnia. See figure 4.7. We saw only normal airway pressures (P_{plateau}) in Study III. See Table 4.2.

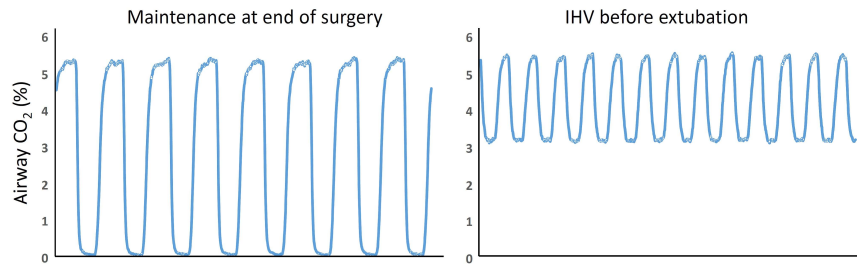


Figure 4.7. Capnography tracing from one patient during isocapnic hyperventilation (IHV) in Study III, showing the stability of the method in a clinical setting.

4.3.2 Effect on intraoperative outcome measures

In Study III where all patients (n=15) received IHV weaning, the time to extubation was 11±2 min after 6±2 hours of general anaesthesia. Time to eye opening was 13±4 min and time to discharge from OR was 21±4 min. Total dose of fentanyl was 155±33 µgram/hour. Airway pressures (P_{plateau}) were within normal limits in Study III (Table 4.2.)

In the randomized study (Study IV) time to extubation was shortened by 50%, time to eye-opening by 34 % and time to discharge from OR by 31 % in the IHV group (n=16) compared to the standard weaning group (n=15). Time to extubation in the IHV group were 13 (11-19) min after 5±2 hours of general anaesthesia. Time to eye opening was 19 (12-37) min and time to discharge from OR was 24 (19-44) min. The total dose of fentanyl was 184±33 µgram/hour. See Table 4.3.

4.3.3 Effect on early postoperative outcome measures

The patients in Study III returned to 62-100% of the preoperative PQRS cognitive score within 60 minutes after arrival in the PACU. Within the first hour nausea or pain was detected in 14-20% of the patients. All patients could verbally respond to command 20 minutes after arrival in the PACU and at 60 minutes 85% of the patients were fully recovered according to the PQRS score. See table 4.3.

In Study IV, the proportion of patients recovering from pain, PONV and impaired cognition at 20, 40 and 60 minutes after arrival in the PACU, did not differ between the IHV and the control group ("standard" wake up procedure). However, a trend towards faster cognitive recovery was seen in the IHV group, where 44% vs. 27% were recovered at 20 minutes and 69% vs. 53 % at 40 minutes. There was also a trend towards faster recovery in pain and nausea, as 88 % in the IHV group vs. 67 % of patients in the control group were recovered at 60 minutes after arrival in the PACU. See Table 4.3.

4.3.4 Effect on perioperative respiratory and circulatory variables

In Study III and IV we found that the use of our nomogram for CO₂ delivery in combination with standardized doubling of mechanical baseline ventilation and an increase of fresh gas flow to 10 L/minute provides a stable FICO₂ and FETCO₂ in patients. This was confirmed by repeated blood gas analysis during the experimental protocols. In study III we could observe an intrinsic peep of 2.7± 1.8 cmH₂O, an increase in plateau pressure from 15±2 to 19±3 cmH₂O and an increase in respiratory system compliance (Crs) from 61 ± 14 to 70 ± 17 ml/ cmH₂O during IHV (p<0.01). In study IV at the end of surgery before weaning, ventilation, circulation and anaesthesia depth were similar in both groups. ETCO₂ and PaCO₂ values were similar between groups at base-line before weaning and just before extubation. Two minutes after extubation, at arrival and all three-time points in the PACU ETCO₂ and PaCO₂ values did not differ in the IHV and control group.

