DEVELOPMENT AND ASSESSMENT OF A NEW SOLUTION FOR CARBON DIOXIDE REMOVAL FROM ANAESTHESIA REBREATHING CIRCUITS

By

Florentin Michael Wilfart

Submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
April 2016

I thank the people
that supported me
on this journey.
Intellectually. Emotionally. Physically.

The people who believe in me.
The people who did not let the
relationship crumble because I
could not keep my ahead above
water sometimes.

I am dedicating this thesis to my extended "family".

The people who have encouraged my talents

and were never tired of giving me opportunities for growth.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Our aging population's rising health care costs cannot be met by the limited numbers of young tax payers. Compounding the cost of surgery are the costs associated with post operative cognitive decline (POCD) that up to 80% of patients experience. Currently, chemical absorbers are mandatory for most anaesthesia procedures yet the resultant by-products are known to contribute to the incidence of POCD.

Approach: This thesis presents a unique approach for a new dense skin poly-methyl-pentene (PMP) membrane based CO_2 filter. The objective is the elimination of chemical absorbers' contribution to POCD in anaesthesia. The main challenge of this application is the exclusion of active components for improved CO_2 removal. Such a passive system is key for fast regulatory approval and adoption in anaesthesia practice.

Methods: *First*, the continued need for CO_2 removal is confirmed in a literature review. *Second*, the optimization of a custom PMP hollow fibre membrane for CO_2 removal and anaesthetic vapour selectivity is successfully demonstrated. A unique characterization approach guided the optimization. *Third*, an application module is modeled and prototypes are built using the optimized custom membrane. Applying membrane system theory, CO_2 removal performance is further optimized; developing a unique double-pass sweep flow arrangement. *Fourth*, the prototypes are verified for the safe use *in-vivo* in animal and human studies. *Fifth*, patient ventilation cases are demonstrated using data recorded at the Nova Scotia Health Authority. These cases are used in conjunction with a unique dynamic system model to optimize the design based on the trade-off between surface area and sweep gas use. The predictions are verified in a bench setup using an anaesthesia machine ventilating a lung simulator with CO_2 feed.

Results and Conclusion: It was shown that (i) CO_2 removal in anaesthesia is required in the future (not replaced by TIVA), (ii) the membrane and system could be optimized for minimal surface area and sweep flow, (iii) such passive membrane systems can match or exceed the performance of chemical absorbents. This confirms that PMP membranes can safely replace chemical absorbents, thus eliminating the contribution to POCD. A clinical study is recommended for the final validation of these study results.

LIST OF ABBREVIATIONS USED

P	Pressure
L	Liters
V	Volume
F, $\dot{V}$	Flow
CO_2	Carbon dioxide
O_2	Oxygen
CH_4	Methane
FGF	Fresh gas flow
MV	Minute volume
TV	Tidal volume
f	Respiratory rate
b/minute	Breaths per minute
$EtCO_2$	Expired CO_2 concentration
$FiCO_2$, $InspCO_2$	Inspired CO_2 concentration
LPM, Lpm	Litre per minute, $L \cdot min^{-1}$
Vol%	Volume percent
Q	Molar flow rate [mol/h]
J	Molar flux [mol/h/m^2]
P	Permeability [mol cm/m^2/bar/h]

S	Solubility coefficient [mol/m^2/bar^2]
alpha, α	Membrane selectivity
NSHA	Nova Scotia Health Authority
QE II HSC	Queen Elisabeth II Health Sciences Center
INT	Interventional Group
CTL	Control Group
SD	Standard Deviation
POCD	Post Operative Cognitive Decline
MAC	Minimum Alveolar Concentration
GWP	Global Warming Potential
ODP	Ozone Depletion Potential
m	meters
m^2	Square Meters
CPB	Cardiopulmonary Bypass
UP	Ultraphobic™
PMP	Poly-Methyl-Pentene
CNS	Central Nervous System
QMS	Quadrupole mass spectrometer
™	Registered trademark

℠	Unregistered trademark
®	Trademark with US Government registration
pH	Acidity or basicity(alkalinity) of aqueous solution
APSF	Anaesthesia Patient Safety Foundation
IARS	International Anaesthesia Research Society
FDA	Food And Drug Administration
MMSE	Mini-Mental State Examination
QoR-40	Quality of Recovery-40 questionnaire
BIS	Bispectral Index
TNFα	Tumor Necrosis Factor alpha

ACKNOWLEDGEMENTS

I thank my co-supervisors

Prof. Geoffrey Maksym, PhD & Prof. Donald Weaver, MD, PhD, FRCP(C)

as well as my committee members

Prof. Orlando Hung, MD, PhD, FRCPC, Prof. Peter Gregson, PhD, PEng,

Prof. Jan Haelssig, PhD & Prof. Andrew Milne, MD, MSc, PEng

for their academic guidance.

I thank Prof. Dr. med. Michael Schmidt, PhD, FRCP(C)

for the topic and his academic guidance.

I want to thank Megan Soehl, BEng, MSc for the productive collaboration.

I would like to acknowledge 3M™, Membranes Business Unit, Germany for supplying customized membrane modules, DMF Medical Incorporated for providing rapid prototypes, materials and equipment for the experiments in this thesis and Abbvie (formerly Abbott) for supplying anaesthetic vapourizers and Sevoflurane.

Chapter I INTRODUCTION

C.I - 1 THESIS STRUCTURE

This thesis is divided into 11 chapters. The main content of each of the chapters is described below. Most of the chapters will be or have been submitted as publications. Please see Appendix C for a statement of my contributions to multi-authored works. The actual or intended publication titles and actual or intended journals are provided in *C.XI - 4 Contributions arising from this Thesis.*

Chapter I	Introduction to the thesis.
Chapter II	Literature review of fields directly related to the thesis.
Chapter III	Literature review exploring the justification for continuous use of anaesthetic vapours in modern anaesthesia, their associated problems and the need for a safer, more affordable and environmentally friendly CO_2 absorber.
Chapter IV	Experimental investigation of material compatibility of dense PMP membranes under investigation in this thesis with anaesthetic vapours. *Presented as posters and podium presentations (C.XI - 4.4)*
Chapter V	Custom experimental approach for characterizing the transport properties of different dense PMP membranes for anaesthesia-relevant gases and anaesthetic vapours, and selection of a suitable membrane for this application.
Chapter VI	Experimental investigation of the suitability of different membrane oxygenators for the delivery of anaesthetic vapours during cardiac surgery. *Published as double-blind peer reviewed conference paper in the Proceedings of the IASTED International Conference Biomedical Engineering (Biomed 2011) and as poster and podium presentations (C.XI - 4.2 and C.XI - 4.4)*
Chapter VII	Design of a membrane system for carbon dioxide removal from gas mixtures under normobaric conditions in anaesthesia circuits.
Chapter VIII	Experimental proof of concept in pigs.
Chapter IV	Experimental verification of module performance in a human clinical study. *Presented in podium presentations (C.XI - 4.4)*
Chapter X	Modeling and experimental verification of a final size and optimized membrane module for clinical application.
Chapter XI	Conclusions to the thesis.

C.I - 2 MOTIVATION

Allow me to take a couple paragraphs to describe my motivation in this field of study. I spent one year in animal research exposing myself to as many clinically and scientifically trained people as I could find once I completed my broadly oriented Medical Engineering degree (major in Biomedical Engineering) in Germany in 2009.

Humanity's knowledge of physiology has been advanced drastically, but I have every reason to believe that plenty of engineering challenges will continue to be available to me during my lifetime. At the same time, using engineering for the purpose of improving quality of life for patients provides a clear and unchallenged purpose for my work, often visible after relatively short cycle times in contrast to environmental engineering tasks that, while also beneficial, can take decades to be demonstrated effective and relevant. However, while this work at its core addresses a safety concern in the medical field, it also aims to reduce the release of anaesthetic vapours into the environment that contribute to global warming and the depletion of the ozone layer. In this instance, both, a medical and environmental need are addressed and also result in the reduction of cost.

C.I - 3 HYPOTHESIS

It is possible to replace current chemical CO_2 absorbers with a CO_2 filter containing membranes that are inert to anaesthetic vapour. The membranes will remove CO_2 to clinically safe levels through passive permeation, while selectively retaining the anaesthetic vapours.

Chapter II LITERATURE REVIEW

This thesis has been written as a publication based cumulative thesis. Therefore, each chapter is intended to stand on its own as a publication with its own introduction, methods, results and discussion and this may lead to redundancies with the literature review. The literature review provides the general background for understanding the subject matter and the state of the art in the field of the thesis work.

C.II - 1 ANAESTHESIA

This section is intended to provide the reader with an introduction to the field of anaesthesia, starting with the history of anaesthetics as well as the safety challenges accompanying anaesthetic vapours since their introduction (C.II - 1.1).

It is important to understand the history of anaesthesia equipment (C.II - 1.2) and operating principles of modern anaesthesia equipment (C.II - 1.3). The section is then completed by a review of modern anaesthetic vapours (C.II - 1.4) and the relevance anaesthetic vapours have in modern anaesthesia (C.II - 1.5).

The continued necessity of CO_2 absorbers in modern anaesthesia based on the continued relevance of anaesthetic vapours (described in C.II - 1). The problems related to the chemical absorbents in these absorbers are explored in C.II - 2.

The relevance of the direct and indirect concerns associated with anaesthetic vapours is put into perspective in C.II - 3 discussing the problem of a decline in brain function after surgery and anaesthesia called Post Operative Cognitive Decline (POCD).

The last section of this chapter reviews the literature necessary for the understanding of membrane-based gas separation processes and how they can provide a safe alternative to chemical CO_2 absorbers in anaesthesia circuits, addressing most of the concerns raised in this literature review.

C.II - 1.1 The History of Anaesthetic Vapours

Medical interventions involving opening the integrity of the human body have led to continued studies to identify efficient and improved methods of pain management and stress reduction. Initial descriptions of anaesthetics administered via inhalation date back to the early use of diethyl ether to induce sleep in chickens in the 16th century.[1] Robert Boyle, Michael Faraday and Isaac Newton made a milestone discovery in medicine when they found that diethyl ether had the ability of triggering sleep in humans.[2] However, Crawford Williamson Long pioneered the use of diethyl ether in surgery when he first used diethyl ether with a towel in 1842.[3,4] The observation that ether induces analgesic (pain relieving) effects at skin contact was the basis for William Thomas Green Morton's investigations into the analgesic effects of inhaled ether. Another advantage was discovered in the safe and easy use of diethyl ether by unskilled "anaesthetists" due to minimal respiratory depression (depression of the breathing reflex) when properly dosed, eliminating the risk of hypoxia. Furthermore diethyl ether could easily be transported in glass bottles.[3,5] In 1929, freshly prepared propylene was discovered by Henderson and Smith to have desirable attributes as an anaesthetic. However, it had the disadvantage of breaking down during storage in steel cylinders.[6] Later that year Lucas and Henderson showed that the breakdown product was actually cyclopropane.[7] Respective studies on the use of propylene as an anaesthetic were halted in Canada due to the adverse effects believed to be associated with cyclopropane. However, in the USA, studies investigating the safety and efficacy of cyclopropane showed excellent clinical outcomes in 1934 even though the substance was highly explosive. [8]

C.II - 1.2 The History of Anaesthesia Equipment

The use of anaesthetic equipment began in the year 1846, with Morton's inhalation flagon, similar to a glass pipe.[9] From that point forward many devices were designed and developed for use. These devices can be categorized into three groups as follows:

(a) Simple ether and chloroform masks, which involved continuous dripping of ether onto the mask covering the nose and mouth of patients as described by Simpson in 1847 to Brown in 1928.[9]

(b) Vapour inhalators, which followed the "draw over" principle. The patients were required to inhale air that was flowing through a chamber containing chloroform or the volatile ether, thus drawing their breath over the anaesthetic substance as described by Snow in 1847 to Oxford in 1941.[10]

(c) Half-closed equipment which involved re-circulation of a patient`s exhaled air through a chamber to the patient. In this system, replenishment of oxygen and reduction of the CO_2 concentration occurred when a portion of the exhaled gas mixture was allowed to mix with fresh air as described by Clover in 1877 to Ombredanne in 1908.[11] From the beginning of 1868, these developments made the incorporation of gas bottles necessary for effective replenishment of oxygen. The introduction of gas bottles was followed by the introduction of mixing-valves for oxygen and nitrous oxide along with flow meters between 1885 and 1890. These systems allowed for partial rebreathing of the patient's exhaled gas mixture, where the vapour concentration in the circuit was controlled via newly introduced vapourizers.[9] The first anaesthetic circuit fitted with a true rebreathing system was designed in 1925 by the Draeger medical device company in Lübeck, Germany. This anaesthetic rebreathing circuit made a CO_2 absorber necessary in order to remove the exhaled CO_2

before returning the gas mixture to the patient. The system was introduced by Paul Sudeck and Helmut Schmidt between the years 1920 and 1925 at the University hospital of Hamburg-Eppendorf, and the outcome of their experiments was published in 1926.[9]

C.II - 1.3 Modern Anaesthesia Equipment

Modern anaesthesia equipment consists of an anaesthesia machine capable of semi-closed or closed loop anaesthesia by employing a rebreathing circuit. A schematic of such a system is shown in Fig. II-1. A Fresh Gas Flow (FGF) carries fresh anaesthetic vapour from the vapourizer (not shown) in a mixture of Oxygen in Air into the circuit (1). As the circuit has a defined volume, the volume vented from the exhaled gas mixture has to match the FGF. The volume is only minimally altered by the amount of oxygen taken up by the patient's lungs and the amount of CO_2 released. As only a small portion of the anaesthetic vapour is taken up by the patient once the system is stabilized, the vented gas mixture (2) contains close to the same concentration of anaesthetic vapour as the FGF (1).

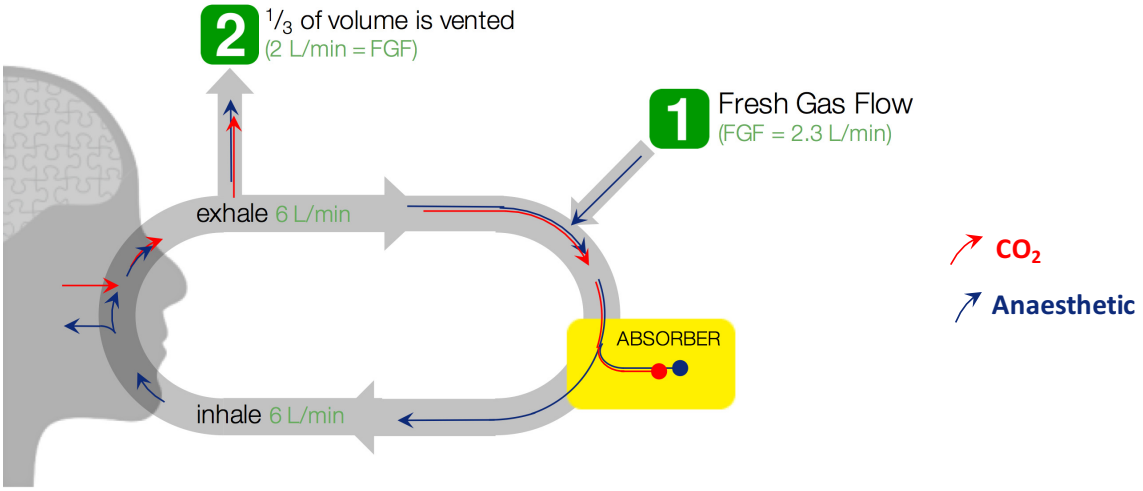

Fig. II-1. Schematic of a modern anaesthesia rebreathing circuit.

It is therefore obvious, that it is desirable to reduce the FGF as much as possible to retain the maximum possible amount of anaesthetic vapour in the circuit. Some modern anaesthesia machines do have the option of direct injection of anaesthetic vapours. In such

systems the FGF is not necessary to carry the anaesthetic vapour into the system. Hence, the FGF is only used to replenish the metabolized amount of oxygen and the direct injection maintains the concentration of the anaesthetic vapour. Such a fully closed system is able to provide so-called metabolic anaesthesia. In order to allow for cost effective and environmentally friendly anaesthesia using anaesthetic vapours, the following needs can be defined:

(i) Keep the anaesthetic vapour in the circuit
(ii) Eliminate CO_2 from the circuit
(iii) Eliminate toxic by-products (see C.II - 2.1 &C.II – 2.2)
(iv) Eliminate absorbent dust in the circuit (see C.II - 2.3)

Needs (i) and (ii) require the separation of CO_2 from the anaesthetic vapour to retain the anaesthetic vapour in the circuit and remove the CO_2 from the circuit. Conversely, needs (iii) and (iv) require CO_2 removal without any chemical reaction or the use of non-inert materials.

C.II - 1.4 Modern Anaesthetic Vapours

Modern anaesthetic vapours contain chlorine and fluorine compounds. Fluorination and chlorination have made modern anaesthetic vapours more stable, by lowering the boiling point and reducing the toxicity.[3] However, this section will show, that modern vapours do not differ much from early diethyl ethers and still carry similar safety concerns.

Research focused on refined uranium-235 in the year 1945 made the production of the first anaesthetic vapour containing fluorine possible, which was an analogue of ethyl-vinyl but containing fluorine, named fluroxene. This compound was sold until 1974.[12,13] Nevertheless, a toxic metabolite caused the use of fluroxene to stop.[14] Halothane was introduced into the market in 1951, and its widespread use began in 1956.[15] Halothane use was followed by methoxyflurane in 1960. Its use continued for approximately ten years. Nephrotoxicity

(toxicity to the kidney), which was believed to be caused by inorganic fluoride, was the main reason for its removal from the market.[16–18] Hepatitis cases were also believed to be related to its dosage.[19] Together, these two concerns warranted research into alternative anaesthetics. The anaesthetic vapours Enflurane and its associated isomer Isoflurane resulted from the screening of over 700 synthesized fluorinated hydrocarbons.[20,21] Production of Enflurane was relatively easy. Therefore, it was introduced in the market in 1965, ahead of Isoflurane, which was introduced with a delay after Enflurane was seen to be cardio suppressive (reducing the heart pump function). Isoflurane was officially introduced into the market in 1971, following resolutions to its purification issues.[22] Its entry into the market was halted by suspicion of its carcinogenic properties until related research studies on animals were completed. As such, Isoflurane is the best researched anaesthetic in history.[3]

The two-most modern inhalation agents, Desflurane and Sevoflurane, were also discovered along with Enflurane and Isoflurane. However, side effects caused by Isoflurane, Enflurane and Halothane seen between 1980 and the 1990s warranted additional research prior to introduction of Desflurane and Sevoflurane, even though limited research already supported the safe use of Sevoflurane in 1960.[23–25] Its use on animals revealed excellent anaesthetic results. However, Baxter-Travenol, who developed it, did not focus on inhaled anaesthetics. Additionally, there were concerns over the toxicity potentiated with release of fluorine and break down of soda lime.[26] In 1983, Baxter formed a contract with a Japanese pharmaceutical company, Maruishi, to conduct a few human trials with Anaquest in 1985. Approval for clinical use was obtained in 1990 in Japan. In 1994, Sevoflurane was available in 60% of the market.[24] Abbott Laboratories and Maruish conducted experiments in the US in 1993, and obtained approval by the FDA for its clinical applications in 1995. However, due to safety concerns, the FDA does not recommend the use with a fresh gas flow of less than 1

Lpm or 2 Lpm at more than 2 hours at 1 Minimum Alveolar Concentration (MAC).[24] This means that even the most modern anaesthetic vapours were in fact discovered in 1960 and have safety concerns in common with earlier anaesthetic vapours. One of the safety concerns that remains occurs when when a chemical CO_2 absorber is used in order to achieve a closed rebreathing system (C.II - 1.3). Harmful substances are produced by the chemical CO_2 absorbent when it comes into contact with anaesthetic vapours (C.II - 2.1). This has caused the FDA to limit all attempts to close the rebreathing circuit, resulting in the loss of expensive anaesthetic vapours to the atmosphere and negative environmental impact.[27–29]

C.II - 1.5 Modern Anaesthesia

Today, approximately two-thirds of all anaesthetic procedures are performed under general anaesthesia, while one third are performed as either a local or regional procedure providing local or regional pain relief. General anaesthesia is different from local and regional anaesthesia and renders the patient unconscious. General anaesthesia has three elements, including hypnosis (within the field, hypnosis is the term for induced sleep), systemic analgesia (systemic pain relief), and relaxation of the skeletal muscle.[30] General anaesthesia affects the whole organism and may be provided by intravenous administration of drugs defined as Total Intra Venous Anaesthesia (TIVA). Most commonly, a combination of Propofol and a short acting opioid (e.g. Remifentanil) is applied via continuous infusion using an automated pump to maintain anaesthesia.[31] General anaesthesia can also be provided via anaesthetic vapour inhalation. Ideal anaesthetics should provide rapid induction and emergence for anaesthesia, excellent analgesia, and relaxation of muscles with fewer side effects.[32] Such mono-anaesthetics are non-existent in nature. As such, intravenous anaesthetics are applied for induction. In many cases, opioids are applied as analgesics and barbiturates for induction of hypnosis, before anaesthetic vapours are added. Anaesthetic vapours provide partial analgesia and standalone

hypnosis. In certain instances, vapours are given in combination with relaxants and/or intravenous analgesics.[31,33] Neuromuscular blockers paralyze the muscles for facilitating intubation and ventilation. Anaesthesia by application of hypnosis-inducing vapours together with continuously applied intravenous drugs is referred to as balanced anaesthesia, as it employs the benefits of several drugs while minimizing the unwanted side effects associated with them.[34]

An exception is the induction of anaesthesia in children. While in adult patients an effort is usually successful in establishing an IV access, mask inductions using anaesthetic vapours are often applied in children due to the problem of accessing veins as it is sometimes difficult to obtain their cooperation in their awake state.[35]

It is important for the reader to understand that there is no real alternative to anaesthetic vapours on the horizon of drug development. The properties of anaesthetic vapours cannot be fully replaced by intravenous drugs. Taking together C.II - 1.3 and C.II - 1.4, it can be concluded that rebreathing systems, even only partially closed systems, for the use of anaesthetic vapours will continue to be necessary in the foreseeable future, and these systems require CO_2 absorbers to operate.