Outcome	Study III	Study IV	
	IHV (N=15)	IHV (N=16)	Control (N=15)
In operation room (OR)*			
Time to extubation	11 (8-14)	13 (11-19)	26 (19-40)
Time to eye opening	13 (8-21)	19 (12-37)	32 (19-53)
Time to discharge OR min; median (range)	21 (16-29)	24 (19-44)	34 (25-57)
In postoperative care unit (PACU)			
Cognition, n (%) of patients recovered**			
T20	4 (31)	7 (44)	4 (27)
T40	10 (77)	11 (69)	8 (53)
T60	11 (85)	14 (88)	14 (93)
Pain and nausea, n (%) of patients recovered			
T20	9 (60)	15 (94)	14 (93)
T40	10 (67)	16 (100)	12 (80)
T60	10 (67)	14 (88)	10 (67)

*Immediate outcome variables (time to extubation, eye opening and discharge from OR in minutes) was measured from the time point when the vaporizer was turned off. The early postoperative outcome variables (cognition, pain and nausea) was measured from the time point (T) when the patient arrived in the postoperative care unit (PACU) at (T20, 40, 60 min). ** N=13 in Study III.

Table 4.3 Immediate and early postoperative outcome variables in Study III and IV*.

5 DISCUSSION

In this thesis, a method that quickly and safely speeds up the recovery after sevoflurane anaesthesia is proposed. The method is based on the known principle of isocapnic hyperventilation used for increasing the elimination rate of volatile anaesthetics. By infusion of a pre-calculated amount of CO₂ via a mixing box into the inspiratory limb of a closed anaesthesia circuit during doubling of minute ventilation, the proposed method is a development of the original approach of IHV, adapted to modern conditions and safety requirements. The procedure is controlled by using the standard monitoring equipment and ventilators of modern anaesthesia delivery units with minimal modifications of the breathing circuit. In study I, the method was tested in a mechanical lung model, where a CO₂ gender and weight based nomogram for maintaining isocapnia during hyperventilation was experimentally calculated. The method was tested in vivo in study II, where it was found that the elimination rate of sevoflurane was increased about three times, without any marked impact on ventilatory or circulatory parameters. The method was also evaluated in two patient studies, where in a clinical pilot trial, study III, it was found that the CO₂ nomogram was applicable in a clinical setting. In the following prospective randomized study, study IV, the time for extubation was reduced by 50% in the IHV group. There was not any unexpected impact on cognition, nociception or any adverse events during the post-operative process. In the studies, it was found that by using the CO₂ nomogram, a FICO₂ of 3.0% was sufficient to maintain a stable and efficient isocapnia and sevoflurane washout, provided that the protocol for mechanical hyperventilation was followed. There was no record of adverse events or hypercapnic incidents during the study periods.

5.1 Methodological considerations

Study I was a bench test performed on a mechanical lung which uses a constant flow of CO₂ into the lung to obtain a simulated CO₂ output.[45] However, a mechanical lung model is not taking into account the effect of oxygen consumption; presence of inhalation anaesthetics; humidification of the airways; spontaneous breathing efforts or potential circulatory effects of HV. Furthermore, perfusion limitations and gas tensions influence the difference in arterial and alveolar gas tensions. Body-stores of CO₂ influence time to steady state after a ventilation change. Thus, the data of Study I could not immediately be transposed to the in vivo situations.

Study II was an experimental in vivo study, in which eight animals served as their own controls and the two interventions were performed in a randomized order in all animals. Applicability to human physiology can be questioned, as there are some known physiological differences between porcine and human lung circulation and ventilation. The time recordings were not blinded and the animals were not completely weaned from anaesthesia, as it was not possible with the present experimental setup. Consequently, it was not possible to extubate them to assess recovery time or potential rebound effects of CO₂ and inhalation anaesthetics.

Study III was a one-armed clinical trial performed on a limited number of patients and the results should be interpreted bearing this in mind. Study IV was a randomized clinical trial. The interventions in the treatment and control groups could not be blinded, as the modifications of the anaesthesia circuit and ventilator settings during IHV was difficult/impossible to mask. The study was underpowered in detecting differences in the postoperative outcome variables. Time to discharge from PACU was not measured as the studied surgical population routinely were scheduled to stay overnight. The randomization procedure was stratified according to gender and age, as they are important influencers of metabolism, which should be taken into account when interpreting the results of Study IV.

In all studies, hand titration of CO₂ was used for performing IHV in contrast to previously described methods, which allow automated titration of CO₂. [12, 13]. In study II and IV a comparison between IHV by doubling minute ventilation and increasing FGF to 10 L/min with a “standard weaning procedure” according to the study protocol by keeping base line ventilation and increasing FGF to 5 L/min. One could question if this really is a “standard weaning procedure”. However, clinical experience and recently published data have shown that a FGF of more than 5 L/min does not further increase elimination of volatile anaesthetics. [62]

5.2 Ethical issues

Ethical considerations were made before planning the studies. Since the IHV method we wanted to study was not in clinical use we decided to begin with experimental studies on mechanical and animal models. For safety reasons we performed a bench test calculation of the optimal CO₂ dosage to avoid hypercapnic incidents (Study I). We also wanted to evaluate potential respiratory and circulatory side-effects of mechanical hyperventilation in an animal model before moving on to clinical studies in patients. It can be questioned whether animals should be used for medical and experimental

reasons. The pigs used in Study II were taken care of by educated personnel and treated in accordance with the European Convention for the Protection of Animals used for Experimental Purposes, Council of Europe, 2010/63/EU. The regional ethical committee of Gothenburg also wanted to see the results of a clinical pilot trial before permitting a full scale randomized study in patients. After presenting the preliminary results of the pilot trial (Study III) we were allowed to continue with Study IV.

5.3 Study population

In Study II pigs of 26-31 kg body weight were used as their airways and metabolism are similar to a grown adult. This porcine population has been used in many studies assessing respiration and lung function.[52, 53, 63, 64] In Studies III and IV we chose ENT patients scheduled for major head and neck surgery as they have to be deeply anaesthetized up until the surgical dressing are removed, to avoid coughing which can cause bleeding. The IHV method has not been studied in this particular surgical population before and we considered it interesting to evaluate IHV in long-duration inhalational anaesthesia. On the other hand, this patient group routinely stay overnight in the PACU, thus we could not measure time to discharge.

5.4 The use of isocapnic hyperventilation today

At present, there are several clinically approved methods for performing IHV in use, mostly in Anglo-Saxon countries.[7, 10, 13] However, they are not widely implemented as they require external breathing or monitoring equipment connected to the patient and/or anaesthesia delivery system. The original IHV method could be performed by simply connecting a CO₂ bottle to the standard breathing circuit and therefore became widespread.[15, 18, 19] The former practice of keeping the CO₂ flow during spontaneous breathing in combination with limited pre- and postoperative monitoring possibilities lead to severe hypercapnic incidents.[65] Today, the anaesthesia delivery systems and the postoperative care units provides continuous, accurate and easily available inspiratory and expiratory gas monitoring, which reduces the risks of persisting gas exchange disturbances. The optimal flow or amount of CO₂ needed has been stated in this thesis (Study I-IV) and eliminates the risk of overdosing CO₂ during IHV. With rather small modifications of the standard breathing circle it would be possible to implement this “fast weaning” method into any modern anaesthesia apparatus. Earlier conclusions that the IHV-method is unnecessary due to the introduction of short acting volatile anaesthetics are in need of a re-evaluation, as several studies besides the studies

included in this thesis, present a marked reduction in time to extubation, eye-opening and time to discharge from operation room. The potential cost reduction and quality of care improvement is considerable.[66, 67]

5.5 Physiological effects of isocapnic hyperventilation

5.5.1 Respiratory effects

In the animal model of Study II, continuous EIT measurements of lung aeration during the experimental procedure allowed monitoring of potential over-distension during hyperventilation, which was not observed. Instead, a small recruitment of lung tissue took place, probably as a result of an increase in intrinsic PEEP. In Study III, during IHV in patients, an increase in respiratory compliance was observed, as a result of an intrinsic PEEP of 2–3 cmH₂O causing possible recruitment of atelectatic lung regions. It could be argued that the 33% increase in tidal volume that we introduced during IHV could over-distend these healthy lungs and induce a “volotrauma”. However, in Study II, using EIT measurements of the lung, a recruitment of end-expiratory lung volume during hyperventilation was seen, as shown also in Study III, but without over-distension of lung tissue. Considering this, and the relatively short duration of the procedure (10-12 min), isocapnic hyperventilation is probably less likely to cause injury in healthy lungs.[68, 69] Postoperative hypoxia and atelectasis is a very common problem postoperatively and a weaning method that reduces this risk by a moderate recruitment of lung volume should be considered a benefit.[70-73] In Study III the patients were very well saturated postoperatively with a normal P/F ratio, suggesting that the technique is not traumatic for the lungs. Considering the rather short time of exposure, the physiological effects could be comparable to a mild recruitment maneuver. No respiratory adverse events were observed during the patient studies (Study III and IV). In this thesis results from blood-gas analysis during isocapnic hyperventilation is presented. In Study IV end-tidal CO₂ measurements and arterial CO₂ tension were normal and without differences between groups during weaning, prior to extubation, directly after extubation and on arrival in the PACU, confirming that isocapnia during IHV as registered in end-tidal gas measurements was successful. Post-operative monitoring of ETCO₂ and analysis of arterial blood gases was normal, without any signs of hypercapnia in Study III and IV. There were no unexpected discrepancies between PaCO₂ and ETCO₂ values measured at baseline or at end of the washout procedure. This is in line with earlier research showing that the difference between arterial and alveolar CO₂ tensions is fairly constant.[74-76]

Provided that the protocol of the method is followed by using the nomogram and keeping FICO₂ at around 3 %, weaning by this IHV-method should be safe, if implemented in clinical routine.