Compressed gases, like oxygen, used to be expensive to purify in the early days of anaesthesia. The U.S. government reported in 1983, that efficiencies for cryogenic processes ranged from 3-20 tons/day/MW (~2,262 – 15,080 liter/kWh).[36] The energy source was reported as mainly natural gas with a CO_2 footprint of 1.22 pounds/kWh (0.55 kg/kWh), resulting in 0.25 – 0.04 kg of CO_2 per 1,000 liters of oxygen. [36,37] Nowadays oxygen is a by-product from the purification of other gases like Argon and the purification uses mainly excess energy from other processes like cracking.[38] This reduces cost as well as the carbon footprint.

C.II - 2 CARBON DIOXIDE ABSORBERS

Modern anaesthesia systems rely on CO_2 absorbers to minimize the loss of expensive anaesthetic vapour by maintaining the exhaled gas mixture in a rebreathing circuit. In an ideal world, a completely closed circuit would only need to replace the amount of oxygen and vapour metabolized by the patient and to extract the metabolic end product, carbon dioxide (CO_2).[29] Unfortunately, even the most modern CO_2 absorbers produce varying levels of by-products that have been shown to be neuro and nephro toxic.[39,40] These by-products result from the degradation of anaesthetic vapours, which occurs when they pass through existing CO_2 absorbers.[39–47] The major degradation products of Sevoflurane are known as Compounds A-E.[39] These compounds have not directly been shown to be linked to a decline in brain function after surgery and anaesthesia, but they have been linked to organ damage on a cellular level that in turn has recently been linked to POCD (C.II - 2.1).[48] Chapter III provides a broad and detailed review of the known effects of both, the anaesthetic vapours and their degradation products on a cellular and system level.

These compounds have been the reason for an FDA requirement of a minimum dilution rate in the circuit, limiting the ability to achieve the ultimate goal of metabolic anaesthesia using a closed rebreathing circuit. However, closed circuits are desirable, as reducing the dilution rate by reducing the fresh gas flow rate, linearly reduces the amount of vapour used.[49] For example reducing the fresh gas flow from 3 L/min to 1.5 L/min reduces the Sevoflurane used from (0.16 ± 0.05) mL/min to (0.07 ± 0.03) mL/min.[50] The released gas mixture from the circuit is usually scavenged and vented to the atmosphere outside the building. Current halogenated anaesthetic vapours contained in the released gas mixture are not only expensive, but also have both ozone depleting potential (ODP) and global warming potential (GWP), which are now being highlighted as significant issues in the use of anaesthesia.[27,51–54] A growing

body of research has established that both Sevoflurane and Desflurane contribute significantly to the 20 year GWP, through their release during anaesthesia.[27] In the US alone, the total production (and therefore use and release) amounts to 2,000 tons/year, equalling the effect of almost 4,000,000 tons of excess CO_2 release.[55] To put these amounts in perspective, this is the equivalent of 18.27 billion kilometers driven in an average car each year, or at an average of 15,000 km driven per year the equivalent of 1.22 million vehicles per year.[56] It is further known that exothermic reactions occur when anaesthetic vapours make contact with chemical absorbents. This poses a huge risk with both fires and explosions occuring.[57–59] Most present day anaesthetic vapours and CO_2 absorbents do not react as strongly, but the absorbers still become very hot.[39,41–45,60,61]

Currently, granulate-based CO_2 absorbers also create disposal issues since the expended granulate, enriched with halogenated anaesthetic vapours and the toxic by-products[62], is considered hazardous waste.

C.II - 2.1 Vapour Degradation Compounds

Research has shown that available CO_2 absorbers generate varying levels of unwanted by-products.[63] These by-products are generated from the breakdown of anaesthetic vapours that occurs when they react with the chemical CO_2 absorbent. The semi-closed design of the ventilation circuit causes the resultant toxic compounds to accumulate in the circuit, thereby exposing patients during surgery. The main degradation products of Sevoflurane are compounds A-E[39] (see Fig. II-2). Recent studies show that these compounds are both nephrotoxic and neurotoxic,[39,40,64–66] likely contributing to increased risks of organ dysfunction. Compound A and its toxicity are best described in literature, but studies have shown that other compounds, independent of Compound A are toxic as well.[40–42,44,45,47,61,67–69]

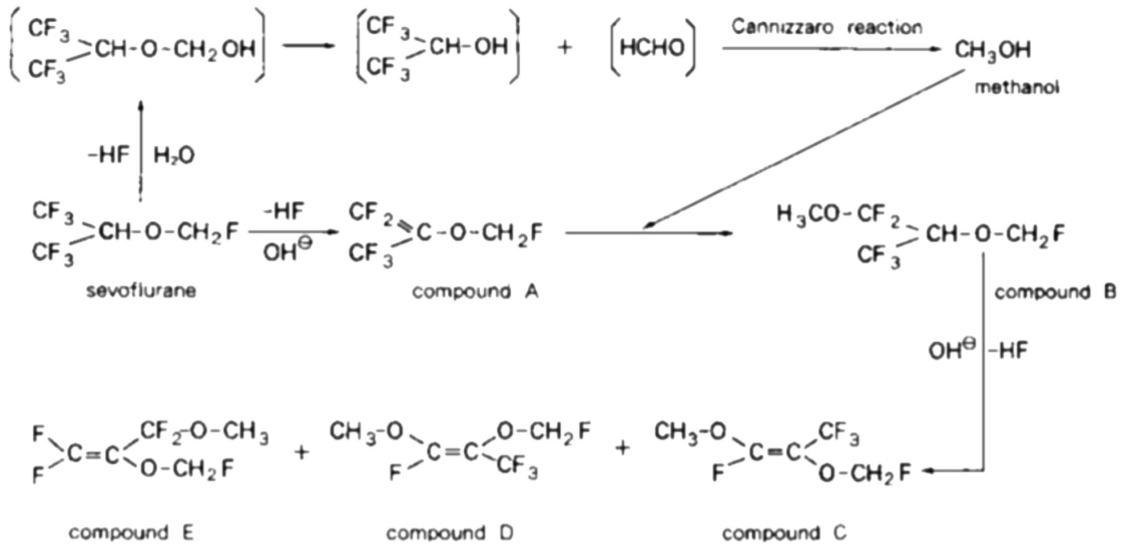

Fig. II-2. Degradation pathway of sevoflurane in several conditions exposed to soda lime. Reprinted with permission by Anesthesiology. [63]

Transient hepatic injury has been demonstrated with the use of Sevoflurane as opposed to Desflurane while employing fresh gas flow at rates of less than 2 Lpm.[70] According to Eger *et al.* it was found that the outcomes of this study ranged from absence of significant injuries to transient nephritic proteinuria.[70] These findings, when combined together have resulted in FDA recommendations for a minimum fresh gas flow rate into the anaesthetic circuit of no less than 1 Lpm in general and not less than 2 Lpm at 2 MAC hours.[24] To reiterate, the minimum fresh gas flow rate limits the achievement of a closed circuit, where all exhaled anaesthetic vapour would be retained and rebreathed.

Rappold *et al.* for the first time, found evidence for the long suspected link between neuronal damage and POCD; Plasma levels of glial fibrillary acid protein (GFAP), a marker for neuronal cell damage,[48,71,72] measured directly after surgery and anesthesia were predictive of POCD 1 month post surgery.[48]

C.II - 2.2 Carbon Monoxide

Chemical absorbents of CO_2 generate differing levels of carbon monoxide depending on the humidity, chemical composition and degree of desiccation.[45,67,68,73] Generally, the volumes of carbon monoxide have been reduced substantially in the latest CO_2 absorbent chemicals.[47] However, together with the breakdown products discussed in section C.II - 2.1 the production of any carbon monoxide generates a demand for a fresh gas flow into the system to avoid dangerous accumulation.

C.II - 2.3 Chemical Granulate Dust

A further problem comes from the different chemicals used in CO_2 absorbers. Current absorbers contain such substances as caustic soda, potassium hydroxide, calcium hydroxide, calcium chloride and calcium sulphate[74] that form corrosive alcalotic dust that may accumulate in the ventilation circuit. Even the best filters available, combined bacterial/viral filters separating the patient from the anaesthetic circuit, allow dust particles smaller than 20 nm to get past the filter and enter the patient's lungs, where they can cause chemical burns.[62,75] Larger dust particles can accumulate on the filter's surface, come into contact with water sitting on the filter and therefore potentially pass through the filter in solution. If this dust or solution is allowed to contact tissue for any length of time, a chemical burn will occur and can potentially lead to laryngospasm, bronchospasm or pneumonia.[76] The dust also accumulates in the circuit and can lead to serious mechanical failures such as a blocked valve.[77] Accumulation of the dust also occurs in the circuit, and if substantial this may cause mechanical failures such as blockage of valves.[77] Again, the risk associated with the CO_2 absorbent is only present due to its combined effect with anaesthetic vapours.

C.II - 3 POST OPERATIVE COGNITIVE DECLINE

In recent years anaesthesia and surgery have been shown to be associated with a syndrome known as Post Operative Cognitive Decline (POCD). [78] Patients with POCD often exhibit impaired cognitive function in their thinking, perception and memory. Additionally, they have a fivefold increased mortality rate in the 12 months after surgery.[79,80] The type of surgery performed and the age of the patient both affect the risk of developing POCD. The most dominant predictor of incidence is the age of the patient. Both, the very young and old are at elevated risk to develop POCD. Patients undergoing cardiac procedures involving the cardiopulmonary bypass are also at the highest risk for POCD.[81,82] The average incidence rate of POCD ranges from 15% to 25%. The highest incidence is reported for cardiac surgery with rates up to 70%.[78,82]

Half of all the surgical procedures performed in the US in 1999 were performed on patients 65 years and older. This age group made up 12% of the population at that time and has been steadily growing since [83]. According to the US Census Bureau this age segment will grow by 53.2% in comparison to the overall population with a predicted growth of 17% from 2010 to 2020, making POCD a growing issue. While the incidence increases, our demographic shift is such that it will be difficult for the smaller percentage of working age people to fund the system. A good example of the challenges associated with the trade-off between treatment benefits and risks of POCD is illustrated in a New York Times article in 2000, were a lawyer describes how he would have rather used the elevator than trade his brain and six-figure income for improved heart function.[84] This example underlines the growing public awareness of POCD. Enough concern has been raised in medical professional circles to warrant the attention of the Anaesthesia Patient Safety Foundation (APSF) of America since 2004.[85,86] Another recently founded program, an initiative of the FDA and International Anaesthesia

Research Society (IARS), is exploring the side effects of vapour anaesthesia on the cognitive development of infants and children.[87] Research findings suggest that even a small improvement in 1-year cognitive outcome could mean thousands of lives saved each year and a significant reduction in society's economic burden.[85]

Removing CO_2 without the use of chemicals to bind the CO_2 can be achieved using membrane technology. Modern membranes can be manufactured to withstand the conditions in anaesthetic circuits and have already been proven safe in other medical applications. Chapter IV and V explore in detail the suitability of different membranes for this application and describe the custom modification and optimization of these membranes. Chapter I will provide the broad background necessary to understand the introduction of each membrane chapter.

C.II - 4 MEMBRANES

Abbéß Nollet observed, over 250 years ago, osmosis through a membrane made of a pig's bladder. Later experiments followed with plant (onion) and animal (bladder) derived membranes and it took about 100 years, before Fick framed his laws of diffusion providing a framework for mass transfer separations. Shortly after Thomas Graham (1860s) discovered the laws of diffusion in gases and the first experiments provided data about gas separations through rubber; Graham also introduced dialysis.[88,89]

The first synthetic membranes were applied by Bechold in 1907. He used them for ultrafiltration under several atmospheres of pressure. He impregnated filter paper with acetic acid collodion.[88] After introduction of the concept of membrane desalination in 1950, Loeb, in collaboration with a large team later developed the so called "Loeb-Sourirajan Membrane" in 1961. One year later they invented the first asymmetric membrane.[88] Another key milestone

was mimicking the channel behaviour in biological membranes with synthetic facilitated transport membranes.

Today, membranes are used in a wide range of separation applications. These applications expose membranes to many extreme conditions regarding pH, temperatures and pressures. Membranes are used to purify liquids and gases as well as to extract them. Synthetic membranes can generally be made of several classes of materials including carbon, ceramics, and polymers, and can be grouped by geometry into symmetric and asymmetric membranes. Either group can have porous and/or homogeneous structures. Where *symmetric* membrane structures are approximately uniform, *asymmetric* membrane structures are more common. Asymmetric membranes have a thin selective layer supported by a thicker structural layer that has relative large porosity. Asymmetric membranes may be integrally asymmetric, where a thin selective layer is formed on a support layer of the same material through a phase inversion technique, or they may be composite structures, where a thin selective layer is deposited on a support in a two-step process. Asymmetric membranes are more common because the open structure of the support leads to a lower resistance to mass transport while providing mechanical stability and is combined with the thin selective layer responsible for the selectivity and therefore resulting in a higher flux than would be observed for equivalent symmetric dense membranes.[90]

Gas separation using membrane technology has attracted particular interest over the last two decades in a variety of industrial fields due to its environmental and economical advantages, such as reduced energy consumption, lower expenditure, and portability. Polymeric materials are promising candidates for fabricating membranes owing to their ease of production, and low capital cost.[91] However, gas separation applications in medicine have not been developed successfully whereas membranes play a large role in blood purification

from toxic metabolic end products in patients with reduced kidney function. Dialysis and pathogen removal, blood oxygenation and CO_2 removal (in the cardiopulmonary bypass and lung support), as well as *ex vivo* and in vitro experimentation and micro dialysis analyzer probes all rely on membrane technology. Membranes used in blood oxygenation are a relevant example for the characterization techniques discussed in this article, as the permeation properties of anaesthetic vapours in poly-methyl-pentene (PMP) used in some oxygenators have been found by Prasser *et al.* to retain uncontrollable amounts of vapour after initial anaesthesia with vapours in the patient when switched over to the cardiopulmonary bypass. The newer type, dense PMP membranes did not allow for efficient permeation of the vapour.[92] Our own studies showed, that this is also relevant for attempts in recent years to introduce vapours through oxygenators into the blood stream.[93] All these applications are liquid-gas or liquid separation applications differing greatly from the challenges for gas separation, described in this thesis.

C.II - 4.1 Dense Membrane Properties

As already partially described by A. Fick over 150 years ago, gas transport through polymeric membranes is usually governed by the solution-diffusion mechanism.[94,95] Selective adsorption of molecules in the membrane occurs on one side (feed side), then the molecules diffuse through the membrane and desorb from the membrane on the other side (permeate side). This transport can be passive or it can be facilitated by carriers.

Carriers are selectively binding components embedded in a membrane, providing a higher selectivity because the carrier sites are much more selective to particular molecules. Carrier-facilitated transport membranes are used in some highly specialized applications, but

although there have been some promising published results, these have major limitations in regards to stability and cost of production and therefore applicability.[96]

C.II - 4.2 Solution-Diffusion Transport

In the 19th century, A. Fick and T. Graham's work showed that the mass transfer in polymeric and liquid films is possible in the absence of pores.[94,97–99] While measuring the permeation rates of different gases through polymeric films, for example through films of natural rubber, T. Graham noted that the expected relation between the permeation rates and known gas *diffusion* coefficients was not given. The permeation rates observed for CO_2, did however correlate with the *solubility* in the membrane materials. This observation held true among all gases tested. These observations led to the description of the "solution-diffusion" mechanism of transport through polymeric membranes governed by diffusibility as well as solubility. According to the solution-diffusion model, the characteristic of the permeation rate, permeability coefficient P_i, can be presetned as the product of a kinetic parameter and thermodynamic factor, the diffusion coefficient (D_i) and the solubility coefficient (S_i) respectively per Equation 1:[98,99]

$$P_i = D_i \cdot S_i \tag{1}$$

The solution-diffusion model has three independent steps: (i) a gas dissolves in the skin layer on the feed side; (ii) then diffuses across, and (iii) finally evaporates/ desorbs at a low pressure on the permeate side. The transport across the film is reviewed in detail in Chapter V .

Another key characteristic of gas separation membranes is their selectivity, describing the ability to let some gases travel through the membrane at a higher permeance than other gases, hence selecting between them. The ideal selectivity (or separation factor) can be defined per Equation 2:

$$\alpha_{AB} = P_A / P_B \qquad (2)$$

where P_A and P_B are the permeability coefficients of gases A and B, respectively. Commonly, the more permeable gas is taken as A, so that $\alpha_{AB} > 1$.[99]

C.II - 4.3 Glassy and Rubbery Polymers

In general, polymers above their glass transition temperature (T_g) are classified as rubbery polymers and have higher free volumes and therefore have higher permeation rates There are exceptions, such as some glassy polymers that have very high free volumes due to their rigid backbones. Rubbery polymers tend to preferentially permeate heavier, more condensable components. Glassy polymers tend to permeate light gases more easily.[100]

The difference is that transport through rubbery polymers is usually dominated by the solubility (more condensable components generally being more soluble). Transport through glassy polymers tends to be dominated by the relative diffusivity of components, with smaller molecules diffusing faster. Some glassy polymers have shown a very high free volume and tend to be even more permeable and selective to highly condensable vapours than rubbery polymers (see Fig. II-3).[101]

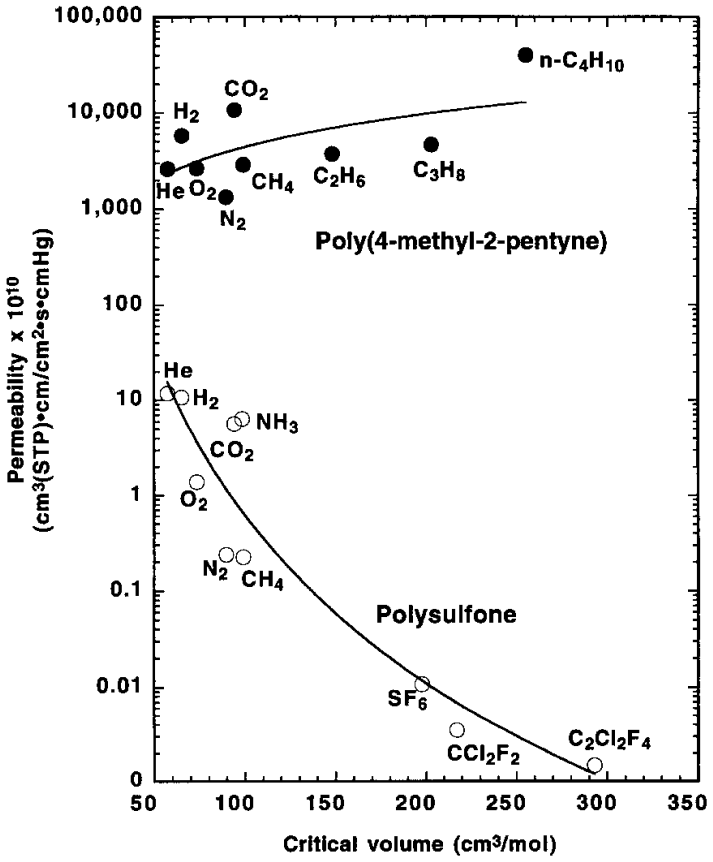

Fig. II-3. Permeability as a function of molar volume for both, a conventional low free volume glassy polymer and poly methyl pentyne. Reprinted from Journal of Membrane Science, 121, A. Morisato, I. Pinnau, Synthesis and gas permeation properties of poly(4-methyl-2-pentyne), 243-250, Copyright (1996), with permission from Elsevier. [101]

Glassy and rubbery polymers used in gas separation are known to have a trade-off between permeability and selectivity, where when they are more permeable, they are less selective. Robeson described this effect in detail, with the most recent updates in 2008 and 2010.[102,103] Fig. II-4 shows examples of such trade-off for CO_2 /CH_4 and CO_2/N_2. Polymers with higher CO_2 permeability will generally also show slightly higher permeability to organic vapours.

C.II - 4.4 Upper Bound Theory

The upper bound relationship describes the trade-off between selectivity and permeability as can be observed in Fig. II-4.[104] Membranes operating with a facilitated transport can exceed permeability and selectivity of the upper bound.[105]

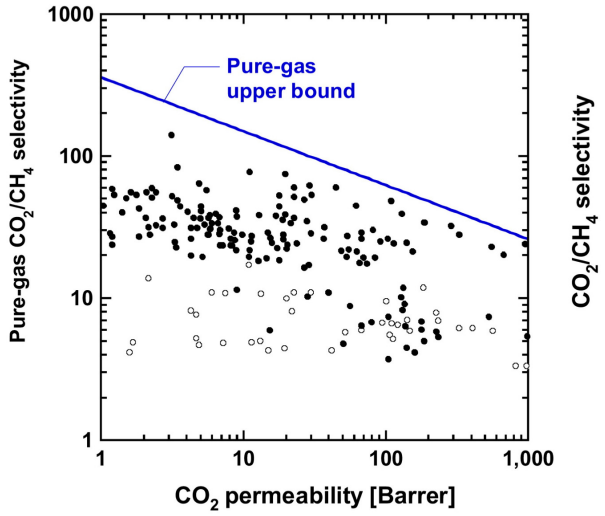

Fig. II-4. Upper bound correlation for pure gas selectivity of CO_2/CH_4 over permeability of CO_2. Reprinted from Journal of Membrane Science, 475, Haiqing Lin, Milad Yavari, Upper bound of polymeric membranes for mixed-gas CO2/CH4 separations, 101-109, Copyright (2015), with permission from Elsevier. [104]

An example of pushing the boundaries of the upper bond for H_2/CO_2 was published by Sanchez-Lainez *et al.* in 2015. The authors presented a one-step crystallization and separation process by centrifugation for mixed matrix membranes.[106] However, for membranes considered for this application, namely dense PMP membranes, the upper bound is valid and describes the trade-off between permeability and selectivity.

C.II - 4.5 Medical Applications of Membranes

Gas separation applications in medicine have not been developed successfully. Membranes play a large role in dialysis, blood purification in patients with reduced kidney function.[107] Dialysis, blood oxygenation and CO_2 removal (in the cardiopulmonary bypass and lung support), as well as *ex vivo* and in vitro experimentation and micro dialysis analyzer probes all rely on membrane technology, where the application is either a gas-liquid or liquid-liquid application.

Membranes used in blood oxygenation are a relevant example for the applicability of membrane characterization experiments discussed in C.II - 4.5 and Chapter VI , as the permeation properties of anaesthetic vapours in poly-methyl-pentene (PMP) used in some oxygenators have been found by Prasser *et al.* to retain uncontrollable amounts of vapour after initial anaesthesia with vapours in the patient when switched over to the cardiopulmonary bypass. The newer type, dense PMP membranes did not allow for efficient permeation of the vapour.[92] Our own studies showed that this is also relevant for attempts in recent years to introduce vapours through oxygenators into the blood stream.[93] All of these applications are liquid-gas or liquid-liquid applications differing greatly from the challenges for gas separation, described in this thesis. The impact of the membrane findings in this thesis on medical practice using anaesthetic vapours with oxygenators for cardiac surgery is further explored in Chapter IV and Chapter VI .

Chapter III ARE ANAESTHETIC VAPOURS A SAFE CHOICE IN ELDERLY PATIENTS OR ARE CO_2 ABSORBERS IRRELEVANT FOR FUTURE ANESTHESIA?

Replacing the CO_2 absorber in anaesthesia circuits, and thereby delivering anaesthetic vapours with a safer technology is the objective of this thesis. This chapter will review the literature to determine if anaesthetic vapours are a safe choice in an aging patient population. This is relevant to the thesis, as alternate anaesthesia techniques like Total Intravenous Anaesthesia (TIVA) theoretically do not require a CO_2 absorber at all. Given the controversy regarding this question, this chapter will provide a structured overview of relevant findings in order to allow for the reader to gain insight into the mechanisms and effects described. Many studies regarding the use of anaesthetic vapours in humans have reported negative effects but failed to differentiate the effect of the CO_2 absorber in an isolated manner. These effects are comingled with the CO_2 effects and are therefore not known to be real drug side effects. Some differentiation is provided by animal experiments, where drug effects exclude the use of CO_2 absorbers. This chapter is intended to be developed into a publication and hence has repetitive material from the literature review in the background section.

C.III - 1 BACKGROUND

Today, approximately two-thirds of all anaesthetic procedures are performed under general anaesthesia, while one third is performed as either a local or regional procedure providing local or regional pain relief. General anaesthesia is different from local and regional anaesthesia as it renders the patient unconscious. General anaesthesia has three elements, including hypnosis (sleep), systemic analgesia (systemic pain relief), and relaxation of the skeletal muscle.[30]

General anaesthesia affects the whole organism and may be provided by (i) Total Intra Venous Anaesthesia (TIVA) or (ii) Vapours Anaesthesia. Most commonly, TIVA uses a combination of Propofol and a short acting opioid (e.g. Remifentanil) via continuous intravenous infusion using an automated pump to maintain anaesthesia.[31] Vapour Anaesthesia is provided using anaesthetic vapours that are vaporized by a vaporizer and provided in the gas mixture for inhalation.

Ideal anaesthetics should provide rapid induction and emergence for anaesthesia, excellent analgesia, and relaxation of muscles with few side effects.[32] Such mono-anaesthetics are non-existent in nature. As such, intravenous anaesthetics are typically applied for induction, before relaxants are added to facilitate intubation and then the delivery of anaesthetic vapours. In such case anaesthetic vapours take over partial analgesia and standalone hypnosis, while the intravenous drugs are used to maintain partial analgesia and provide relaxation. [31,33] Anaesthesia provided by combining anaesthetic vapours with continuously applied intravenous drugs is referred to as balanced anaesthesia, which employs the advantages of benefits of several drugs while minimizing the unwanted side effects associated with them.[34] An exception is the induction of anaesthesia in children. While in adult patients an effort is usually successful in establishing an IV access, mask inductions using

anaesthetic vapours are often applied in children due to the problem of accessing veins as its sometimes difficult to obtain their cooperation in their awake state.[35]

The following sections review the toxicology and pharmacology as well as cognitive outcomes after surgery and anaesthesia for the three most modern anaesthetic vapours. These sections provide a structured overview of a number of elaborate studies and findings. As controversy regarding the meaning and applicability of these findings and the variability of the experimental settings demand a full summary of all the findings, they are provided in detail to allow for a proper discussion.

C.III - 2 TOXICOLOGY

C.III - 2.1 Isoflurane

According to Baxter Health Care, decomposition products of Isoflurane are hazardous, and are comprised of halogenated compounds. Acute toxicity has been associated with effects on the nervous system, gastrointestinal tract, respiratory tract, and cardiovascular system. Chronic toxicity has been associated with mutagenicity and carcinogenicity. Reproductive toxicity has been reported for organs such as liver and heart and the nervous system. No animal data has revealed drug related tumorigenic and feto-toxic effects. Epidemiological data shows that higher than normal pregnancy related complications occur among exposed medical attendants. [108] For toxicity data please refer to Table 1.

C.III - 2.2 Desflurane

Desflurane is associated with cardiovascular effects, including changes in blood pressure and chest pain, respiratory effects including respiratory depression and bronchospasm, and gastrointestinal effects like upset stomach and nausea. Effects on the nervous system, like tremor and ataxia have also been reported. Target organs for Desflurane

are the nervous system, but there also effects on other organs such as the heart, the muscle and the kidneys. Desflurane is teratogenic at doses that are maternally toxic. It does not cause mutation in a standard battery or genetic toxicological examinations. Epidemiological data reveals higher than expected pregnancy complications among exposed medics. FDA pregnancy Category: B. [109] For toxicity data please refer to Table 1.

C.III - 2.3 Sevoflurane

According to Baxter Health Care decomposition products of Sevoflurane contain halogen traces and are hazardous. Acute toxicity has been associated with respiratory, cardiovascular, nervous system and gastrointestinal effects. Chronic toxicity has been associated with mutagenic and carcinogenic effects. Reproductive toxicity has been shown for the heart, liver, and nervous system. Sevoflurane has no mutagenic effects at the standard battery of tests of genetic toxicology. Regarding animal data, Sevoflurane is not fetotoxic. [110,111] Again, for toxicity data please refer to Table 1.

Table 1. Toxicity Data for Iso, Sevo and Desflurane [108–111]

				Isoflurane	Sevoflurane	Desflurane
Rat	**LD50**	mg/Kg	OL	4,770	10,800	n/a
	LD50	mg/Kg	IP	4,280	n/a	n/a
	LC50	ppm/3H	INH	16,300	28,800	n/a
Mouse	**LD50**	mg/Kg	OL	5,080	18,200	n/a
	LD50	mg/Kg	IP	n/a	n/a	n/a
	LC50	ppm/3H	INH	16,800	28,300	n/a

Intra Peritoneally (IP), Inhalation (INH), Oral (OL)

C.III - 3 PHARMACOLOGY

Induction of anaesthetic conditions by anaesthetic vapours is dependent on the uptake of the respective anaesthetic agents into the body via the lung. Thus potency of these agents is based on the ability of permeation of plasma membranes and their distribution in various tissues for the body based on their solubility in tissues, fat and blood. This section will present a structured overview of the overall effects of the agents on the central nervous system, side

effects such as hepatic, cardiac, cerebral, and muscular effects caused by anaesthetic vapours, as well as the side effects caused by degradation products generated following breakdown of the anaesthetic vapours by chemical absorbents of carbon dioxide. The main pharmacological pathways, such as toxicity, inflammation, apoptosis, and neurological outcomes will be covered in the discussion.

C.III - 3.1 Cell Membrane Permeability

As potency of anaesthetic vapours depends on the uptake into the human body, the following section provides a short overview explaining the underlying mechanisms.

A simple rule for prediction of permeability of membranes was established by Meyer and Overton 115 years ago.[112,113] This rule does not explain the active transport processes that are mediated by membrane carriers, pumps that had not yet been known during that time. The rule also ignores homogeneities like rafts that may be present in biological membranes.[114] Nevertheless, the concept that the minimum alveolar concentration (MAC) of the anaesthetic vapours corresponds to the solubility in fat in a linear manner, and does not depend on the mode of delivery is still valid.[115,116]

C.III - 3.2 Direct Side Effects of Anaesthetic Vapours

The next sections describe undesired direct effects of anaesthetic vapours. These are important to understand, as they have to be considered in the broad consideration of their safety when comparing to other anaesthetics.

C.III - 3.2.1 Malignant Hyperthermia

The presentation of malignant hyperthermia occurs as a rapid acceleration of metabolic reactions in skeletal muscles. It is triggered by an abrupt rise in calcium concentration within the muscle. This has been shown to be facilitated mainly by genetic dispositions. Many

researchers have revealed the existence of a linkage between the intercellular pH (pHi) and intracellular Ca^{2+}. However, a study done by Robin *et al.* recently revealed that the transporters which control the pHi at rest is the Na^+/H^+ exchange system (NHE), and partially the Na^+ and Cl^- dependent bicarbonate dependent transport systems.[117] Induction of malignant hypothermia has been associated with Isoflurane, Sevoflurane and Desflurane use and is lethal if not intercepted.[111,118,119]

Typically, patients known to be prone to malignant hyperthermia are ventilated using an anesthesia machine with a fresh tubing system and CO_2 absorber. Chemical CO_2 absorbers are reported to take up to 80% of anaesthetic vapour and hence also can release anaesthetic vapour.[120] A new CO_2 filter intended to stay on the machine for months compared to days with chemical absorbers can therefore not store and release any anaesthetic vapour.

C.III - 3.2.2 Respiratory Irritation

Irritation of the airway, breath holding, coughing and laryngospasm are associated with the use of anaesthetic vapours.[121–124] Sevoflurane is less irritating, as compared to Desflurane and Isoflurane. Therefore, mask induction using Sevoflurane may be appropriate in children. [125] The chemical granulate dust from the CO_2 absorbent (C.II - 2.3) may also contribute to these negative outcomes.

C.III - 3.2.3 Relationship with Epilepsy

According to Lijima *et al.*, it was demonstrated that the risk of epilepsy with the use of Sevoflurane is high as compared to Isoflurane.[126] Additionally, in humans, hyperventilation and N_2O may work against this property, as has been evident in children and cats.[125] Fukuda *et al.* conducted an investigation on the effects of Isoflurane and Sevoflurane on seizures and cardiac arrhythmias induced by bupivacaine in rats.[127]

C.III - 3.2.4 Chromatid Changes

Occupational exposure to low levels of anaesthetic vapours in operating rooms,[128–131] post operative care units (PACU)[132] and exposure of partners of medical personnel previously exposed to exhaled anaesthetic vapour is well described.[133] Additionally, destruction of chromosomes,[134] sister chromatid changes[131,134–137] and testicular changes[138] have been associated even with these low doses of anaesthetic vapours as well as increased abortion rates.[139] Many of these risks have not been correlated with short-term exposures among patients. Nevertheless, long term effects of the exposures to anaesthetic vapours is usually not observed during long-term follow-ups for patients since attention is directed on shorter term recovery, cognitive outcomes, and mortalities. However, Baxter Health Care reports that the safety associated with the use of Isoflurane and Sevoflurane in pregnancy has not yet been established, while no changes with respect to reproduction in rats at half of the MAC have been reported.[111] Overall problems evident with the lack of balance in personnel of operating rooms have been documented supporting the existence of occupational hazards, due to the use of anaesthetic vapours.[140]

C.III - 3.2.5 Effects on the Liver

Metabolism of anaesthetic vapours occurs in the liver to varying degrees. The metabolism involves enzymatic degradation generating fluoride ions.[24] Approximately half of the fluoride ions are generated by cytochrome P450 2EL. This occurs in the primary enzyme system in the liver. Baxter and Abbott revealed contraindications of Desflurane, Sevoflurane, and Isoflurane for patients with impaired liver function. All anaesthetic vapours have been shown to cause severe hepatic dysfunction and hepatitis, as mainly shown in case of Halothane. Even though some studies do not demonstrate impaired liver function, they fail to

challenge the risk for development of hepatitis.[141] Nevertheless, present anaesthetic vapours are associated with a substantially reduced risk, as compared to Halothane. [111,118,142,143]

C.III - 3.2.6 Effects on the Kidney

Following the introduction of anaesthetic compounds bearing fluorine compounds, concerns have been raised by cases of nephrotoxicity. Nephrotoxicity has been shown to be caused by fluoride ions, which are released during metabolism of anaesthetic vapour. These concerns have caused a delay in the introduction of the latest anaesthetic vapours. Baxter and Abbott reveal contraindications associated with the use of anaesthetic vapours in patients suffering from renal damage.[109,111,118] This section focuses on the discussion of direct effects and those caused by metabolism without inclusion of products generated by chemical carbon dioxide absorbents.

Table 2. Cardiovascular Effects of Modern Inhalation Anaesthetics. Reprinted from Pharmacotherapy, 25, 12,E Sakai, L Connolly, J Klauck, Inhalation Anaesthesiology and Volatile Liquid Anaesthetics: Focus on Isoflurane, Desflurane, and Sevoflurane, 1875-9114, Copyright (2005), with permission from John Wiley & Sons, Ltd [125]

Effect	Isoflurane	Desflurane	Sevoflurane	Comments
Sympathetic nervous system activation at 1 MAC	–	+	–	Isoflurane causes sympathetic nervous system activation with abrupt and large increases in concentration at 5–6%, but not at 1–2%.
Coronary steal syndrome	+/–	–	–	
Blood pressure	↓↓	↓↓	↓	Decreases in systemic blood pressure for isoflurane, desflurane, and sevoflurane are due to peripheral vasodilatation and decreases in systemic vascular resistance. When a portion of volatile anesthetic gas is substituted by nitrous oxide, the magnitude of decrease in systemic blood pressure at the same MAC is smaller. However, patients with severe hypotension (hypovolemia, shock, or coronary artery disease) have higher risk of developing cardiac adverse effects.
Systemic vascular resistance	↓↓	↓↓	↓	When a portion of volatile anesthetic gas is substituted by nitrous oxide, the decrease in systemic vascular resistance is smaller, attenuating decreases in systemic blood pressure.
Heart rate	↑	NC or ↑	↓ or NC at lower MAC, but ↑ at > 1.5 MAC	Stimulation of the carotid sinus baroreceptors increases heart rate as isoflurane, desflurane, and sevoflurane decrease the systemic blood pressure, thus maintaining cardiac output. Preoperative administration of morphine sulfate or fentanyl during induction has shown to blunt the heart rate increase caused by volatile anesthetics. Many other confounding variables influence heart rate during surgery besides the volatile anesthetics, such as an increased sympathetic nervous system activity due to anxiety or increased preoperative parasympathetic nervous system activity.
Cardiac output	NC	NC or ↓	NC or ↓	
Myocardial contractility in vitro in animal studies	↓↓	↓↓	↓↓	Depression in papillary muscle tissues from animals with chronic heart failure is greater than in normal cardiac tissues, thus patients with impaired myocardial contractility may be at higher risk. Cardiac depression is not consistent in vivo due to compensatory homeostatic mechanisms (e.g., autonomic nervous system activity).

MAC = minimum alveolar concentration of inhaled anesthetic at 1 atmosphere; + = effect present; – = effect absent; ↑ = increase; ↓ = decrease; NC = no change.

C.III - 3.2.7 Effects on the Cardiovascular System

The major side effects include extended QT intervals in children and adults. Preoperative medications and some of the underlying disease conditions among patients exacerbate these effects. Associations between isolated post-market instances of cardiac arrhythmia and extended QT have been reported.[111,118,119] An excellent overview of cardiovascular side effects has been presented by Sakai *et al.* as depicted in Table 2.[125]

C.III - 3.2.8 Effect on Brain Cells

C.III - 3.2.8.1 Mouse Studies

In one study, Xie *et al.* demonstrated, that exposure to Isoflurane results in stimulation of Caspase, and an increase in levels of the β-site APP-Cleaving Enzyme (BACE), six hours following administration of anaesthesia, in the brain of a mouse.[144] The results were obtained via a model where they used naïve mice exposed to 1.4% Isoflurane for two hours. Isoflurane causes Caspase activation, and raises the BACE and Aβ levels up to 24 hours following anaesthesia administration. Additionally, clioquiol, which is an inhibitor of Aβ aggregation was able to counter the *in vivo* activation of Caspase, which was induced by Isoflurane.[144] A study done by Valentine *et al.* (2010) on mice, demonstrated that 1.0% Isoflurane compared to 1.5% and 2.0% resulted in impairment of special learning, as was opposed to other doses. According to research by Bianchi *et al.*, Tg2576 Mice showed no changes in the cognitive abilities following five days of intermittent 0.9-1% Isoflurane (120 min per day) and 0.9-1% Halothane.[145] However, more amyloidopathy was discovered in Halothane as compared to Isoflurane treated mice, particularly in the CA1 area of the non-exposed transgenic mice. Nevertheless, exposure to Isoflurane resulted in impaired cognitive function in the non-transgenic mice, showing existence of neuro-degeneration caused by alternative mechanisms. It was suggested that inhaled anaesthetics affect cognition and amyloidiogenesis, even though

the mechanism is not fully comprehended.[145] A study by Zhang *et al.* revealed that exposure to Isoflurane caused activation of Caspase-3.[146]

Additionally, it was shown that Propofol and Mg^+ blocked the mPTP opening induced by Isoflurane. This would reveal that Propofol and Mg^+ might function in protecting the brain from Isoflurane induced neurotoxicity, via inhibition of the mitochondrial dysfunction. These outcomes resembled results obtained from in vitro use of H4 human neuroglioma cells.[147]

Wu *et al.* conducted a study using transgenic and wild type mice, using Isoflurane at clinically relevant concentrations and 6h, 12h and 24h exposure times.[148] The authors reported increased protein and messenger ribonucleic acid (mRNA) levels of TNF-α , IL-6, and IL-1β, and increased amounts of TNF-α immunostaining positive cells, majority of which were neurons. Isoflurane increased TNF-α levels in primary neurons, and not microglia cells and induced an intensification in TNF-α increase in the AD transgenic mice more than in the wild-type mice. The authors concluded that the results suggested that Isoflurane may increase the levels of pro-inflammatory cytokines, which may cause neuroinflammation.[149]

In a study done by Lin *et al.*, mice were tested in groups one and two for 0.5 and two hours at 0.7% Isoflurane, and groups three and four at 1.4% (1 MAC).[150] The groups one and two exposed in low concentrations, demonstrated impaired cognitive abilities, which corresponded to the changes regarding expression of NR2B and ERK1/2 activation. Elevation of protein expression of Caspace-3 was evident in groups three, following exposure for 24 hours and group four, which was exposed for 24 hours for a period of two weeks. Acute and long-term increase in protein expression of NR2B term occurred in groups one and two while a decrease was seen in group four. Acute decrease was seen in group three, which then normalized. The ratio of Phospho-ERK1/2 to total-ERK increased acutely in groups one and

two, which went to normal in the second week, while in groups three and four, there was acute and long-term reduction.[151]

C.III - 3.2.8.2 Rat Studies

In a study done by Culley *et al.* (2004), old rats aged 18 months were used to compare 2 hours of 1 MAC Isoflurane with a 100% oxygen compared to 70% N_2O. Independent use of N_2O was associated with impairment of spatial memory after two weeks following induction of general anaesthesia using Isolflurane.[152] In a different study conducted by Culley *et al.* (2005), the experiment was repeated with rats aged 22 months. No difference in mortality was revealed in this experiment.[153] A study done by Kalenka *et al.* (2010) revealed that three hours of 1 MAC (1.2%) Isoflurane in 21% oxygen resulted in altered synthesis of proteins in the hippocampus.[154] According to Lin *et al.* (2011), exposure of four months aged rats for two hours of 1.2% Isoflurane resulted in declined long-term cognitive abilities. This research specifically demonstrated impairment of spatial memory, fear memory, and fear learning. Increase in the levels of IL- 1β and activated Caspase-3 were noted in the hippocampus. Both IL-1β and activated Caspase-3 were at baseline after 29 days. There was no change in the levels of Aβ 1-42 and TNFα after 29 days. A decrease in the neuronal density in the CA1 region was observed after 29 days. There was no change in beta-amylid-peptide.[150] A study conducted by Zhou *et al.* (2011) demonstrated in seven days old rats developing brain that a six hours exposure to 0.75% Isoflurane at 70% N_2O caused a significant increase in the number of cells positive for caspase-3 in the CA1 sub-region of the hippocampus, substantia nigra, and cingulated cortex. No increase was noted in the basal forebrain. Glutamatergic and GABAergic neurons formed 14% and 54% respectively of the apoptotic cells in the CA1 sub-region of the hippocampus. Glutamatergic and GABAergic neurons formed 37% and 30% of the apoptotic cells in the cingulated cortex respectively. In the substantia nigra, dopaminergic

cells formed 22% of the apoptotic cells. It was concluded that exposure to anaesthetic substantially increases neuroapoptosis of glutamatergic, GABAergic and glutamatergic neurons in the developing brain as opposed to the cholinergic neurons present in the basal forebrain.[155] According to Callaway *et al*, it was demonstrated in 3 months and 12 months old rats that four hours of exposure to 1.2% Isoflurane caused no change in learning. However, memory retention was noted in the rates following 24 hours of exposure. Middle-aged rats, when compared to sham, showed a reduction in memory retention following four weeks of exposure.[156] Zhang *et al.* (2013) demonstrated using 8 months old rats that one injection of 8% emulsified Isoflurane resulted in a reversible memory and learning impairment. It was also revealed that there was up-regulation and down-regulation of expression of NGF and BDNF, respectively.[157]

A study conducted by Callaway *et al* (2012) demonstrated in eight to ten week old and 20-24 months old rats that exposure to Sevoflurane for four hours significantly enhanced the speed of determining the hidden platform in both age ranges following a week of exposure to anaesthesia. This improvement on performance was maintained for four weeks in young rats.[158] In a study done by Zhou *et al.* (2013), it was shown that *in vitro* and *in vivo* exposures to 3% Sevoflurane or Sevoflurane in combination with SEW2871 (selective agonist of S1P1 receptor), FTY720 or combination of FTY720 and VPC23019 (SIP antagonist) resulted in significant reduction in neuronal apoptosis induced by Sevoflurane with FTY720. On the other hand, VPC23019 decreased the FTY720`s neuroprotective effect on combined administration. FTY720 was associated with a substantial preservation of the level of phosphorylated ERK1/2, administration of 1 mg/kg of Bcl-2 and Bax caused significant reduction of neurocognitive impairment induced by Sevoflurane. In study done by Ren *et al.* (2014), seven day old rats were subjected to brain hypoxia-ischemia (HI) and post conditioning

with Sevoflurane in the presence or absence of 5-hydroxydecanoic acid, which is an inhibitor of mitochondrial KATP channel. It was shown that post conditioning, depending on the dosage of administration, reduced the loss of brain tissue observed with the seven days following subjection on brain HI. Additionally, it was reported that this particular effect was triggered by concentrations that were clinically appropriate and eliminated by 5-hydroxydecanoic acid. As such, it was concluded that these outcomes suggested that post conditioning channels with Sevoflurane protects brains of neonates from brain HI through mitochondrial KATP channels.[159] According to Zhang *et al.* (2014), it was shown in rats that a bilateral injection of SB269970 (100 pmol/0.2μl) into the basolateral amygdala (BLA) could lead to inhibit amnesia induced by Sevoflurane and reverse the inhibitory effects of Sevoflurane on expression of Arc in the hippocampus. On the other hand, injection with AS-19 (50 pmol/0.2 μl) could aggravate the effect of amnesia and lead to further inhibition of the Arc expression. Pre-training six hours inhalation of 2% Sevoflurane failed to trigger apoptosis in the hippocampus. It was concluded that the effects of amnesia induced by Sevoflurane may partially contribute to impairment of memory formation in the hippocampus through stimulation of the 5-HT7 receptors found in the BLA.[160]

In a study that was done by Callaway *et al.* (2015), it was demonstrated in three months and 20-24 months old rats exposed to (1.0 and 1.5 MAC) Desflurane for four hours that an effect that was dependent on the dose and age related significant impairment on acquisition of task, increased time of travel and distance of swimming was evident following two weeks of exposure.[161] A study conducted by Hinkelbein *et al.* (2010) revealed in rats of 280 ± 21 g that a three hours exposure to normobaric hyperoxia triggers changes in expression of antioxidant, which go undetected for a maximum of seven days. Analysis of bioinformatic pathways showed a link between Alzheimer`s disease and the identified proteins.[162] According

to Cullet *at al.* (2007), it was demonstrated in rats aged 18 months that 70% N_2O anaesthesia for a period of four hours resulted in inhibition of cortical methionine and liver synthetase. Activity of the liver was continually depressed for two days following anaesthesia when recovery of cortical enzyme activity was restored. Memory and learning were not impaired but there was a difference in the overall speed of test completion.[163] In a study conducted by Lee *et al.* (2008), the experimental design by Cullet *et al.* (2007) was employed to test the effect of Propofol rather that of N_2O.