5.5.2 Circulatory effects

In Study II, during washout of sevoflurane with IHV in the porcine model, an increase in SVR and MAP was observed, which probably was a result of the decreasing vasodilatory influence of inhalation anaesthetics on vascular tone. The effect would probably have been more prominent if the weaning procedure had been completed as intravenous anaesthesia had to be reintroduced before sevoflurane was completely exhaled. This could also be the explanation for the observed decrease in cardiac output and stroke volume during isocapnic hyperventilation considering the negative inotropic effect of pentobarbital and the increased afterload by the washout of sevoflurane. Considering that the mechanical hyperventilation induces recruitment of lung tissue, the decrease in CO could also be an effect of increased intrathoracic pressure. The increase in VO₂ and VCO₂ seen during sevoflurane washout at normoventilation could be explained by an increase in basal metabolic rate. It is not immediately evident why this did not take place when sevoflurane was washed out during IHV. In the patient studies (Study III and IV) we did not observe any circulatory side-effects of the mechanical hyperventilation during weaning as the MAP and HR increased as expected due to the outwash of sevoflurane. However, during anaesthesia maintenance, most of the study patients needed support of vasoactive drugs to keep MAP > 65 mmHg according to the study protocol, as the surgical procedure demands deeply anaesthetized patients. Muscle relaxants was only administered at intubation and was not repeated. The purpose of this approach was to not disturb the weaning procedure and still have immobilized patients during surgery.

5.6 Perioperative outcome

In Study II there was a threefold increase in washout rate of sevoflurane but it was not possible to measure time to extubation or eye-opening in the animal model for ethical reasons. In Study III, 15 patients undergoing sevoflurane anaesthesia with a duration of 3.5–11, was extubated within 8–14 min, after discontinuing inhalation anaesthesia, without anaesthesia rebound effects or impaired quality of recovery. In Study IV, including 31 patients undergoing long-term sevoflurane anaesthesia, it was found that time to extubation was reduced by 50 % or 14 minutes on average using IHV compared to a control group. Time to discharge from the operation room was shortened by about 11 minutes, which could be considered a significant amount of time in a

perioperative production context. Randomized trials assessing current IHV-methods have found similar marked reductions in time to extubation, eye-opening and discharge from OR. The results from the clinical trials confirm earlier published data regarding IHV, hence being an effective method in reducing time to emergence after inhalational anaesthesia. [5-8, 23, 24] There are minor differences in time to eye-opening, extubation and discharge from OR between the IHV-groups in study III and IV. This could be a result of the use of two different anaesthesia delivery systems (ADU and FLOWi) and ventilator modes (VCV and PRVC). [62] The two IHV-groups in Study III and IV also differs in mean age and weight. (Table 3.3 and 4.3)

5.7 Postoperative outcome

In Study IV, when assessing postoperative pain, PONV and cognition from the time point of arrival in the PACU up to 60 minutes after arrival, there was no statistically significant difference between treatment groups but a trend toward improved performance in the IHV-group. This indicates that IHV-weaning method, is at least, not associated with anaesthesia rebound effects, less effective pain reduction or greater negative impact on cognitive abilities. In contrary we found that 44 % of patients in the IHV-group vs. 27 % of patients in the control group were cognitively recovered 20 minutes after arrival in the PACU. However, the cognitive difference between groups decreased over time and was equalized at 60 min after arrival in the PACU. Furthermore, at 60 minutes after arrival in the PACU, nausea and pain were recovered faster in patients from the IHV-group, 88 % vs. 67 % in the control group. Previous research from Katznelson et al [8, 10, 11] have shown that the IHV-method shortens duration of stay in PACU. The data from the patient studies (Study III and IV) may also be comparable with a study published by Royse et al. 2014 evaluating PQRS in an orthopedic surgery groups of elderly patients > 65 years, who had undergone either orthopedic arthroscopic knee or total knee arthroplasty (TKA) during general anaesthesia. Recovery of cognitive function at 40 min post-operatively was 60% in the arthroscopic knee group, and 20% in the TKA group. In Study III, the patients with a mean age of 57 years performed better in the cognitive tests at 40 min compared with the patient groups in the study of Royse et al. 2014. Furthermore, the patients of Study III and IV had a PONV frequency comparable with the elderly orthopedic patient population, although patients were anaesthetized 2–3 times longer. Isocapnic and hypercapnic hyperventilation has been shown to decrease time spent in the PACU but the assessment tools used in these studies has not been able to detect the reasons behind this positive effect on postoperative recovery. Patients with a rapid cognitive recovery in the early postoperative period is more able to