It was established that continuous infusion of Propofol (0.6 ± 0.1 mg/(kg min)) in rats aged 18 months resulted in non-affected memory and learning abilities.[164] Feldman *et al.* (2008) demonstrated in rats aged one year and 576 ± 64 g in weight, that chronic corticosterone reduced in significant levels, expression of rat hippocampal PEBP1, and triggered impairment of working and reference memories. It was hypothesized that PEBP1 may be a new molecular mediator which had effects on cognitive integrity during instances of exposure to chronic corticosterone in the hippocampus.[165]

C.III - 3.2.8.3 Human In Vitro Studies

According to a study conducted by Zhongcing *et al.* (2007) it was demonstrated in a model with naïve human H4 neuroglioma cells and over expressing H4-APP cells that Isoflurane led to increase in the level of secreted Aβ, BACE and γ-secretase in the H4-APP cells. Aβ generation was inhibited by the broad-based Caspase inhibitor Z-VAD. The inhibitors of Aβ aggregation, clioquiol and iAβ5, caused selective attenuation of activated Caspase-3. Activation of Caspase-3 occurred without detectable changes in generation of Aβ even though Aβ aggregation was prompted. Activation of Caspase-3 under induction by Isoflurane was facilitated by Aβ in the H4 cells. These facts support the hypothesis that

Isoflurane had the ability of inducing apoptosis, stimulating levels of β-Secretase and BACE and secretion of Aβ thus causing more cycles of apoptosis.[166] In a study conducted by Zhang *et al.* (2008), it was discovered that activation of Caspase-3, which was induced by Isoflurane depended on cytosolic calcium. Attenuation of activated Caspase-3 could be caused by Memantine. Assessment of effects of concentration of extracellular calcium on activation of Caspase-3 induced by Isoflurane in H4 human neuroglioma cells that have been transfected for expression of full-length H4-APP cells. The effects of RNA interference (RNAi) silencing of IP3 receptor, NMDA receptor, sacro-/ER calcium ATPase (SERCA1) and calcium pump in endoplasmic reticulum (ER) were also evaluated. Examination of the effects of Memantine on NMDA receptor in brain tissue and H4-APP cells of naïve mice. Memantine caused inhibition of increase in levels of cytosolic calcium attributed to Isoflurane induction and attenuation of Isoflurane induced activation of Caspase-3 and apoptosis thus maintaining cell viability in mice and human cells. These results demonstrated that interference of calcium homeostasis underlies activation of Caspase and apoptosis under Isoflurane induction. Memantine could cause inhibition of activation of Caspase by Isoflurane as well as apoptosis both *in vitro* and *in vivo* . These results show that apoptosis and activation of Caspase-3 induced by Isoflurane depend on levels of cytosolic calcium, should facilitate the provision of anaesthetic care that is safe, particularly for Alzheimer`s and old age patients.[167] Cultured cells and primary neurons in mice were studied by Zhang *et al.* (2010). Exposure to 2% Isoflurane for six hours resulted in increased levels of pro-apoptotic factor Bax levels, decreased levels of anti-apoptotic factor Bcl-2, increased accumulation of reactive oxygen species, facilitation of release of cytochrome from mitochondrion to the cytosol, induced activation of both Caspase-3 and 9 and apoptosis in comparison with the control. Isoflurane is able to elevate the levels of mRNA of Bax and lower the mRNA levels of Bcl-2. Intracellular calcium chelator

BAPTA can trigger attenuation of accumulated reactive oxygen species induced by Isoflurane. Activation of the mitochondrial apoptotic pathway cannot be induced by administration of anaesthetic Desflurane. This partly reveals the molecular mechanism through which Isoflurane triggers apoptosis.[168] Xu *et al.* (2011) investigated primary neurons from naïve mice and human neuroglioma cells, which were treated with Isoflurane and/or Aβ. Regarding in vitro experiments, apoptosis and Aβ-induced caspase-3 activation were potentiated with 2% Isoflurane and attenuated with 0.5% Isoflurane. Regarding *in vivo* experiments, the Aβ-induced Caspase-3 activation was potentiated with 1.4% Isoflurane and attenuated with 0.7% Isoflurane. High concentrations of Isoflurane potentiated the Aβ-induced reduction in the ration of Bcl-2/Bax and resulted in a strong elevation of levels of cytosolic calcium; low concentrations resulted in inactivation of the Aβ-induced reduction ration of Bcl-2/Bax and resulted in a mild increase in the level of cytosolic calcium. Isoflurane may have double effects including protection and facilitation, on Aβ-induced toxicity, which is known to act via cytosolic calcium and the Bcl-2 family proteins.[169] According to a study done by Zhang *et al.* (2012), it was revealed that in H4 human neuroglioma cells *in vitro*, exposure to Isoflurane was associated with induction of Caspase-3 activation and the Propofol and Mg^{+} inhibited the mPTP opening that was triggered by Isoflurane. These results suggested that Propofol and Mg^{+} had the ability of protecting the brain cells from effects of neurotoxicity and inhibition of mitochondrial dysfunction induced by Isoflurane. These results were backed by similar results that were obtained from *in vivo* experiments using six months-aged mice.[147] Zhang *et al.* (2008) showed that Desflurane induces Caspase activation and increases amyloid hypoxic conditions using H4 human neuroglioma cells (H4 naïve cells) as well as those over- expressing APP (H4-APP cells).[170] In Zhang *et al.* (2014), human neuroglioma cells and wild type mice aged six days were tested. It was shown that anaesthesia with three percent Sevoflurane for two hours daily

raised the levels of P-AKT(ser473) and P-GSK3 (ser9) but anaesthesia with three percent Sevoflurane every day for three days resulted in a decrease in their concentration. Treatment with 4% Sevoflurane for two hours resulted in increased concentration of P-AKT (ser473) and GSK3 (ser9) in the H4 human neuroglioma cells while the same treatment for six hours caused a decrease in the level of concentration of P-AKT (ser473) and GSK3β (ser9) in the H4 human neuroglioma. It was concluded that Sevoflurane may induce a double effect involving an increase and decrease in the activation signalling pathway of AKT/GSK3β.[171]

C.III - 3.3 Indirect Side Effects of Anaesthetic Vapours

All mice, rat, and human cell line experiments discussed in the context above share the common fact that they address effects directly associated with use of anaesthetic vapours alone. Regarding clinical applications, a chemical absorbent for carbon dioxide is a necessary element of a semi-closed anaesthetic circuit. To minimize the loss of expensive anaesthetic vapour agents, present systems adopt semi-closed systems (see C.II - 1.3). Ideally, a completely closed circuit would only require a replacement of the volume of oxygen and vapour that has been metabolized by the patients and removal of products of metabolism. It is well known that when the anaesthetic vapours make contact with chemical absorbers, exothermic reactions have occurred, causing fires that are sometimes accompanied with explosions.[58] Present day vapours and carbon dioxide absorbents do not react as heavily, but they can get hot, and are causing the break down of anaesthetic vapours to products namely compounds A, B, C, D, E, and F. Generation of formaldehyde is also known to occur during the process (see C.II - 2.1).

C.III - 3.3.1 Vapour Degradation Compounds

Available absorbers of carbon dioxide generate varying levels of the above mentioned by-products.[63] These by-products are generated from the breakdown of anaesthetic vapours (C.II - 2.1). The semi-closed design of the ventilation circuit (C.II - 1.3) causes the resulting toxic compounds to accumulate in the circuit, resulting in patients` exposure to them during surgery.[42] Over the last several years, studies have been conducted showing that these compounds are both nephrotoxic and neurotoxic.[39,40,64–66] They may contribute to brain damage following completion of surgery, also known as Post Operative Cognitive Decline (POCD). The main product of degradation of Sevoflurane are compounds A-E, with little knowledge on Compound F.[39] Compound A and its toxicity are best described in literature, but studies have shown that other compounds, independent of Compound A are toxic as well.[40–42,44,45,47,61,67–69] Transient hepatic injury has been demonstrated with the use of Sevoflurane as opposed to Desflurane while employing fresh gas flow at rates of less than 2 Lpm, suggesting a role of accumulating by-products in the circuit..[70] According to a study done by Eger *et al.* (1998), it was found that the outcomes ranged from absence of significant injuries to transient nephritic proteinuria.[70] These findings have resulted in FDA recommendations for a minimum flow of gas into the anaesthetic circuit. Unfortunately, this limits the concept of a closed circuit to a semi-closed circuit.

C.III - 3.3.2 Carbon Monoxide

Chemical absorbents of carbon dioxide generate differing levels of carbon monoxide, depending on the humidity, chemical composition and degree of desiccation.[45,67,68,73] Generally, the volumes of carbon monoxide have been reduced substantially in the latest carbon dioxide absorbent chemicals.[47]

C.III - 3.3.3 Chemical Granulate Dust

The presence of chemical absorbents, which is necessary in modern anaesthetic circuits is associated with generation of alcalotic dust, which is corrosive and breaks off granulate elements. Accumulation of these duct particles may occur in the ventilation circuit. Even though, best filters have been designed, combined viral/bacterial filters separating the patient from the ventilation circuit, they may enable dust particles that are almost the size of viruses and bacteria to penetrate through the filters and lodge in the patients` lungs. Accumulation of larger particles occurs at the surface of the filters, make contact with water molecules resting on the filter, and hence penetrate in solution form. It the solution or dust particles are allowed to make contact with tissues for any period of time, a chemical sensation will occur leading to development of bronchospasm, pneumonia, or laryngospasm.[76] Accumulation of the dust also occurs in the circuit, and this may cause mechanical failures such blockage of valves.[77] Again, the risk associated with the CO_2 absorbent is only present, and therefore linked to the use of vapours.

C.III - 4 COGNITIVE OUTCOME IN HUMANS

Cognition after anaesthesia and postoperative decline are discussed widely, especially in relation to seniors. Cognitive results of patients after surgical interventions, influenced by effects of anaesthetic vapour, can be categorized into various clinical and non-clinical diagnoses. Rundshagen *et al.* presented a summary of the various diagnoses with their manifestations, methods of diagnosis, timing and lastly, prognosis.[172] Recently, anaesthesia and surgery have been reported to facilitate development of Post Operative Cognitive Decline (POCD) syndrome.[78] This syndrome is specifically manifested in old age patients under cardiopulmonary bypass (CPB) procedures.[82] Approximately 50% of all the surgical operations done in the 1999 were on old–age patients with 65 or more years. This population constituted

12% of the present population.[83] Patients suffering from POCD often present with impaired cognition functioning such as thinking, memory, and perception. The rate of mortality in this population is also high with the first year after surgery.[79,80] The type of surgery, and the patient`s age are risk factors for development of POCD. Very young and old age patients are at a higher risk of developing POCD.[81] The average incidence rate of POCD ranges from 15% to 25%.[78] The highest incidence (up to 70%) has been documented for cardiac surgery.[82] Enough concern has emerged in appropriate medical circles to necessitate immediate attention by the Anaesthesia Patient Safety Foundation (APSF) of America since the year 2004. An article published in the New York Times in 2011 covered the FDA's Smart Tots program, which involves exploration of the side effects associated with use of anaesthetic agents particularly on cognitive functioning in children, further highlighting the recognition of this issue in the public`s consciousness. Additionally, the population of people aged 65 years and above is increasing at a very faster rate compared to other age groups. Statistics given by the United States Census Bureau predicted that, between 2010 and 2020, this population will grow by 53% while the overall population will grow by 17%. This information makes POCD a growing public health issue, which can cause incurrence of expenses. According to research, even a slight improvement in one-year cognitive results could imply that thousands of lives are secured yearly and a substantial reduction in burden on the economy.[85] According to a study conducted by Tachibana *et al.,* pilot investigations were focused on patients` recovery from postoperative cognitive functioning in old age patients following an extended period of Desflurane exposure. A total of 45 patients aged 65 years and above scheduled for a four hours surgery were selected randomly and assigned to groups S (Sevoflurane 1 %) and D (Desflurane 3.5 %). The Mini-Mental State Examination (MMSE) was applied 24 hours prior to and after surgery. In group D, the postoperative MMSE score showed significant improvement than in

comparison to the preoperative stage. It was concluded that old age patients undergoing Desflurane anaesthesia have a significantly improved cognitive functioning in comparison to their counterparts on Sevoflurane anaesthesia.[173] In a study conducted by Ding *et al.,* focus was directed on the results presented by Tachibana *et al.* These were based on patient-related factors such as level of education and use of alcohol as well as intraoperative factors including extent of anaesthesia. Additionally, the researchers also evaluated the MMSE test results, where the two groups were above the cut-off points of 24 of 30 and the variations were only one point in comparison to the two points that are usually classified as relevant in clinical settings.[173,174] According to a study conducted by Rasmussen *et al.* it was demonstrated in the elderly patients, age 60 and above undergoing non-cardiac surgery, that POCD developed in 19.7% and 12.5% of the patients after general and regional anaesthesia in seven days after surgery respectively. It was also shown that 14.3% and 13.9% of patients on general and regional anaesthesia, respectively, developed POCD. Significant increase in the rate of mortality was also evident in general anaesthesia. Finally, it was concluded that there was no cause relationship between general anaesthesia and development of POCD while regional anaesthesia was associated with decreased mortality and early development of POCD.[175] In a study conducted by Farag *et al.* it was noted that, when developing a comparison between patients with a high level of BIS (average BIS 50.7) and patients with a lower level of BIS (median BIS 38.9), patients having a lower level of BIS demonstrated a faster speed in processing information as determined by Processing Speed Index (PSI) than patients with higher levels of BIS four to six weeks postoperatively.[176] This supports a study by Monk *et al.* describing the link between cumulative deep anaesthesia time and POCD.[177] According to Xie *et al.* exposure of H4 human glioma cells to 2% Isoflurane for a period of 6 hours resulted in induction of dose dependent cellular apoptosis, which was counteracted by Congo red.[178] Xie

et al. also concluded that Isoflurane facilitates a well comprehended mechanism of neuropathogenesis of Alzheimer`s disease, thus providing a probable linkage between acute effects of anaesthesia, which is a known risk factor for delirium development, and the long-term sequelae of dementia.[179] These findings indicate that Aboligomerization and apoptosis induced by Isoflurane may facilitate development of cognitive dysfunction in the post operative phase and that provide a probable pathogenic linkage between dementia and delirium development.[180] A study conducted by Lee *et al.* was focused on female patients aged between 20 and 65 years on thyroid surgery. The outcomes of the study demonstrated that Quality of Recovery-40 questionnaire (QoR-40) score on postoperative day 1 in the TIVA group was significantly higher compared to Desflurane group. These results indicated that the quality of recovery of the TIVA group was better than the Desflurane group. Therefore, it was concluded that, when compared to Desflurane anaesthesia, TIVA significantly elevates the quality of recovery among female patients who have had thyroid surgery.[31]

C.III - 5 SUMMARY

In ancient times, rapid surgical procedures were necessary in order to complete the procedure before the patient died from pain induced stress, due to a lack of proper anaesthesia (also described in C.II - 1).[181] Starting 1865, Chloroform was used in the majority of procedures on the European continent, until improved equipment for administering controlled anaesthetic doses and the discovery of newer and safer anaesthetic vapours took over.[9,11]

The introduction of semi-closed circuits, allowing a large portion of the gas mixture to be retained in the loop made chemical absorbers necessary for removing exhaled CO_2 from the circuit.[29] We have come a long way in the last 50 years when surgery was still considered

hazardous for patients 50 years or older.[182] Today, with the improvements of modern anaesthesia, longer and more complex surgeries are possible in even older patients.[183] Today, two thirds of all procedures are performed under general anaesthesia and one third is performed using local or regional pain control with optional sedation. The vast majority of general anaesthesia procedures use vapours. These vapours have been shown to potentially induce malignant hypothermia[184] or epilepsy[185], irritate the respiratory system, induce chromatid changes[86,136], damage the kidneys[70,186,187] and the liver[143], and have direct negative effect on the cardiovascular system including limiting the auto regulation of the brain[125] and indirect effects through necessary CO_2 absorbers[39,45,188]. Furthermore, research in the last 10 years involving human cell lines as well as mouse and rat models, found that Isoflurane introduces a dose and time-dependent change in protein synthesis, levels of inflammatory cytokines, levels of activated Caspase-3, TNFα and introduces loss of neurons in the Substantia Nigra, Cortex and CA1 sub region of the Hippocampus. Several of the identified pathways seem to be common with pathways for the development of Alzheimer's disease.[179,189,190] The cognitive outcome in the animal models was commonly described as reversible. This stands in contrast to observed loss of brain cells in all models and long-term cognitive decline in human outcome studies, challenging the adequacy of these animal models beyond mechanistic investigations. Rappold *et al.* for the first time provides evidence for an association between observed cell damage and POCD.[48]

C.III - 6 CONCLUSION

To date, no differences in neurological outcome after TIVA versus vapour anaesthesia could be shown in clinical studies.[191] However, recent publications claim that a lack of validated cognitive tests for neurological pre- and post testing is a major contributor to the lack of clear outcomes in POCD studies. Ignoring cost and complexity aspects, the multitude of side effects and not-well-understood changes caused by the use of anaesthetic vapours, in contrast to the lack of such undesired effects for Propofol and modern opioids, suggests TIVA as the safer anaesthetic in an elderly patient population presenting with a multitude of comorbidities. However, in contrast, some studies show neuroprotective effects of low doses of anaesthetic vapours. Furthermore, the haemodynamic stability and ease of application including fast wakeup times make these vapours still desirable.

At this point, not enough evidence has been provided in order to decide what anaesthesia drugs are most appropriate. It is foreseeable however, that different drugs will be the right choice for specific patients with varying comorbidities. Either way, the authors do not expect anaesthetic vapours to disappear from anaesthetic practice soon, making the development of a safer and environmentally friendly CO_2 absorber an important step to better patient outcomes after surgery and general anaesthesia using anaesthetic vapours. This is important as it signifies a clear need to reduce the damage linked to the use of CO_2 absorbers, which is the goal of this thesis.

Chapter IV INVESTIGATION OF DEGRADATION OF ANAESTHETIC VAPOURS BY PMP MEMBRANES

As explained in C.II - 4, dense poly-methyl-pentene (PMP) membranes are predicted to permeate CO_2 at a much higher rate than anaesthetic vapours, making them a suitable candidate for the application in anaesthesia circuits. Porous and dense variations of PMP membranes are used in oxygenators for delivering anaesthetic vapours during cardiac surgery (C.VI).

This chapter describes the investigation into possible degradation products from anaesthetic vapours when in contact with PMP membranes and possible solvent residues therein.

This is relevant to the thesis aim of developing a membrane based CO_2 filter, but also provides guidance for clinical use of anaesthetic vapours in cardiac surgery.

C.IV - 1 INTRODUCTION

The only poly-methyl-pentene (PMP) membranes approved for medical use are produced using a thermally induced phase separation (TIPS).[192] The PMP material of the hollow fiber membranes under consideration meets the requirements of the FDA*. The material and process for producing hollow fibre membranes from PMP have regulatory approval for the manufacturing of oxygenators for cardiac surgery. These membranes are considered safe for the direct contact with the patient's blood.[193] However, the intended use of many oxygenators does not include the use with anaesthetic vapours.[194] The membrane samples tested include two dense skin hollow fibre membranes with varying density. The samples were supplied by 3M Membranes Business Unit, Wuppertal, Germany from commercially produced stock. During production, solvents are used to create the desired transport properties of the hollow fiber membranes wall. While solvents potentially remaining in the membrane are deemed safe by regulatory bodies, the interaction of anaesthetic vapours with possible solvent residues in such membranes has not yet been explored.

C.IV - 2 RATIONALE

The solvents used during the TIPS process are oil-based. The exact makeup of the solvent is a trade secret. The solvent is washed off with alcohol after the membrane has been formed. The manufacturer claims that this washout process is 99% successful; therefore, some residual solvent might still be present in the membrane material. While unlikely, reactions with remaining solvent may lead to the release of vapour phase compounds that may be harmful to patients.

* FDA CFR Title 21 Sec. 177.1520 Olefin polymers (C) 3.3b
for TPX(4-methylpentene-1-based olefin copolymer)

This chapter therefore describes the investigation into possible degradation products from anaesthetic vapours when in contact with PMP membranes and possible solvent residues therein. If solvent was present, the high solubility of halogenated compounds in oil could potentially lead to the creation of measurable volatile compounds as result of the reaction of other chemicals comprising the solvent beside the oil with anaesthetic vapours.