communicate presence of nausea and location of pain. Consequently, the patient receives appropriate treatment which further enhances recovery. A faster cognitive recovery also enhances the patients' ability to follow instructions in the early postoperative period.[57-61, 77] This is probably reflected by the less variability of the PQRS score in the IHV-group of Study IV displayed in Figure 5.1., although there is no statistically significant difference between the treatment groups

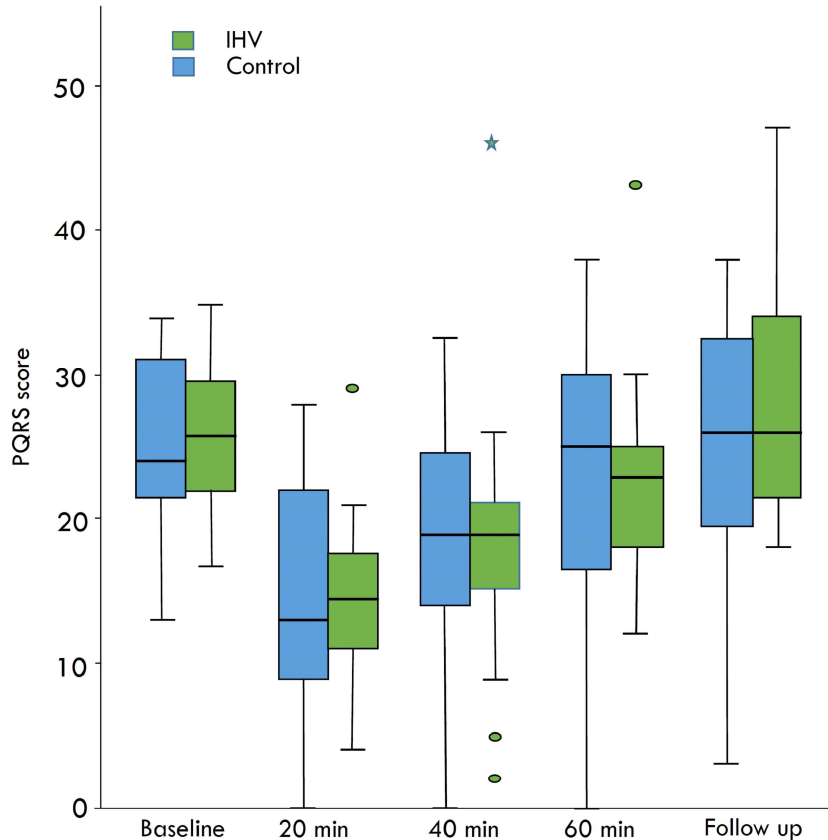


Figure 5.1. Boxplot showing median, 25th to 75th percentile and 10th to 90th percentile, outliers as individual points, of PQRS score at pre-operative evaluation (Baseline), 20, 40 and 60 minutes after arrival in the PACU. Comparison between the treatment groups (IHV vs. control) of the randomized clinical trial (Study IV).