C.IV - 3 MATERIALS AND METHODS

Hollow fiber membrane samples were supplied by 3M Membranes Business Unit, Wuppertal, Germany. Samples of Ultraphobic® (dense skin) and Oxyplus® (dense skin) were exposed to a 100% vapour saturated environment. Gas tight micro-tubes (2 mL, PP, Sarstedt AG, Nuremberg, Germany) were each filled with 0.25 mL of Sevoflurane (Abbvie, North Chicago, Illinois, United States), Desflurane and Isoflurane (both from Baxter Corporation, Deerfield, Illinois, United States) and capped. The membrane samples (0.5 m per sample, 380 µm diameter, 3M, Wuppertal, Germany) were exposed for one hour. One tube per vapour served as control with no membrane present. To achieve vapour saturation in the tube, the volume of liquid anaesthetic was chosen to exceed the amount soluble in 2 mL of air. In this extreme setup, unrealistic for real patient settings, liquid vapour was placed in direct contact with the membranes. This experimental design resulted in 9 micro-tubes. There were 3 tubes for each of the 3 anaesthetic vapours (Sevoflurane, Isoflurane or Desflurane) and in each group one tube contained the vapour only (control), 0.5 m Ultraphobic® or 0.5 m Oxyplus® hollow fibre samples (see Fig. IV-1).

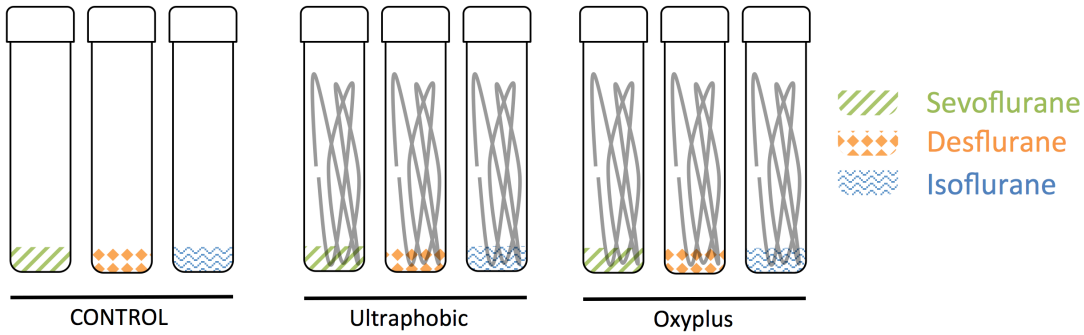

Fig. IV-1. Schematic of the experimental layout. 2 fibers and 3 vapours lead to 3^2=9 scenarios.

To assure more than sufficient contact of the liquid anaesthetic vapour with the membrane samples the micro-tubes were shaken vigorously for five minutes. They were then left to sit for 1 hour prior to sampling. The mass spectrum of each micro-tube was measured with a quadrupole mass spectrometer (QMS, Omnistar Model PTM81217131, Pfeiffer Vacuum, Aßlar, Germany).

To ensure minimal leakage of the micro-tubes, sampling was achieved using a needle puncturing the top cap, drawing the sample volume from the head space in the tube through the needle into the capillary of the mass spectrometer (see Fig. IV-2). The capillary and inlet heater were turned on to avoid condensation of heavy compounds in the capillary.

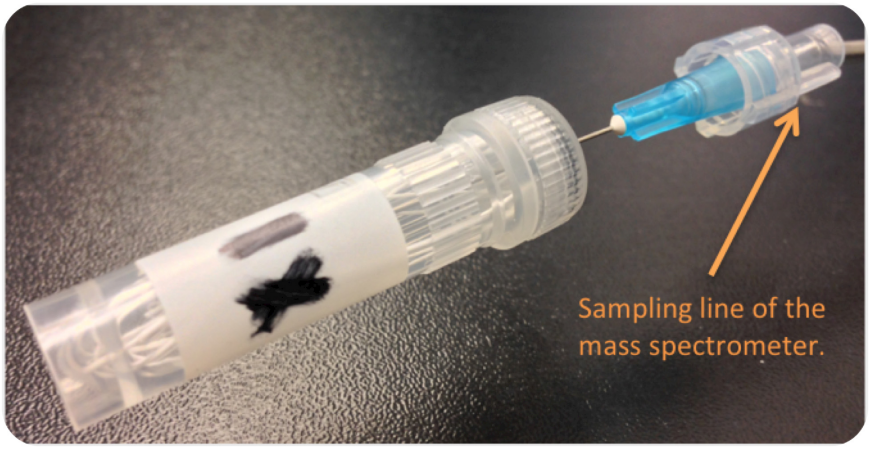

Fig. IV-2. Micro-tube with fiber sample (Ultraphobic®) and vapour (Desflurane) attached to the mass spectrometer-sampling capillary using a fine needle

A QMS was used to measure the gas composition of the feed, retentate and permeate streams for the mixed-gas tests. The mass spectrometer was controlled through Pfeiffer Vacuum's Quadera software (v4.50.004). Mass spectrometer operation, data analysis, display and storage were all controlled via Quadera. The QMS was operated using Secondary Electron Multiplier (SEM) ion detection to achieve a higher resolution and to enable accurate detection at low concentrations. The same operating conditions were used for all of these experiments (SEM voltage of 910 V, Ion Current of 5.1^{-09} A, Spectral Resolution of 50 and a dwell of one second). The mass spectrometer was calibrated for mass specific concentration determination per Pfeiffer Vacuum's recommended calibration procedure.[195] An offset calibration was performed to eliminate any inherent offset of the measured SEM signal. A mass scale adjust calibration was then conducted to tune the mass scale to adjust the measured value of each mass of interest to an integer value. A background determination calibration was then performed to identify any mass peaks from residual gases that were not associated with the gases being measured. Background spectra from this calibration were subtracted from subsequent measurements. The final calibration was the gas specific calibration, where ion peaks were translated to concentration by the gas specific calibration, which entails the assignment of compounds to mass peaks. A calibration factor library was then constructed using certified calibration gas mixtures. The mass spectrometer calibration was maintained throughout the course of the experimental testing. Anaesthesia calibration mixtures were mixed by manually injecting a defined amount of liquid Sevoflurane, Desflurane, or Isoflurane into a syringe filled with oxygen and agitating it to vapourise the liquid. The composition was calculated using the compound properties and the ideal gas law (see Appendix A). The mixture

was then used to calibrate the mass spectrometer. The concentrations supplied by the vapourizers were then verified with the calibrated device.

Before measuring each anaesthetic vapour group, an air sample was recorded (see Fig. IV-3). The air samples were compared for differences and used as validation such that the QMS reading was returned to base line on all masses before the next vapour group was recorded.

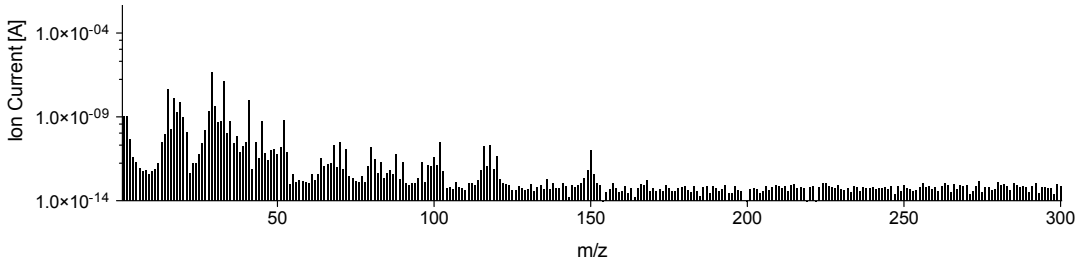

Fig. IV-3. Sample mass spectrum of air as raw data of single run

For the investigation of possible volatile by-products created upon contact of the membrane with possible solvent residues and the anaesthetic vapour, the vial with the corresponding vapour only was recorded as control group. This was accomplished by recording eight full runs for the full mass spectrum (1-300 amu) of the anaesthetic vapour and subtracting the average from the corresponding eight sample average of the micro-tube volume containing the vapour and the membrane sample. Averaging of eight runs reduced the noise and established a baseline for all masses in the spectrum (Fig. IV-4).

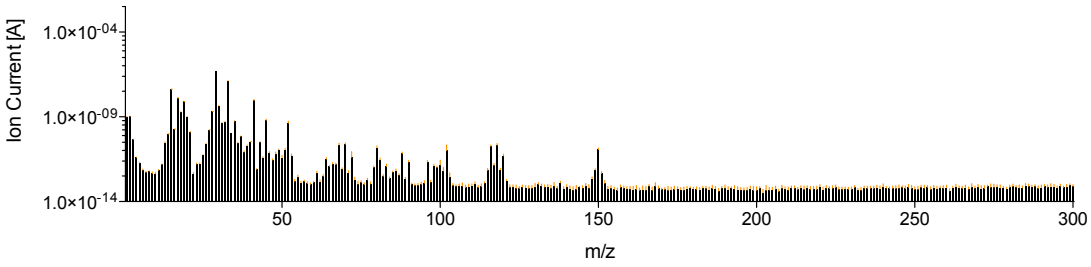

Fig. IV-4. Sample mass spectrum of air, averaged over of 8 runs, mean ± SD. The noise floor clearly evens out

The raw data was then exported as an ASCII file and analysed using Prism 5 (Graphpad, La Jolla, CA, USA). Samples were analysed using a one-way ANOVA. The comparison of each exposed membrane to the corresponding vapour control was conducted by Dunnet's multiple comparison.

C.IV - 4 RESULTS

There was no significant difference between the first air sample and air samples taken in between the vapour groups (ANOVA: P=0.7616, r^2=0.0006, Dunnett: ns). There was also no significant difference between the Sevoflurane, Isoflurane and Desflurane (control) samples and the respective samples with Ultraphobic® and Oxyplus® fiber samples (Table 3).

Table 3 Results from Ultraphobic and Oxyplus fibers exposed to Sevo-, Iso- and Desflurane compared to vapour alone

Anaesthetic	Test	Ultraphobic	Oxyplus
Sevoflurane	ANOVA	ns (P=0.9978, r^2=4.9e-6)	
	Dunnet's	ns	ns
Isoflurane	ANOVA	ns (P=0.8727, r^2=0.0003)	
	Dunnet's	ns	ns
Desflurane	ANOVA	ns (P=0.7670, r^2=0.0006)	
	Dunnet's	ns	ns

C.IV - 5 DISCUSSION

Unfortunately, I was not able to receive samples of the solvent, or information about its contents, used in the production of these membranes (3M trade secret), limiting my ability to

predict potential chemical reactions between the solvent and the anaesthetic vapours. This means that I was not able to calibrate the mass spectrometer for quantitative analysis of putative target compounds.

As an alternate approach, I devised a different experiment to detect if there was a change in the mass spectrum when anesthetic vapours came into contact with the fibers. After exposing the membranes to 100% anaesthetic vapour concentration, the mass spectrum of pure vapours compared to the spectrum of fibers exposed to anaesthetic vapours in very high concentrations, did not show significant differences. Thus, while I could not theoretically predict the interaction of anaesthetic vapours with the solvent used in commercially producing these membranes, I was able to show in a worst case situation exposing the membrane to highly concentrated liquid anaesthetic vapours, that no clinically significant level of vapour phase compounds was created upon direct contact of the vapours with the membrane. The limits of the measurement are discussed below. The fact that there was no significant difference between the air samples recorded before each vapour group was sampled, means that the measurements were not influenced by residual masses left in the mass spectrometer from previous measurements. There were no significant differences between the vapour (control) and Ultraphobic® or Oxyplus® in combination with the vapour. This means that no measurable levels of by-product were created when the membrane fibers contacted Sevo-, Iso- or Desflurane and implies one of two scenarios: a) no solvents were present, b) solvents were present, but did not react with the anaesthetic vapours vapours in measureable amounts. Only the creation of volatile compounds would have been relevant for patients, as only volatile compounds can reach the patient as part of the gas mixture entering the airways. The mass spectrometer model used in this experiment has been validated for accuracy in clinical settings[196,197] and is able to detect levels down to 1×10^{-13} mmHg equal to around 1×10^{-10} ppm

(Pfeiffer Vacuum). Typical detection limits for occupational volatile organic compounds are around 1×10^{-2} ppm,[128,130,131,133] therefore any changes below the detection limit were deemed not relevant in clinical practice. This means, that there are no clinically significant levels of volatile compounds created when these polymeric membranes tested are exposed to anaesthetic vapours.

C.IV - 6 CONCLUSION

The results of this investigation showed no significant difference between the mass spectrum of the gas mixture sampled from a test vial containing only anaesthetic vapour (control) in comparison to a vial containing fiber material exposed to anaesthetic vapour. Levels of volatile compounds in anaesthesia are commonly investigated in the parts per million ranges. Given the minimum detection threshold of the QMS, the production of volatile compounds in concentrations relevant to anaesthesia can therefore be excluded. The findings successfully showed, that the tested polymeric membrane eliminates the production of by-products, commonly seen in state of the art, chemical based, absorbers.

Chapter V MEMBRANE CHARACTERIZATION

Characterization of dense PMP membranes for the separation of carbon dioxide from anaesthetic vapours in low pressure applications

F Wilfart, M Soehl, N Kilcup, I Voigt, J Haelssig

Unpublished manuscript

Membranes have been identified as a solution for CO_2 removal from anesthesia circuits (Chapter I). The selectivity for CO_2 and anaesthetic vapours has to be balanced with the CO_2 removal capacity of the membrane. As the system is limited to passive transport only by the partial pressure difference of CO_2 across the membrane, the CO_2 transport can only be optimized by changing the membrane properties and the system design. A unique approach for characterization is developed and applied to guide custom modifications of the membrane properties by 3M.

ABSTRACT

Developed countries are facing a significant rise in healthcare spending, partially driven by a fast growing and frail population segment of senior patients. This is compounded by the shrinking relative population of young people working and paying taxes to provide the funds for this increased burden on the health care system. Medical advances allow for limited mortality after operating on patients as old 100 years of age or even older. However, these interventions come with a hefty price tag: a 25-80% of patients over 65 years old who undergo surgery have some level of reduced brain function post operatively. The majority of all surgeries are performed under general anaesthesia, typically using anaesthetic vapours. To allow for rebreathing of these anaesthetic vapours without accumulating CO_2, chemical absorbers are used. Chemical absorbers produce compounds, harmful to patients, therefore requiring dilution of the gas mixture. This causes large vapour losses to the environment. These vapours are expensive and also harmful to the environment. The use of a dense polymeric membrane to separate accumulated CO_2 from the anaesthesia circuit would prevent the production of the toxic by-products (i.e. increase patient safety) and retain the expensive anaesthetic vapour (i.e. minimize financial and environmental costs). A tailored characterization approach, close to the operating conditions during anaesthesia was developed, to evaluate membrane performance in order to optimize membrane properties. Specifically, the selectivity and permeance of a custom series of hollow fiber poly(methyl-pentene) (PMP) membranes produced with different polymer/solvent ratios was evaluated for pure gasses and gas mixtures using O_2, CO_2 and anaesthetic vapours vapour (Sevo-, Des-, Isoflurane). Generally, an increase in solvent ratio increased CO_2 permeance, maintained the selectivity for O_2, CO_2, and N_2, and for anaesthetic vapours in all but the two highest solvent ratios. CO_2 permeance did vary significantly for mixtures with Isoflurane in comparison to Sevo- and Desflurane. It appears that the best CO_2 permeance with maintained selectivity for anaesthetic vapours can be achieved by using a solvent ratio of 0.77 for production.

C.V - 1 INTRODUCTION

Developed countries are facing a significant rise in healthcare spending.[198] In 2013 healthcare expenditures, reported as a percent of GDP, were 17.1% in the US, 10.9% in Canada, 10.1% in the European Union and worldwide it was 10%.[199] One of the drivers in the industrialized world is a fast growing population segment of senior patients that will require US$136,000 – US$145,000 (1998 US$) per person in their 11.6-14.3 years beyond 70 years of age.[200] This is exacerbated by the fact that the younger population segment is shrinking and will be required to support the healthcare costs of the rapidly growing frail senior population.[201] For this reason, regulatory bodies now take into consideration not only the safety and efficacy of a given therapy but also the overall cost to the healthcare system when approving a new device or treatment.[202]

The many advances in medical sciences over the last decade have made it possible to perform surgical procedures, previously deemed unsafe, on patients as old as 103 years of age with limited mortality rates.[203] However, in recent years, 25-80% of patients have been shown to have permanently reduced brain function after surgery.[200] This permanent decline in brain function is recognized under the term Post Operative Cognitive Decline (POCD). The long-term impact of POCD ranges from loss of ability to work or to live alone, which places a significant load on the social services to provide for these people.[204] Patients with brain damage persisting up to 3-months have a five times greater probability of dying in the first year after surgery.[205]

The majority of all surgeries are performed under general anaesthesia. In most cases, the anaesthetic is delivered to patients in vapour form, supplied via mechanical ventilation in a rebreathing circuit. Vapour is delivered as a component of a pre-mixed gas mixture to the lungs and the exhaled breath remains in the anaesthesia circuit. This necessitates the removal

of the carbon dioxide (CO_2) from the gas stream. To do this, anaesthesia circuits are equipped with a granulate-based CO_2 absorbent that chemically binds the CO_2 (Fig. V-1). However, the chemical absorber also reacts with anaesthetic vapours, producing compounds that have been shown to be harmful.[39,41–43,46,67,69,187]

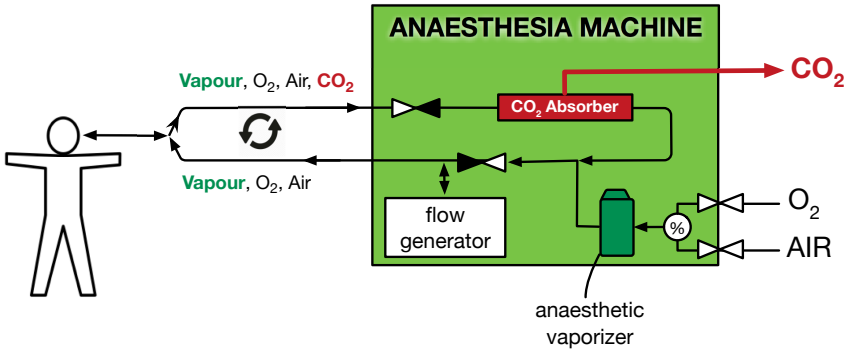

Fig. V-1. Schematic of an anaesthesia machine with rebreathing circuit. The absorber is replaced when desiccated.

This causes a dilemma: CO_2 absorbers are employed in order to allow for efficient rebreathing of the exhaled anaesthetic vapour, but at the same time the compound production has led to a required minimum dilution rate of 1-2 Lpm (country dependent). This in turn leads to a constant loss of anaesthetic vapour in the gas mixture displaced in the rebreathing circuit. If there was no issue of vapour breakdown in the absorber, the system could be rebreathing 100% of the anaesthetic vapour after removing the CO_2 and replenishing the 100-250 mL of oxygen. Such an ideal closed system is referred to as metabolic anaesthesia. The cost of the wasted vapour equates to the dilution rate, the Fresh Gas Flow (FGF). There is a linear relationship between FGF and vapour wasted.[206–208] These vapours are not only expensive; they are also harmful to the environment. The global warming potential (GWP†) for these vapours ranges from 1,401-3,714 times of that of CO_2 for up to 10 years.[51,209] Additionally, some even damage the ozone layer.[210]

† GWP is defined as the cumulative radiative forcing integrated over a period of time from the emission of gas in relation to reference gas (carbon dioxide CO_2)[209]

Hypothesis: A membrane, selective for CO_2 over anaesthetic vapours, would be able to keep the desired anaesthetic vapour in the circuit while removing the CO_2, without creating any harmful substances. This would allow for safe, metabolic anaesthesia and the associated direct cost savings; both environmental and financial.[125,211]

The breathing gas mixture is very high in water vapour. This, and that anaesthetic vapours are hydrocarbons, suggests dense hydrophobic PMP membranes. Prasser *et al.* (2008), Wiesenack *et al.* as well myself have previously discussed that PMP membranes are already approved and used in order to remove CO_2 from the patient's blood in cardiac surgery.[92,93,212]

It is important to maximize the CO_2 transport and minimize the loss of anaesthetic vapours. Typically, membrane transport is optimized by fitting the system with compressors and/or vacuum systems. As this system is limited to the pressure existing in the anaesthetic circuit, the CO_2 transport can only be optimized by changing the membrane properties and the system design. This study will develop a tailored characterization approach, close to operating conditions, and explore the optimization of the membrane properties in order to increase CO_2 permeance while limiting the loss of anaesthetic vapour.

This study seeks to characterize and optimize a membrane, developing and using an appropriate method, that is able to retain the halogenated and fluorinated hydrocarbons in the anaesthetic circuit while removing the CO_2. The membrane has to withstand the high humidity conditions and operate in a passive, low pressure environment in an anaesthetic ventilation circuit.

The characterization of volatile hydrocarbons introduces limitations to the applicability of classic characterization techniques, as the vapour state is sensitive to the temperature and pressure conditions during the characterization. Since membrane performance is dependent

on operating conditions, the experiments have to be performed as close to the proposed operating conditions as possible[213,214] limiting the selection of characterization techniques.[213,215–218] In this case, the operating conditions in an anaesthetic circuit are close to atmospheric pressure.

C.V - 2 TAILORED MEMBRANE CHARACTERIZATION APPROACH FOR LOW PRESSURE CO_2 / HYDROCARBON SEPARATION

Since A. Fick and T. Graham's work in the 19th century, it is known that gas permeation through nonporous membranes has two components: solution and diffusion.[94,97–99] Components in the feed gas dissolve in the polymeric membrane material at a high pressure and then diffuse down their concentration gradient through the membrane to the permeate side of the membrane. Membrane selectivity is determined by combining the differences in component solubility and diffusivity.

The solution-diffusion model assumes that the pressure across the membrane is constant at the feed pressure (p_0), so diffusion is driven by concentration differences.[94] The model is able to describe permeability as a function of solubility and diffusivity. Henry's Law relates the concentration of a solute in the membrane to the bulk partial pressure applied to the membrane and accounts for the discontinuity between the bulk and membrane concentration. It is therefore possible to express the flux, J_i, in terms of partial pressures incorporating the solubility coefficient per Equation 3:

$$J_i = \frac{D_i S_i}{l}\left(p_{i0} - p_{il}\right) \qquad (3)$$

Where S_i is the solubility coefficient of component i (mol m^{-2} bar^{-2}), relating the partial pressure of the component to the concentration in the membrane phase, and p_{i0} and p_{il} are the partial pressures (bar) of component i at the feed and permeate membrane interfaces,

respectively. A schematic representation of the typical bulk pressure, partial pressure and concentration profiles across a symmetric dense membrane is displayed in Fig. V-1.

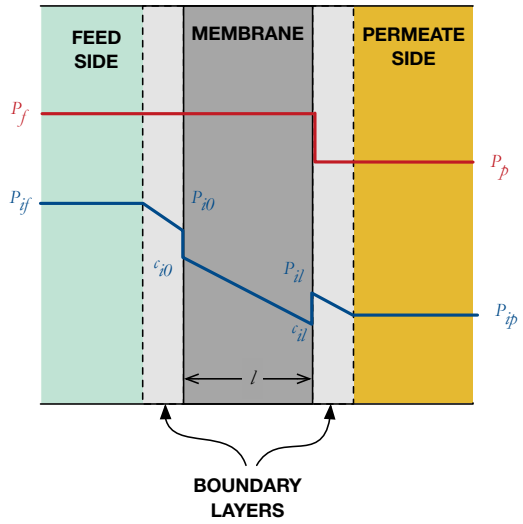

Fig. V-2. Schematic of the bulk and partial pressures profile for solution-diffusion mass transport through a dense membrane

The permeability, P_i, describes the flux, J_i, normalized to time, area, and driving force. P_i is the product of the solubility coefficient, S_i, and diffusion coefficient, D_i, in the membrane. Since it is often difficult to define the membrane thickness in a consistent manner, especially for asymmetric membranes, where the proportional thickness of the support layer and the dense skin can vary, the permeability and membrane thickness are often lumped together into a single parameter referred to as the permeance K_i. The permeance can be directly calculated by normalizing the flux for the driving force, using Equation 4:

$$K_i = \frac{P_i}{l} = \frac{D_i S_i}{l} = \frac{J_i}{p_{i0} - p_{il}} \qquad (4)$$

It is usually possible to assume that the component partial pressures at each membrane interface (*0* and *l*) are equal to the average partial pressure of the feed and permeate, respectively. The membranes selected for this application are hollow fiber membranes with the dense layer on the outer surface (Fig. V-3).

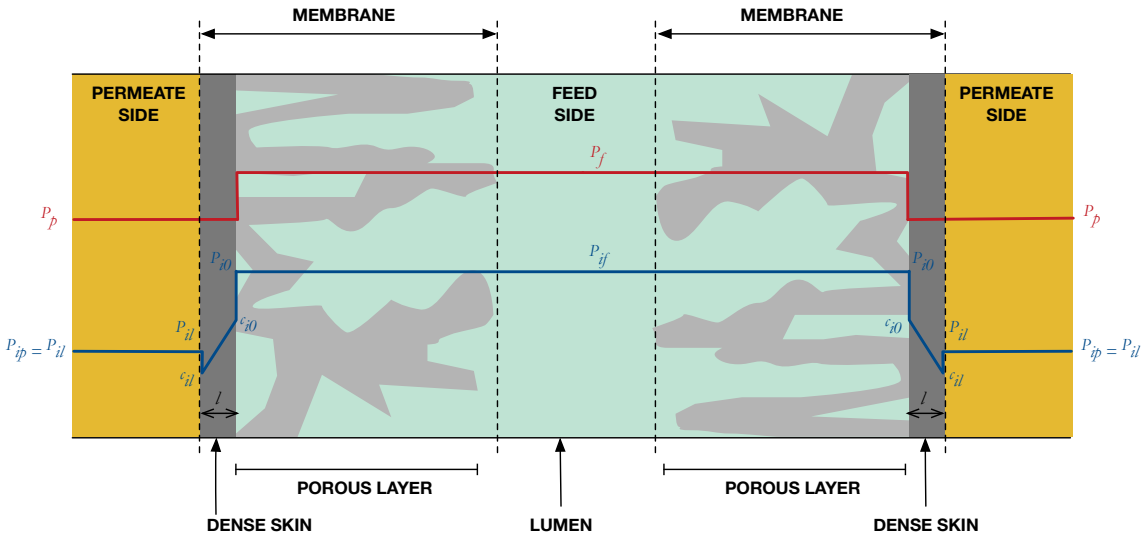

Fig. V-3. Schematic of the pressure profiles for this specific application Since the diffusion coefficient in the gas phase is significantly higher than in the membrane, and the lumen-side pressure is maintained by supplying sufficient gas flow, P_{if} is assumed to be equal across the lumen and porous layer of the membrane, neglecting boundary effects. The lumen for this purpose is defined as the volume up to the inside boundary of the dense skin.

During characterization, the feed is going to be on the lumen side and the permeate will be on the shell side of the module containing these fibers. In this case, the permeance can be calculated by dividing the flux J_i of component i across the membrane by the average partial pressure difference of that component between the feed and the permeate side. On the shell-side, the permeate is assumed to be perfectly mixed, so its partial pressures are assumed to be equal to the measured outlet partial pressure.

In this case, the permeance can be calculated using Equation 5, where the driving force is estimated using the log-mean partial pressure difference (Equation 6):

$$K_i = \frac{J_i}{\Delta p_{i,LM}} \tag{5}$$

$$\Delta p_{i,LM} = \frac{\left(y_{if,in}P_f - y_{iP}P_P\right) - \left(y_{if,out}P_f - y_{iP}P_P\right)}{\ln\left(y_{if,in}P_f - y_{iP}P_P \,/\, y_{if,out}P_f - y_{iP}P_P\right)} = \frac{P_f\left(y_{if,in} - y_{if,out}\right)}{\ln\left(y_{if,in}P_f - y_{iP}P_P \,/\, y_{if,out}P_f - y_{iP}P_P\right)} \tag{6}$$

In addition to permeability and permeance, membrane selectivity is an additional intrinsic membrane property used for characterization. Membrane selectivity (a_{ij}) is defined as the ratio of the permeability or permeance of two components (i and j) through a membrane, per Equation 7:

$$\alpha_{ij} = \frac{K_i}{K_j} = \frac{P_i}{P_j} \qquad (7)$$

Selectivity can be reported as a ratio of pure gas permeance, or when measured in a mixture of the several components, as the ratio of permeance of the gas components in the mixture.

C.V - 3 MATERIALS AND METHODS

C.V - 3.1 Membrane Test Modules

Membrane modules were supplied by 3M equipped with Luer Lock™ connectors (see Fig. V-4). The fibers were potted in the modules using polyurethane. The UltraPhobic™ membranes were manufactured with varying solvent to polymer ratios to enable the identification of the optimal membrane for the application of anaesthetic vapour separation. A minimum of three modules of each membrane type were supplied to allow the examination of variability between modules.

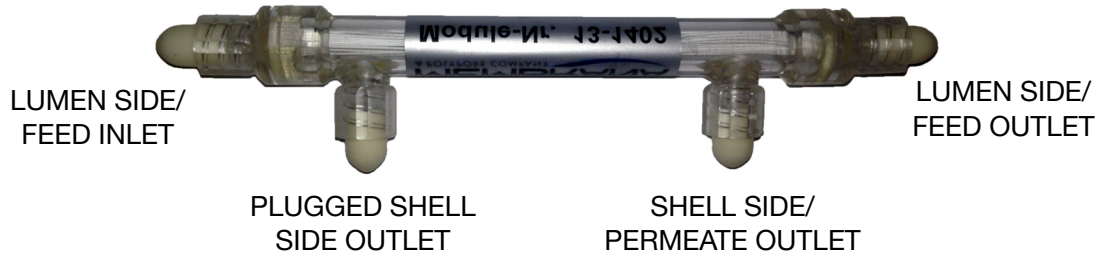

Fig. V-4. Test module supplied by 3M™

Table 4 summarizes some of the characteristics of the membrane modules.

Table 4. Summary of some characteristics of the membrane modules

Membrane	UP – 1a	UP – 1b	UP – 2	UP – 3	UP – 4	UP – 5	UP – 6
Extraction method	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Solvent to polymer ratio	0.72	0.72	0.73	0.76	0.77	0.84	0.90
Fiber wall thickness (μm)	90	90	90	90	90	90	90
Fiber internal diameter (μm)	200	200	200	200	200	200	200
Active inside area (cm^2)	24	26	26	26	26	26	26
Active outside area (cm^2)	45	49	49	49	49	49	49
Module filling degree	20.00%	20.06%	20.06%	20.06%	20.06%	20.06%	20.06%

The solvent used for manufacturing these membranes describes a solvent per the Thermally Induced Phase Separation (TIPS) process. The solvent to polymer ratio increases from 0.72 to 0.90 for membranes UP-1 to UP-6. UP-1a and UP-1b are the same membrane type but were supplied from different manufacturing runs. The solvent ratio was increased in comparison to UP-1 up to UP-6, with a predicted increase of CO_2 permeance. The selectivity was expected to be maintained until the dense skin becomes very thin, increasing the likelihood of inconsistencies at higher solvent ratios, decreasing the selectivity for hydrocarbons.

C.V - 3.2 Gases and Vapours

A certified mixture of 5% CO_2 balanced in O_2 was used as a carrier gas in the ternary gas mixture experiments and for calibrating the mass spectrometer. A certified calibration gas mixture of He, O_2 and N_2 was also used to calibrate the mass spectrometer. The gases and gas mixtures used are listed in Table 5:

Table 5. List of the gases used

Gas	Specification	Supplier
CO_2	USP grade, 99.5% pure, DIN: 02014459	Praxair, Mississauga, ON, CAN
O_2	USP grade, 99.99% pure, DIN: 02014408	Praxair, Mississauga, ON, CAN
N_2		Air Liquide, Dartmouth, NS, CAN

5% CO_2 balanced in O_2	USP grade, 99.5% pure, DIN: 02014432	Praxair, Mississauga, ON, CAN
He, O_2 and N2	SPG-3MX0021714	Air Liquide, Dartmouth, NS, CAN

Sevoflurane (Abbvie, North Chicago, Illinois, United States), Desflurane and Isoflurane (both from Baxter Corporation, Deerfield, Illinois, United States) were administered with anaesthesia vapourizers (Draeger, Lübeck, Germany). The permeation apparatus was assembled with plastic Legris 1/4-inch vacuum rated PTFE fittings and 1/4-inch polyethylene tubing, as well as TruWave 1/8-inch tubing and fittings for the permeate line and mass spectrometer sampling point.

C.V - 3.3 Mass Spectrometer

A quadrupole mass spectrometer (Omnistar Model PTM81217131, Pfeiffer Vacuum, Aßlar, Germany) was used to measure the gas composition of the feed, retentate streams as well as the permeate streams for the mixed-gas tests. The mass spectrometer was controlled through Pfeiffer Vacuum's Quadera software (v4.50.004). Mass spectrometer operation, data analysis, display and storage were all controlled via Quadera. It was operated using Secondary Electron Multiplier (SEM) ion detection to achieve a higher resolution and to enable accurate detection at low concentrations. The same operating conditions were used for all of these experiments (SEM voltage of 910 V, Ion Current of 5.1^{-09} A, Spectral Resolution of 50 and a dwell of one second).

The mass spectrometer was calibrated for mass specific concentration determination per Pfeiffer Vacuum's recommended calibration procedure.[195,219] An offset calibration was performed to eliminate any inherent offset of the measured SEM signal. A mass scale adjust calibration was then conducted to tune the mass scale to adjust the measured value of each mass of interest to an integer value. A background determination calibration was then

performed to identify any mass peaks from residual gases that were not associated with the gases being measured. Background spectra from this calibration were subtracted from subsequent measurements. The final calibration was the gas specific calibration, where ion peaks are translated to concentration by the gas specific calibration, which entails the assignment of compounds to mass peaks. A calibration factor library was then constructed using certified calibration gas mixtures. The mass spectrometer calibration was maintained throughout the course of the experiment testing.

Anaesthesia calibration mixtures were mixed by manually injecting a defined amount of liquid Sevoflurane, Desflurane, or Isoflurane into a syringe filled with oxygen and agitating it to vapourise the liquid. The composition was calculated using the compound properties and the ideal gas law (see Appendix A). The mixture was then used to calibrate the mass spectrometer. The concentrations supplied by the vapourizers were then verified with the calibrated device.

C.V - 4 MEMBRANE CHARACTERIZATION

Permeation characteristics of the membrane modules were measured using a variation of the constant-pressure variable-volume method.[220] Fig. V-5 shows a schematic of the experimental system.

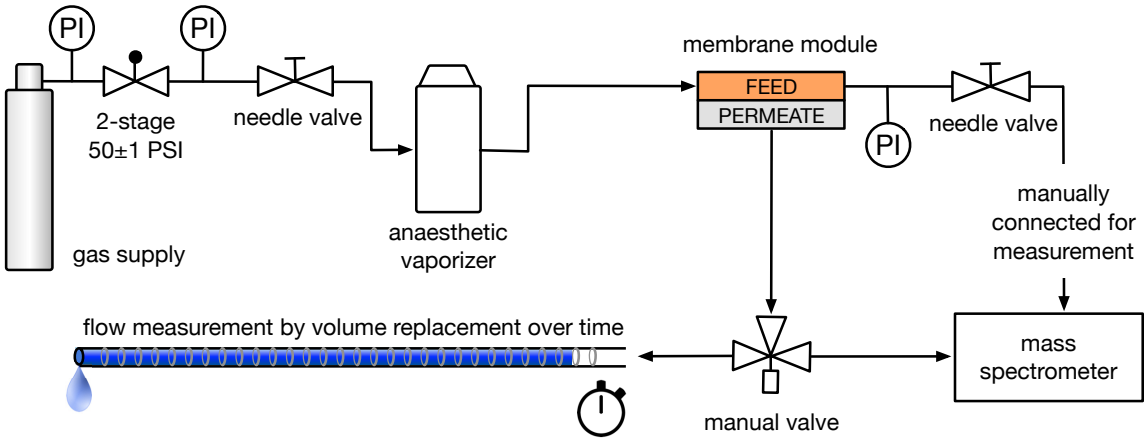

Fig. V-5. Schematic of the setup for the permeation experiments

The feed gas flow rate was controlled using a needle valve and flow was measured using a glass tube flow meter (Scott Specialty Gases, Plumsteadville, PA, USA) and the feed pressure using an analogue pressure gauge (Speidel Keller, Jungingen, Germany, accuracy: ± 5 mmHg or ~6.67 mbar) connected to the lumen outlet stream. The feed pressure on the lumen side was held constant at 1.2 bar for each experiment. The permeate pressure on the shell side was atmospheric. One port of the shell side of the module was plugged and the other port was fed through a 3-way valve either to a modified, horizontally placed glass pipette (Fischer Scientific, 5 mL total volume) for flow measurements or to the mass spectrometer for concentration determination.

To calculate the mean flow rate, the pipette was filled with water prior to each trial and time measurements were taken at 0.5 mL intervals as the permeated gas displaced the water. Immediately following the volumetric flow rate measurement, the permeate was then fed to the mass spectrometer sampling port and the gas composition only for the mixed gas experiments. Feed gas concentrations were measured when both shell-side ports on the

module were plugged. The gas composition was measured from the retentate port of the module. The system was purged with oxygen between each trial.

C.V - 4.1 Pure Gas Permeation Measurements

The pure gas permeance of the membranes was determined for pure carbon dioxide (CO_2), oxygen (O_2), and nitrogen (N_2) supplied at 1.2 bar. Once the concentration of the gases stabilized, the permeate line was connected to the pipette setup. Four time readings were then measured every 0.5 mL as the permeate displaced the water. These readings were averaged and counted for one trial. A minimum of three trials were performed for each module at each set of operating conditions. A minimum of three trials were performed for each module at each set of operating conditions. The pure gas permeance was calculated according to Equation 8:

$$K_i^P = \frac{Q}{A\left(p_f - p_p\right)} \tag{8}$$

Where Q is the permeate molar flow rate (mol/h), p_f is the absolute pressure of the feed (bar), p_p is the absolute pressure of the permeate (bar), and A is the inside active membrane area (m^2). Permeance is reported in units of mol/h/m^2/bar. The pure gas selectivity (α_{ij}^P) was calculated based on the ratio of the mean permeance of two pure gases i and j per Equation 9:

$$\alpha_{ij}^P = \frac{K_i^P}{K_j^P} \tag{9}$$

Where K_i^P and K_j^P are the pure gas permeances for components i and j, respectively.

C.V - 4.2 Mixed Gas Permeation Measurements

The mixed gas permeation procedure was similar to that of the pure gas system but also required concentration measurements of the permeate. The feed and retentate compositions

were determined as described above. In addition, following the flow measurements, the permeate was directed to the mass spectrometer for determination of the permeate composition.

Anaesthetic vapour concentrations for the experiments were chosen around their Minimum Alveolar Concentration (MAC). The MAC is a measure of potency of the anaesthesia gas and is defined as the minimum concentration of vapour required to immobilize 50% of patients. The MAC for Sevoflurane, Desflurane and Isoflurane is defined as 2.13%, 6.0% and 1.13% respectively.[221–223] The vapour experiments were conducted with vapour concentrations at the MAC for each vapour. This set of experiments was performed near clinically relevant operating conditions, at room temperature and low feed pressure (1.2 bar) with either Sevoflurane, Isoflurane or Desflurane at their MAC mixed into a 5% carbon dioxide/oxygen gas mixture to mimic exhalation during anaesthesia administration. Three modules of each membrane type were used and three runs of each module were performed for a total of $n = 9$ trials for Sevoflurane, Isoflurane and Desflurane.[2]

The mixed gas tests entailed monitoring the feed, retentate and permeate gas composition with the mass spectrometer, in addition to the flow rate. The permeances of the mixed gas components were calculated using Equation 10:

$$K_i^M = \frac{y_p Q}{A \Delta p_{i,ave}} \qquad (10)$$

The log-mean driving force (Equation 6) was used to compute $\Delta P_{i,ave}$ .The mixed gas selectivity, alpha^M, was calculated using the permeance of two components *i* and *j* in a gas mixture per Equation 11:

$$\alpha_{ij}^{M} = \frac{K_i^M}{K_j^M} \qquad (11)$$

C.V - 5 RESULTS AND DISCUSSION

C.V - 5.1 Pure Gas Experiments

The pure gas permeances for carbon dioxide (CO_2), oxygen (O_2) and nitrogen (N_2) are shown in Fig. V-6. The property of most interest for this application is the carbon dioxide permeance. However, the permeance of nitrogen and oxygen has been determined in order to facilitate comparison with literature and manufacturer permeance results. The mean permeance differs significantly for the membrane type in each of the gas groups (P = 0.0002) determined with a Kruskal-Wallis test (Gaussian approximation).

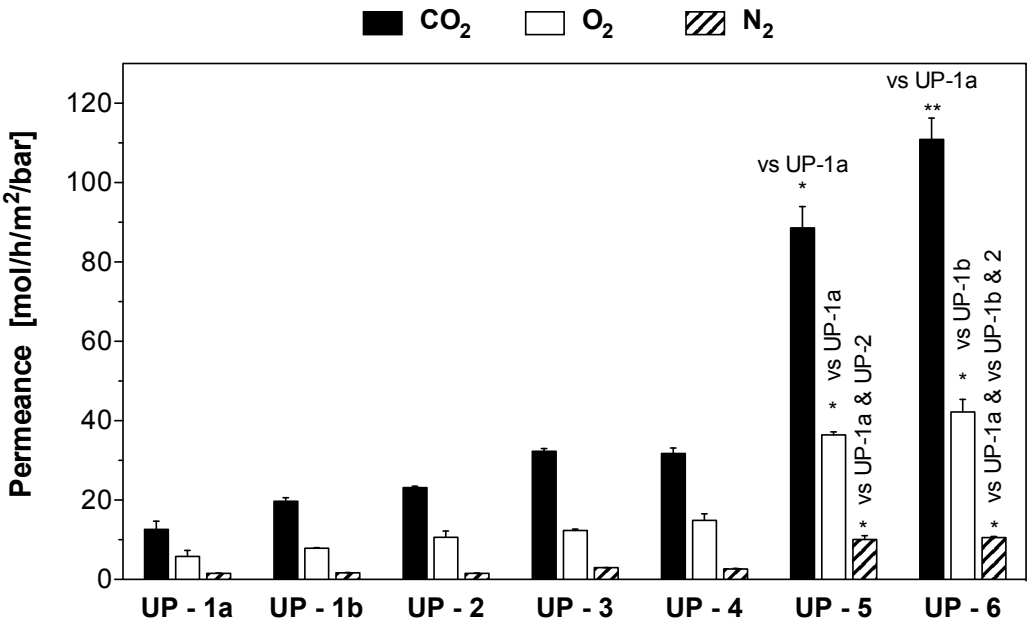

*Fig. V-6. Pure gas permeance for CO_2, O_2 and N_2 as mean ± SD. Kruskal-Wallis test, P=0.0002, Gaussian Approximation. Column stats by Dunn's Multiple Comparison Test are considered significant for P≤0.05 * and P≤0.002 ***

The column statistics were determined by a Dunn's Multiple Comparison Test and results are considered when $P \leq 0.05$ * and $P \leq 0.002$ **. An increase in mean CO_2 permeance

can be observed from UP-1 to UP-6, while the mean permeances for O_2 and N_2 are nearly constant for UP-1 to UP-6 and only differ for Up-5 and Up-6.