5.8 Environmental considerations

CO₂ is a greenhouse gas as well as anaesthetic gases which also are a source of greenhouse gas emissions. Health-care services and in particular operation theatres are resource intensive with high energy demands and waste volumes. The patient security and quality of care stand in contrast to global health and climate change issues. However, the amount of CO₂ emissions from volatile anaesthetic gas is very small compared to the CO₂ emissions emanating from the hospitals energy consumption and waste disposal, which account for about 25 times more CO₂ per year, measured during 2011 in a U.K. hospital.[78] Use of sevoflurane results in the lowest CO₂ emission rate of all volatile anaesthetics.[79] The wide-spread use of low-flow anaesthesia minimizes consumption of all anaesthetic agents and thus reduces both costs and emissions.[80] Some anaesthesia machines are also more effective in reducing anaesthesia agent consumption.[62] Furthermore, operation theatres are three to six times more energy intense than hospitals as a whole due to high heating, ventilation and air conditioning requirements.[78] Thus, the small amount of CO₂ given in a closed anaesthetic circuit during a short wash-out time period of sevoflurane, should not constitute a considerable global carbon footprint. An approximation of the yearly CO₂ emissions in Sahlgrenska hospital would be 66 kg CO₂ emanating from the IHV procedure alone. In comparison with emissions of several thousand tons of CO₂ per year from large university hospitals in North America and Europe.[78] From a work environmental point of view, it could be considered a benefit reducing the amount of sevoflurane that are expired to room air outside the anaesthetic circuit. Technological departments in Sweden and other Nordic countries are currently working with low-energy solutions to capture CO₂ directly from air and during combustions processes called “Negative CO₂”. A technology that enables CO₂ capture and negative CO₂ emissions with low cost and energy penalty.[81, 82] We must keep in mind that the first priority in health care should be patient security and quality of care.[83]

6 CONCLUSION

In this thesis methodological research has been performed to develop a clinically applicable technique to enhance recovery after long duration sevoflurane anaesthesia. With the modified isocapnic hyperventilation method which can be incorporated into any modern anaesthesia delivery system, it would be possible to implement isocapnic hyperventilation in routine clinical practice. Future studies and clinical experience will show if this technique will be useful for the clinician to improve immediate and early postoperative recovery for patients after inhalational anaesthesia.

7 FUTURE CLINICAL IMPLICATIONS

Hyperventilation facilitates and accelerates the development of anesthetic gases if hypocapnia can be prevented. The potential cost reduction and health care benefit, considering the wide spread use of inhalational agents for general anaesthesia, is vast.[1, 66, 67] Today's advanced anesthesia machines can automatically control all gas concentrations that can be measured in the patient's expiration and inhalation air via digital feedback systems, i.e. end-tidal gas control. This gives new opportunities to directly add carbon dioxide to a closed anesthetic circle during the wake-up phase. This thesis presents a simple method of directing a known amount of carbon dioxide into a closed anesthetic circle. This alternative IHV method suggests direct infusion CO₂ to the inspiratory limb of the breathing circuit through a mixing box while using mechanical hyperventilation according to a standardized protocol. To avoid the risk of CO₂ overdose and hypercapnia, a CO₂ delivery gender and weight nomogram has been developed, to be used when doubling the minute ventilation from a stable normocapnic base-line ventilation. The CO₂ dosage according to this nomogram produces a stable isocapnic hyperventilation with an FICO₂ at around 3%, provided that the CO₂ absorber is disconnected. The hyperventilation and CO₂ delivery can be controlled and monitored by using a modern anaesthesia delivery system and its' monitoring capacities. With rather small modifications of the standard breathing circle it would be possible to implement this "fast weaning" method into any modern anaesthesia apparatus. Earlier conclusions that the IHV-method is unnecessary due to the introduction of short acting volatile anaesthetics are in need of a revaluation, as several studies besides the studies included in this thesis, present a marked reduction in time to extubation, eye-opening and time to discharge from operation room. The method should not be used in patients with severe lung or circulatory disease or patients that preoperatively is scored with ASA>3 as the mechanical hyperventilation could produce heart-lung interactions similar to a mild recruitment maneuver. This could however be seen as a benefit in ASA 1-3 patients as postoperative atelectasis is very common and circulatory side-effects probably are counteracted by simultaneous rapid out-wash of the inhalational anaesthetic.

8 FUTURE PERSPECTIVES

In study IV there was a marked reduction in time to extubation when using isocapnic hyperventilation after long-duration sevoflurane anaesthesia. It would be interesting to assess the method in shorter surgical interventions or using other volatile anaesthetics such as desflurane or combinations of sevoflurane and nitrous oxide. The increasing use of remifentanyl in combination with low dose volatiles for maintenance of general anaesthesia urges a randomized comparison with and without IHV-weaning. Furthermore, it would be interesting to compare the active CO₂ infusion method presented in this thesis to the passive CO₂ rebreathing method, currently in clinical use in Europe and USA. There is also a need for testing the stability of the method in combination with other anaesthesia delivery systems, i.e. other than those two tested in this thesis. Larger randomized studies are needed for evaluation if postoperative recovery can be improved using the IHV-method assessed in this thesis.

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