The pure gas selectivities for each membrane variation for CO_2/O_2, O_2/N_2 and CO_2/N_2 are reported as the mean ± SD of pure gas permeance ratios of each component (Fig. V-7). The means are significantly different with $P = 0.0255$ for CO_2/O_2, $P = 0.0014$ for O_2/N_2 and $P = 0.008$ for CO_2/N_2, as determined with a Kruskal-Wallis test (Gaussian approximation). The column statistics were determined by a Dunn's Multiple Comparison Test and the results are considered significant with $P \leq 0.05$ * and $P \leq 0.002$ **. It would be desirable to optimize the selectivity of the membrane for carbon dioxide over oxygen, but in rubbery polymers, high gas permeabilities are typically coupled with low selectivities for gases. This is because selectivity is dominated by high solubility selectivity and low diffusivity selectivity.[224]

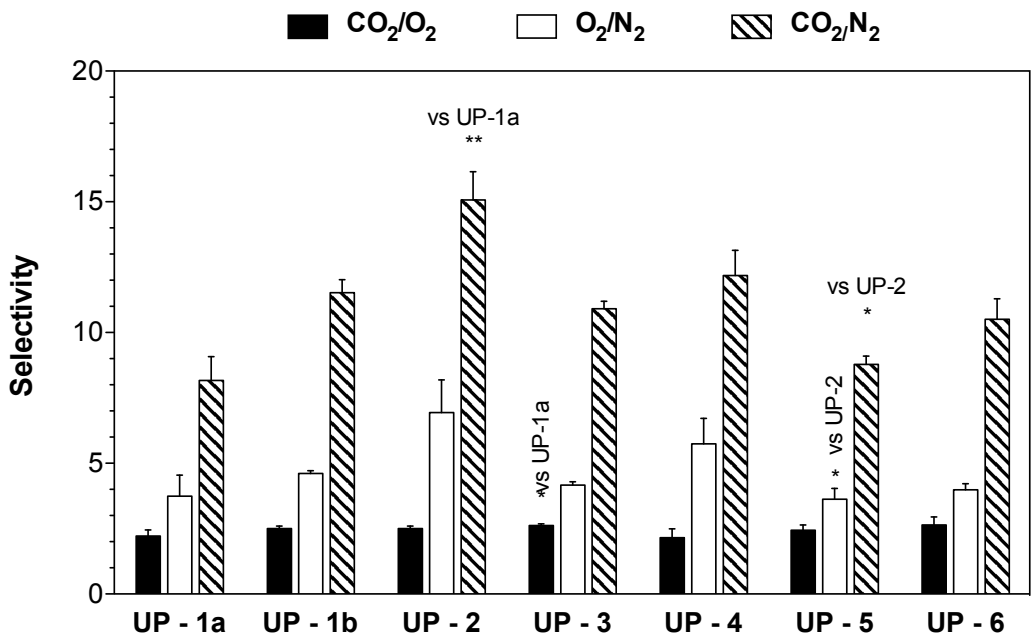

*Fig. V-7. Pure gas selectivity expressed as a ratio of the average pure gas permeance of each measurement as mean ± SD of the selectivity measurements for each membrane type. Kruskal-Wallis test, CO_2/O_2 P=0.0255, O_2/N_2 P=0.0014, CO_2/N_2 P=0.008, Gaussian Approximation. Column stats by Dunn's Multiple Comparison Test are shown with * for P≤0.05, ** for P≤0.002.*

The vapour permeation experiments, discussed below, explore the trade-off between carbon dioxide permeance and selectivity, and discuss the implications of the vapour loss.

C.V - 5.2 Comparison of Pure Gas Data to other Polymers

Polymeric materials are generally defined as being either rubbery or glassy, based on the glass transition temperature. Glassy high free volume membranes typically present a high permeance for CO_2. However, the high free volume is associated with low material stability. Poly[4-methyl-1-pentene] (PMP) membranes provide a convenient combination of stability and permeance for CO_2 as the glass transition temperature of 29°C is close to room temperature. Other materials commonly used for CO_2 permeation are poly[1-phenyl-1-propyne] (PPP), poly[1-trimethylsilyl-1-propyne] (PTMSP), poly[1-phenyl-2-[*p*-[trimethylsilyl]phenyl]-acetylene] (PTMSDPA). An overview of the permeances and selectivities for these materials is provided in Table 4.

Table 6. Experimental and literature permeability and selectivity of various glassy polymers

	P_{ip} (10^3 mol cm/m²/bar/h) [a]			Selectivity α_{ij}		
Polymer	**CO_2**	**N_2**	**O_2**	**CO_2/O_2**	**O_2/N_2**	**CO_2/N_2**
Literature:						
PTMSP [b,225]	387	71.7	110	3.5	1.5	5.4
PMP [b,226]	125	14.8	30.7	4.1	2.1	8.5
PTMSDPA [b,227]	55.7	6.37	13.6	4.1	2.1	8.8
PPP [b,228]	2.96	0.24	0.65	4.6	2.7	12.4
This study:						
UP – 1a	150	21	64	2.3	3.1	7.2
UP – 1b	178	15	71	2.5	4.6	11.5
UP - 2	208	14	96	2.2	6.9	15.0
UP - 3	291	27	111	2.6	4.2	10.9
UP - 4	286	24	134	2.1	5.7	12.1
UP - 5	797	91	328	2.4	3.6	8.8
UP - 6	998	95	380	2.6	4.0	10.5

[a] The permeabilities for the measurements in this study were found by multiplying the calculated permeance by the membrane thickness;
[b] The literature permeabilities were determined at 25°C and a feed pressure of 50 psig;

The trade-off between permeability and selectivity in glassy and rubbery polymers has been investigated in detail by Robeson *et al.* (2000) with recent updates in 2008 and 2010.[103,229–231,230] The efficiency of CO_2 removal in anaesthetic circuits will be optimized by

selecting a membrane that performs near the Upper Bound. In this case the selectivity between CO_2 and anaesthetic vapour will limit the choice of membrane.

C.V - 5.3 Comparison to Pure Gas Data of 3M™

The membrane manufacturer, 3M, provided data on the membranes collected from their own experimental testing. The data provided by 3M is measured as one time measurements and is in good agreement with means and standard deviations of our own measurements.

C.V - 5.4 Mixed-Gas Experiments

C.V - 5.4.1 Influence of anaesthetic vapour presence on permeance

In order to characterize the membranes with volatile hydrocarbons, a carrier gas was necessary. The carrier was chosen as 5% CO_2 balanced in O_2 as this mixture is close to the final operating conditions. The effect of the presence of these hydrocarbons on CO_2 permeance was examined by comparing the pure CO_2 permeance results from the earlier experiments to the mixed-gas CO_2 permeance in gas mixtures containing either Sevoflurane, Isoflurane, or Desflurane (Fig. V-8). The CO_2 permeance in a mixture of 2.0/6.13/1.13% Sevoflurane/ Desflurane/ Isoflurane with a balance of 5% CO_2 in O_2 is compared to the permeance of pure CO_2. Permeances are shown as Mean ± SD.

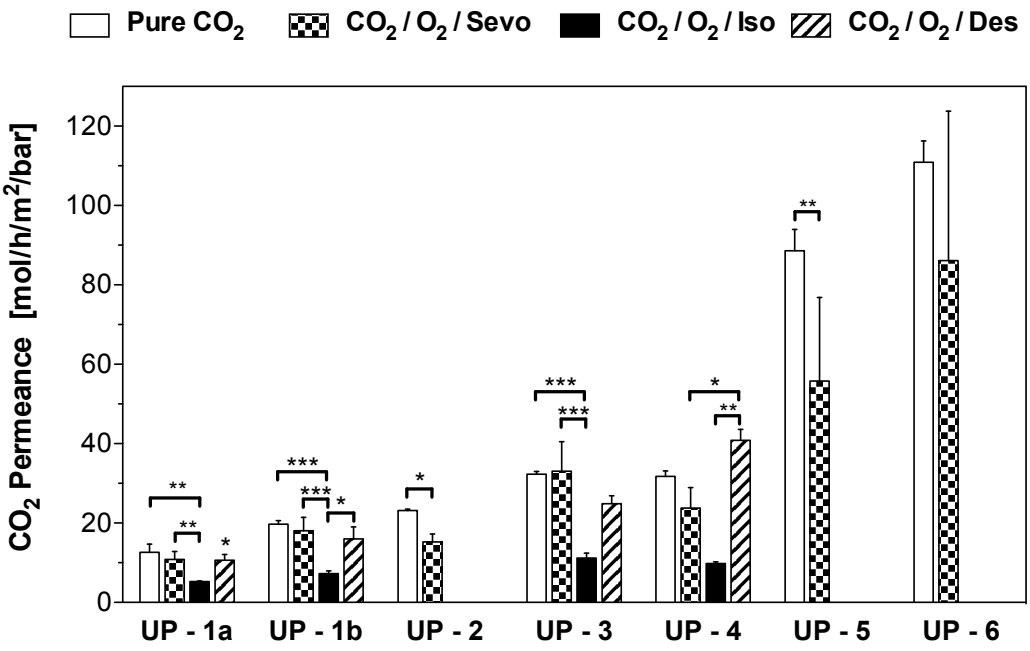

*Fig. V-8. Carbon dioxide mixed gas permeance in a mixture of 2.0/6.13/1.13% Sevoflurane/ Desflurane/ Isoflurane with a balance of 5% CO_2 in O_2.Permeance as mean ± SD. Kruskal-Wallis test, UP-1a P=0.002, UP-1b & UP-3 <P=0.0001, UP-4 <P=0.0001, Gaussian Approximation. T-test for UP-2, UP-5, UP-6 are shown with * for P≤0.05. Column stats by Dunn's Multiple Comparison Test are shown with * for P≤0.05, ** for P≤0.002 *** for P≤0.001.*

The CO_2 permeance was significantly lower for the Isoflurane mixture from the Sevoflurane and Desflurane mixture in all membrane versions, where there was no difference between the Sevoflurane and Desflurane mixtures. Generally, the permeance in the mixtures was lower than the pure gas permeance of CO_2. The measurements for UP-2 could not be completed as the mass spectrometer had to be sent out for service but will be completed upon return from service and will be added after the paper comes back from review, before it gets published. The measurements for UP-5 and UP-6 were not continued due to the insufficient selectivity for hydrocarbons (see Fig. V-10). The permeance of CO_2 was significantly reduced in some instances, especially with the high permeance membranes UP-5 and UP-6. Presenting the data in a scatter plot allows for a better visualization of the CO_2 permeance on the solvent/polymer ratio (Fig. V-9).

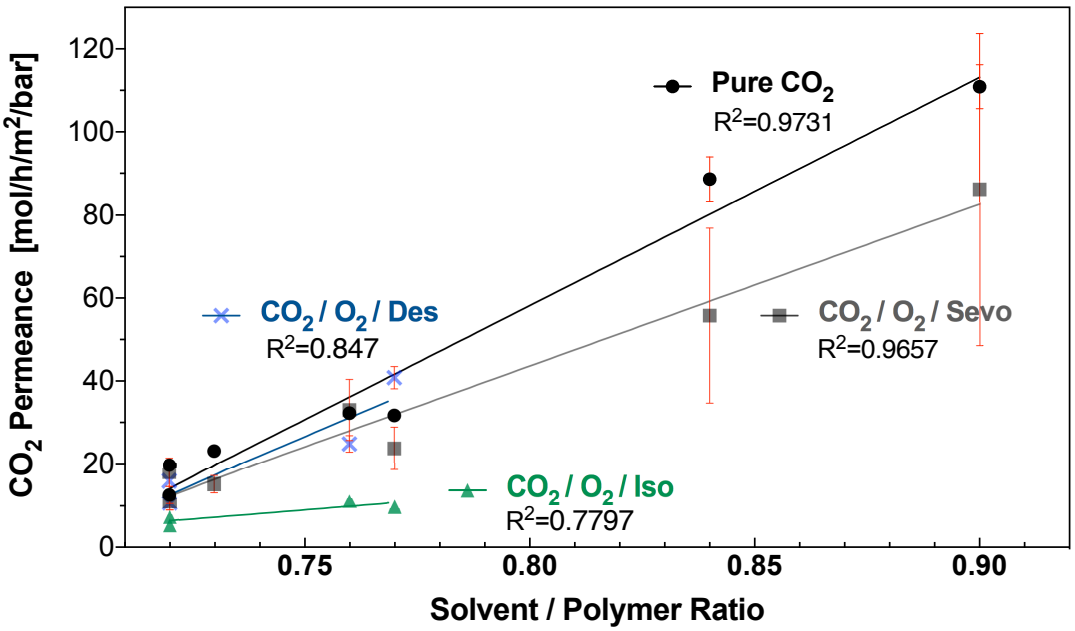

Fig. V-9. Scatter plot of the CO_2permeance over the solvent/polymer ratio in different gas mixtures in comparison to the pure gas results for CO_2 (mean±SD). The slope of the linear regressions for pure CO_2 and the Sevoflurane mixture are significantly different from zero (P<0.0001), the slopes of the linear regressions for the Desflurane and Isoflurane mixture are not.

C.V - 5.4.2 Influence of Anaesthetic Vapour Presence on Selectivity

The membrane performance objective is to maximize CO_2 transport while retaining the hydrocarbons. The trade-off between CO_2 permeability and selectivity over hydrocarbons should be carefully balanced. This relationship will be explored in detail to maximize the removal of CO_2 while retaining anaesthetic vapours. Fig. V-10 shows the selectivity of CO_2 over Sevoflurane, Desflurane, and Isoflurane as a function of CO_2 permeance.

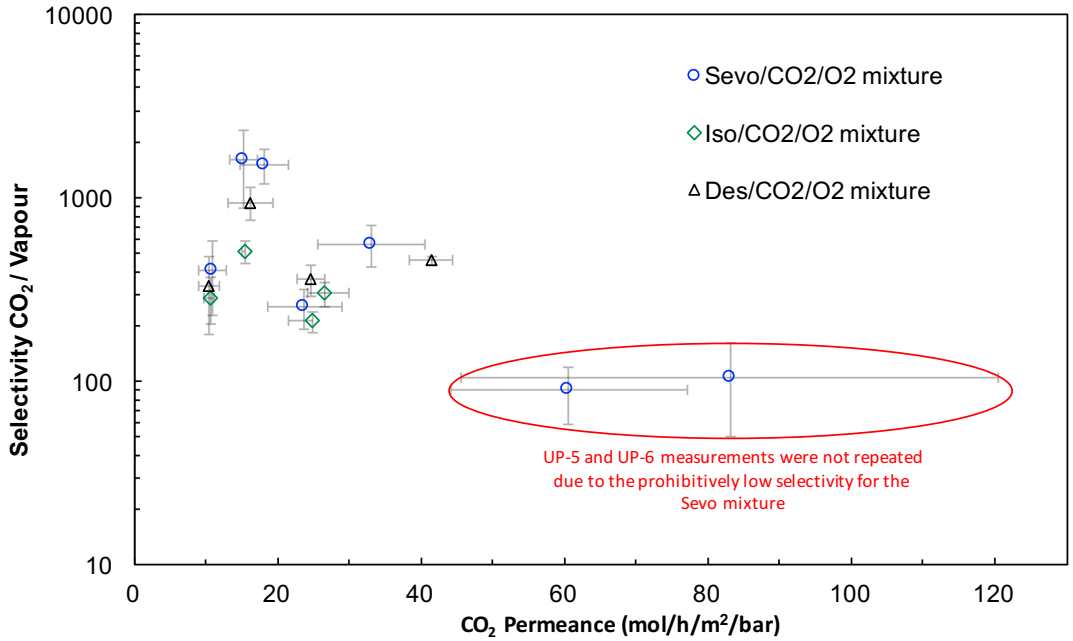

Fig. V-10. Selectivity of carbon dioxide over Sevoflurane/Desflurane/Isoflurane as a function of carbon dioxide permeance in a gas mixture of 2.0/6.13/1.13% Sevoflurane/Desflurane/Isoflurane with a balance of 5% CO_2 in O_2. Permeance as mean ± SD, Selectivity as Mean ± $\sqrt{(SD^2+SD^2)}$

The trade-off between permeability and selectivity is evident for all three vapours, where UP-5 and UP-6 show an obvious loss of selectivity in comparison to the permeance for CO_2 gained. The selectivity for all three hydrocarbons is in agreement. The limitation of UP-5 and UP-6 is not only based on the low selectivity, but also on the difficulty to reliably manufacture these membranes to a target permeance.

C.V - 5.4.3 Influence of Membrane Polymer Concentration

In Fig. V-10 it could be observed, that increased CO_2 permeance comes with a trade-off of selectivity. Fig. V-11 shows the CO_2 / Sevoflurane selectivity as a function of polymer concentration. Selectivity decreases with the concentration changing from 0.72 to 0.9.

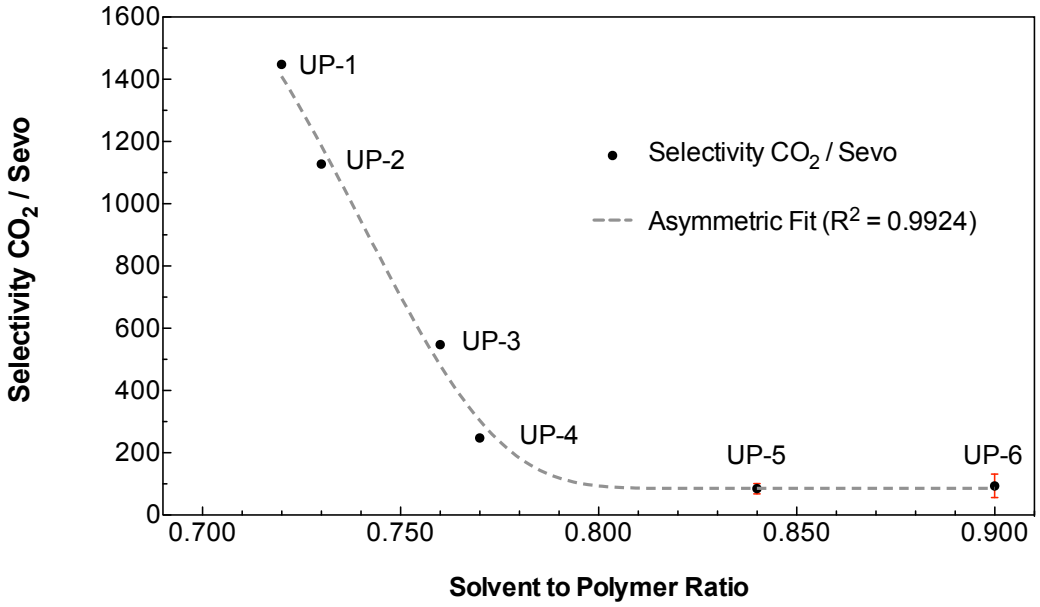

Fig. V-11. Effect of membrane polymer concentration on CO_2/Sevoflurane selectivity measured in a tri-gas mixture (O_2 / CO_2 / Sevo) as Mean ± √(SD^2+SD^2)

C.V - 5.4.4 Error Handling

The aim of this study was to compare the permeance and selectivity of different PMP membrane versions. Since all measurements were conducted under the same controlled and repeatable conditions, systematic errors in the collection of the data have not been considered in the standard deviations of the results. The variance differed between the experimental datasets, and they were not normally distributed. Therefore, a Kruskal-Wallis test was employed for group analysis and a Dunn's Comparison Test for the comparison of each dataset. Since these tests are normally considered conservative, the statistical statements should still be valid. Therefore, the comparison with literature and manufacturer data was only done qualitatively, not statistically.

C.V - 6 CONCLUSION

This study employed a low-pressure characterization technique to investigate and optimize the performance of PMP membranes for the removal of CO_2 from anaesthesia

circuits. In these systems, it is critical to achieve high CO_2 permeation rates while minimizing the losses of anaesthetic vapours, which are expensive and can cause damage to the environment.

The hollow fiber membranes used in this study were supplied by 3M, with the main difference being the polymer concentration used in the spinning process. The membranes were characterized as close as possible to the conditions that would actually be used in an anaesthesia application. The results indicate that the membrane performance could be tailored to achieve a good separation between CO_2 and the anaesthetic vapours. The simple method that was used to perform the characterization was also shown to perform well under the conditions investigated, giving comparable results to data provided by 3M. Such a method would therefore also be suitable for other low-pressure characterization experiments.

Chapter VI SUITABILITY OF DIFFERENT MEMBRANE OXYGENATORS FOR THE DELIVERY OF ANAESTHETIC VAPOURS

Delivery of vapours on cardiopulmonary bypass using different oxygenator membranes

F Wilfart, A McFadgen, B Kent, K Gardiner, M Schmidt

Reprint from Biomedical Engineering (Biomed 2011, APPENDIX A).[93]

This article investigates oxygenators based on two different membrane types for their suitability to deliver anaesthetic vapours to patients during cardiac surgery as cases exist for such off label use (C.II). Using a bench setup, it was shown that oxygenators using dense skin PMP membranes severely restrict the vapour delivered to the patient, wasting the majority of anaesthetic vapours and hence causing excessive and unnecessary costs. Furthermore, despite best efforts, these oxygenators, for safety reasons, are not capable of reliably delivering all of the anaesthetic vapour passing through the oxygenator to a scavenging system, exposing operating room personnel to occupational hazards (e.g. birth defects, etc.)

ABSTRACT

Objectives: World wide about 1,000,000 patients undergo cardiopulmonary bypass (CPB) related procedures every year. Anaesthetic vapours, such as Sevoflurane and Isoflurane, have shown neuro- and cardio-protective effects and are used widely during CPB. Modern oxygenators are using different types of hollow-fibers and the question arises, if vapour molecules effectively travel through these membranes to be delivered to the patient blood during CPB.

Methods: An artificial CPB circuit study (human blood, haematocrit 30, 30°C) is presented. An oxygen-mixture with 2% vapour at 1l/min is delivered to the oxygenator. The vapour concentration in the reservoir is recorded over time until a stabile concentration is obtained, then the gas stream is switched to vapour free room air.

Results: The Quadrox D, Maquet (dense polymethylpentene membrane) as compared to the Synthesis, Sorin (micro-porous polypropylene membrane) shows relative limited performance in delivery of vapours (Sevoflurane < Isoflurane).

Conclusions: An artificial CPB circuit is used to test physico-chemical properties of different membranes. The oxygenator model using a plasma-tight (as compared to porous) membrane shows relative limited performance in delivery of vapours through the membrane, suggesting a limited use of plasma-tight membranes for clinically relevant and cost-effective delivery of vapours during CPB to achieve neuro- and cardio-protection.

C.VI - 1 INTRODUCTION

One of the basic problems with the use of Cardiopulmonary Bypass (CPB) in cardiac surgery is the delivery of anaesthetic drugs to the patient. Maintenance of anaesthesia during CPB can be achieved by two basic principles: Delivering anaesthetic drugs solely intravenously (TIVA, Total Intravenous Anaesthesia) or by administering a volatile anaesthetic agent via the membrane oxygenator. The second principle, however, supposes that the administered volatile anaesthetic can penetrate the various types of membranes of the different membrane oxygenators used in clinical practice.

Dense (PMP, poly-4-methyl-1-pentene) membrane oxygenators were introduced to overcome the well known problems regularly appearing when using conventional micro porous (PPL, polypropylene) membrane oxygenators such as the generation of micro bubbles, blood trauma or plasma leakage during long-term application of CPB.

Considering that glassy polymers used in dense PMP membranes usually show a preferred permeability to smaller molecules this effect may be caused by a very low perfusion coefficient of the volatile agent in the solid layer of the dense membrane due to its molecular size. Own studies using the noble gas Xenon as an anaesthetic and organ protective showed that this gas is traveling easily through different membranes of oxygenators.[232]

Coronary artery bypass grafting (CABG) and valve repair have become standard methods in cardiac surgery. World wide about 1,000,000 patients undergo cardiopulmonary bypass (CPB) related procedures every year. [233] With the improvement in surgical technique and anaesthesia, CABG is now being offered to patients with more severe underlying disease and co-morbidities that may further increase the risk of its complications. The complications following CABG include minor and major postoperative neuro-cognitive

decline and other organ dysfunction. Cognitive studies carried out within days or weeks after surgery have revealed a wide range of short-term cognitive decline. [234,235]

Although the past 50 years have brought improvements in extracorporeal technology, including improved gas exchange devices, venous reservoir construction, and heparin-coated circuits, the modern CPB is still remarkably similar to that developed a half century ago. However, over the last decade, a large body of research has substantially improved our understanding of the pathophysiology induced by CPB. Although we have learned much, the substantial morbidity still suffered by patients managed with CPB, amply demonstrates that we have more to learn than we have mastered. Adverse outcomes associated with bypass (Type I central nervous system events, 3%–6%; long-term cognitive dysfunction, 15%; renal dysfunction, 7%–9%; haemodialysis, 1%–2%) are substantial. [236] In the variety of clinical indications, the need for neuro protection is described best for cardiac patients. Ischemic cerebral complications represent the leading cause of morbidity after cardiac operations. The reported incidence of peri-operative stroke as a major neurologic complication varies from 0.4 to 5.4%, and in-hospital neuropsychological dysfunction as a minor neurologic problem occurs in 25–79% of the cases. [237] The underlying pathology consists of a variety of mechanisms, e.g., hemodynamic fluctuations, cerebral embolization of atherosclerotic plaque, air, fat and platelet aggregates caused by CPB and surgical procedure. These mechanisms induce an imbalanced state of oxygen supply and demand causing major (type I, fatal cerebral injury and nonfatal strokes) and minor (type II, new deterioration in intellectual function or new onset of seizures) neurologic complications.[237–240] One of every $10 spent on surgical treatment of coronary disease is related to a complication in the United States. As compared with patients without adverse neurologic outcome, type I neurologic complications are responsible for an additional $10,266 per

patient in in-hospital boarding costs, and type II events are responsible for an additional $6,150 per patient. When one applies these estimates to the 800,000 patients per year who undergo coronary surgery throughout the world, the additional in- hospital cost is approximately $400 million annually. The expense of long-term out-of-hospital medical and rehabilitative services probably results in additional expenditure of some $2 billion to $4 billion annually. [237] With the growing awareness of their social and economic importance, increasing attention is being given to neuro- protective strategies, not only in cardiac anaesthesia.

Recently anaesthetic vapours such as Sevoflurane and Isoflurane have shown neuro and cardio protective effects and are used widely during CPB. [241] These vapours also do not show the well-known disadvantages of Xenon such as high price and, low availability and other limitations.

As the transfer characteristics of volatile anaesthetic agents through different membranes are to date not fully understood, several studies are published to elucidate the physico-chemical properties of micro porous and dense membranes.

Philip *et al.* performed a prospective randomized study comprising 75 patients to study the transfer rate of Isoflurane in five different types of membrane oxygenators. An extraction of volatile anaesthetic agent could be clearly demonstrated for micro-porous capillary membrane oxygenators.[242] Administering a defined inspiratory concentration of 1,0 % Isoflurane into the gas inlet port of these types of oxygenators yielded significantly lower expiratory concentrations measured at the gas outlet port, after an equilibration period of 10 minutes. The expiratory Isoflurane concentrations, measured in the dense membrane type oxygenators (QUADROX D und Hilite 7000 LT), was, however, only negligibly lower than

the inspiratory concentrations. Consequently, Schienagel postulated that there is no adequate transfer of the volatile anaesthetic agent across the new type of diffusion membrane. [242]

Prasser *et al.* have demonstrated that volatile anaesthetics have cardioprotective properties during open-heart procedures, especially when administered continuously. Since the uptake of volatile anaesthetics via diffusion membrane oxygenators is severely reduced, Prasser *et al.* hypothesized that clinically relevant concentrations of Sevoflurane will remain in the patients' blood following saturation with a volatile agent before start of CPB.[92]

This study was designed to compare conventional and diffusion membrane oxygenators regarding their *in vivo* elimination of Sevoflurane. Twenty patients undergoing elective coronary bypass surgery were randomly allocated to two groups, either using a micro porous membrane oxygenator or a dense membrane oxygenator in a miniaturized extracorporeal circuit. Anaesthesia was maintained with Sevoflurane, which was stopped at the start of CPB. During CPB, the Sevoflurane concentration was measured in blood and in the exhausted gas from the oxygenator. The elimination of Sevoflurane, expressed as the relative blood concentration, was significantly increased in micro porous membrane oxygenators as compared to dense membrane oxygenators. This resulted in an approximately threefold higher Sevoflurane blood concentration in the dense membrane group over the course of CPB. With the incorporation of dense membrane oxygenator in a miniaturized bypass circuit, relevant concentrations of a previously applied volatile agent could be maintained even without further supply throughout CPB. Prasser *et al.* concluded that this might be an alternative approach to cardio-protection when Sevoflurane cannot be administered through CPB. [92]

Modern oxygenators are using different types of hollow fiber membranes that are specifically designed for the exchange of CO_2 and O_2 and the question arises, if those different membranes allow larger molecules like Sevoflurane and Isoflurane to effectively travel through the membrane to be delivered to the patient blood during CPB.

The present study was designed to compare in vitro the membrane performance of two different oxygenators regarding differences of the transfer over the membrane for Sevoflurane or Isoflurane in a realistic artificial circuit to overcome the limitations of former *in vivo* studies performed in different patients using different treatment regimes.

The question arises whether there are differences in performance between the two different membrane oxygenator types carrying either a conventional micro porous hollow fiber membrane or the dense hollow fiber membrane.

C.VI - 2 MATERIAL AND METHODS

An artificial CPB circuit is designed consisting of a venous reservoir, oxygenator, roller pump, water bath, Sevoflurane Vapourizer, Isoflurane vapourizer and two patient monitors (see Fig. VI-1). The venous reservoir (Sorin Synthesis, Germany) is modified by removing the filter unit and resealing it airtight. All unused ports are sealed tight. The reservoir is connected to a gas circulating fan unit to avoid layering of the heavy vapours in the air space. Two patient monitors (Datex Engstrom, Finnland) are used for continuous measurement of the different pressures, blood temperature and for gas sampling in the reservoir and the gas feed. The sampling gas stream from the reservoir is re-circulated to the reservoir to not influence the closed volume. Both patient monitors are calibrated after a warm-up time of 15 minutes prior to the experiment. The reservoir is filled with 1.3 litres of human blood adjusted to a haematocrit of 30 using Normosol-R (pH 7.4, Hospira, Canada)

that is normally used for priming the Cardiopulmonary Bypass. The blood is circulated from the reservoir outlet by a roller pump (Stöckert Shiley, Germany) at 2l/min into the venous inlet of the oxygenator and from the arterial outlet back into the reservoir using the venous inlet. The blood pressure pre and post the oxygenator are monitored. The temperature exchange unit of the oxygenator is connected to a refrigerated and heated circulating water bath (Polyscience, USA) that allows the temperature of the blood to be adjusted to (30 ± 0.3)°C. The gas input of the oxygenator is connected to 2 gas sources controlled by a flow meter (Scott Specialty Gases, Canada) carrying either pressurized room air or premixed 5 % CO_2 in Oxygen (Praxair, Canada), Sevoflurane (Abbott, Canada) and Isoflurane (Baxter, Canada) can be added to the gas stream by a Sevoflurane or Isoflurane vapourizer (Draeger, Germany). The gas input pressure and composition as well as the output gas composition is monitored by a patient monitor. At the start of the experiment the blood is circulated at 2l/min while de-nitrogenising the reservoir and the oxygenator by flushing both with 5% CO_2 in Oxygen at 6 l/min until a stabile gas concentration and temperature is reached in the whole system. The gas delivery to the reservoir is then stopped and the reservoir is closed. The flow to the oxygenator is adjusted to 1 l/min of 5 % CO_2 in Oxygen and Sevoflurane or Isoflurane respectively are added with 2,0 % (t = 0 hours). The Sevoflurane reservoir concentration is recorded over time along with the exhaust concentration over time. After a stabile concentration in the reservoir is reached, the gas stream is switched to vapour free room air at 1 l/min (t = 2 hours for Sevoflurane and t = 2 h 22 min for Isoflurane).

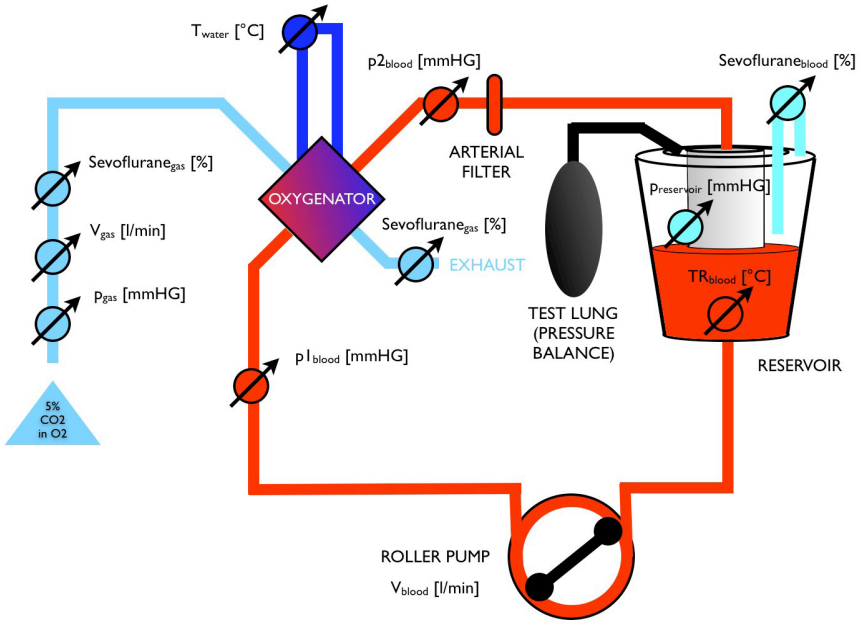

Fig. VI-1. Schematic setup of the artificial CPB circuit for Sevoflurane (Isoflurane is identical)

C.VI - 3 RESULTS

The Quadrox D oxygenator, containing a dense, as compared to the Synthesis oxygenator, containing a porous membrane, shows very limited performance in delivery of vapours through the membrane whereas the Isoflurane performance is superior to the Sevoflurane performance.

C.VI - 3.1 Results for Sevoflurane

After de-nitrogenising the system, the Sevoflurane concentration of 2% was achieved and the delivering gas mixture measured 5% CO_2 in Oxygen. The gas flow was measured at 1l/min. From 0 to 2 hours (wash-in phase) the concentration of Sevoflurane in the blood is measured by means of headspace gas measurement in the reservoir and recorded over time (see Fig. VI-2): Using the Synthesis oxygenator, the Sevoflurane concentration in the blood eventually reached a steady state at 1.5% after 1h 30min. Using the Quadrox D oxygenator,

the Sevoflurane concentration in the blood slowly increased up to 0.25 % not reaching a steady state. Within a realistic time frame of two hours it was not possible to reach a clinically relevant concentration of Sevoflurane in the blood. After 2 hours, the gas stream is switched to room air at 1 l/min (wash-out phase), which was proven to not be contaminated by Sevoflurane: Using the Synthesis oxygenator, the Sevoflurane concentration in the reservoir reached the lower threshold of the analyser (0.1 %) after 1h 30min. As no clinically relevant concentration of Sevoflurane in the blood could be reached with the Quadrox D oxygenator, no wash-out phase was recorded.

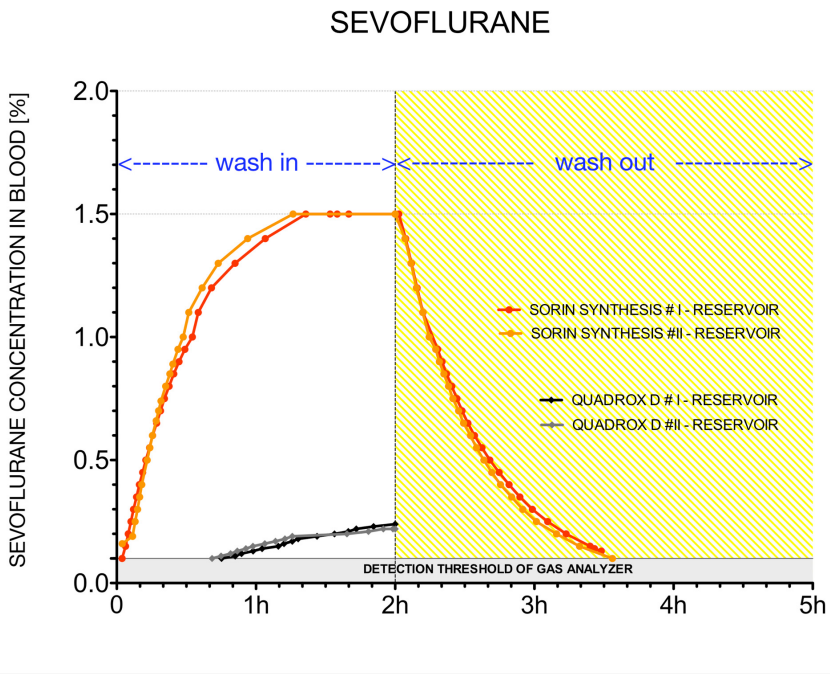

Fig. VI-2. Sevoflurane concentration in blood (%) for Sorin Synthesis (red/orange) and Quadrox D (black/grey) over time during wash-in and wash-out procedure as a function of transport of vapour through the different membranes.

C.VI - 3.2 Results for Isoflurane

After de-nitrogenising the system, the Isoflurane concentration of 2 % was achieved and the delivering gas mixture measured 5 % CO_2 in Oxygen. The gas flow was measured at 1 l/min. From 0 to 2 hours (wash-in phase Sorin oxygenator) and from 0 to 2 h 20 min

(wash-in phase Quadrox D oxygenator) the concentration of Isoflurane in the blood is measured by means of headspace gas measurement in the reservoir and recorded over time (see Fig. VI-3): Using the Synthesis oxygenator, the Isoflurane concentration in the blood eventually reached a steady state at 1.5% after 1 h 30 min. Using the Quadrox D oxygenator, the Isoflurane concentration in the blood eventually reached 0.96 %, reaching a steady state after 2h 20min. After 2 hours the gas stream is switched to room air at 1 l/min (wash-out phase), which was proven to not be contaminated by Isoflurane: Using the Synthesis oxygenator, the Isoflurane concentration in the reservoir reached the lower threshold of the analyser (0.1 %) after 1h 30min. Using the Quadrox D oxygenator, the Isoflurane concentration in the reservoir reached the lower threshold of the analyser (0.1%) after 2h 40min. As the Quadrox D oxygenator #I broke after the Sevoflurane experiment, only data for Quadrox D oxygenator #II were recorded.

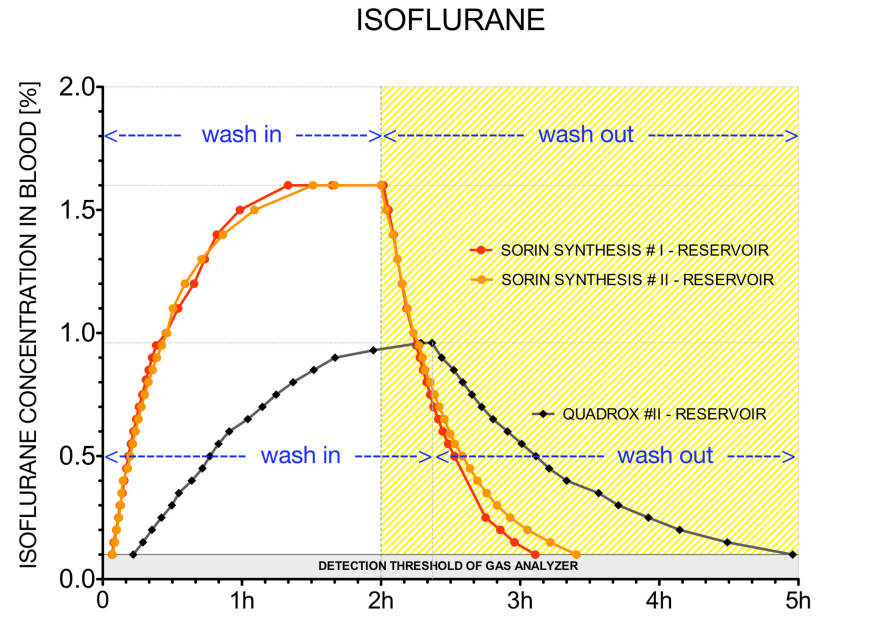

Fig. VI-3. Isoflurane concentration in blood (%) for Sorin Synthesis (red/orange) and Quadrox D (black) over time during wash-in and wash-out procedure as a function of transport of vapour through the different membranes.

C.VI - 4 CONCLUSION

Our study demonstrates a markedly different performance of oxygenators using either a conventional micro porous hollow fiber membrane or the dense hollow fiber membrane in an artificial CPB setting. Thus, the hypothesis, that different membranes with different physico-chemical properties result in a different performance levels for delivering Sevoflurane or Isoflurane on the CPB are confirmed. Diffusion membrane oxygenators have primarily been developed to eliminate the well known problems that regularly appear when using conventional micro porous hollow fiber membrane oxygenators, e.g. the generation of micro bubbles, blood trauma during CPB or plasma leakage during long term application. The wall structure of the dense hollow fiber membrane consists of a highly porous support matrix and a thin (0.05 μm) tight membrane on the blood side of the matrix, which constitutes a solid barrier between the blood and the gas phase. The homogeneous tight membrane and the complete separation of blood and gas phases obviously provide a better biocompatibility with less blood trauma. Crossing of micro bubbles as well as plasma leakage does not occur due to tightness of the membrane.

Unfortunately, the uptake of Sevoflurane and Isoflurane into blood via dense membrane oxygenators during CPB is severely limited in patients as recently demonstrated by Wiesenack[212] and Prasser *et al.*[92].

These results published by Prasser, who investigated the washout phase and elimination of Sevoflurane during minimal CPB, are supporting our observations. Prasser could show a relative decrease in the Sevoflurane blood concentrations after start of CPB with micro porous and dense membranes. Furthermore, he described the Sevoflurane concentration in the oxygenator gas exhaust, where there was no measurable washout of

Sevoflurane in the dense membrane group as compared to wash-out concentration of the micro porous membrane group. As Prasser could only show wash-out concentrations and only for Sevoflurane we could reconfirm these results. But furthermore we show performance data for the wash-in and wash-out phase for Sevoflurane and Isoflurane.

In an other study by Birnbaum *et al.* the exhaust gas concentrations of Isoflurane, measured in the dense membrane oxygenators, was only negligibly lower than the concentration in the gas flow into the oxygenator, he postulated that there is no adequate transfer of Isoflurane across the dense membrane.[242] He investigated wash-in of Isoflurane with a constant concentration of 1.0% of Isoflurane in the gas flow into the oxygenator and also wash-out with Isoflurane free gas flow into the oxygenator. The limitation of that study consists in the restriction of only measuring concentration differences in the Isoflurane concentration in the gas stream into the oxygenator versus the concentration in the gas stream out of the oxygenator.

The indirect conclusion of Schienagel was that there is no adequate transfer of the anaesthetic agent across the dense membrane type. These data support our observation during the wash in phase using a dense membrane where we could demonstrate no relevant transfer of Sevoflurane and only a retarded and less effective transfer of Isoflurane into the blood.

To our understanding it is not enough to ventilate patients with vapours and consecutively use a dense membrane oxygenator on the CPB and discontinue the application of the anaesthetic vapour as suggested by Prasser.

According to the results of De Hert *et al.* the duration and timing of administration of volatile anaesthetics seem to correlate with the extend of myocardial protection.[243] After

comparison of different anaesthetic protocols in coronary surgery patients, using CPB it could be demonstrated that the cardio protective effects of Sevoflurane as measured by postoperative levels of Troponin1 and indices of myocardial function, were clinically most evident when the volatile anaesthetic was administered throughout the entire period of surgery. Even during use of a dense membrane oxygenator the concentration of vapours in the blood of the patient are diminished by evaporation and metabolic breakdown in the patient. To our understanding it is remarkable that there is no certification for oxygenators used for the delivery of vapours during CPB in North America.

Nevertheless, Carotid Artery Bypass Grafting (CABG) and valve repair have become standard methods in cardiac surgery. World wide about 1,000,000 patients undergo CPB related procedures every year with an increasing percentage of elderly patients that have more co-morbidity. Anaesthetic vapours such as Sevoflurane and Isoflurane have shown neuro- and cardio-protective effects and will be used even more widely during CPB. As a result, there is a growing need for suitable membranes in oxygenators for the use of vapours on the CPB.

Chapter VII MEMBRANE SYSTEM DESIGN

Design of a Membrane System for Carbon Dioxide Removal from Gas Mixtures under Normobaric Conditions in Anaesthesia Circuits

F Wilfart, M Soehl, N Kilcup, D Roach, M Schmidt, G Maksym, J Haelssig

Unpublished manuscript

With the optimized custom membrane discussed in Chapter V , the next challenge was the design of a passive gas separation membrane module with low pressure drop and also optimized effectiveness of the sweep flow and membrane area. The passive system cannot use any active components to successfully reduce the residual CO_2 concentration below 0.5 % for 95 percentile patient cases, ultimately lowering the inspired CO_2 concentration. This is key in making the passive application of membranes for CO_2 removal in anaesthetic circuits possible.

C.VII - 1 INTRODUCTION

Seniors make up the fastest growing segment of the population in industrialized nations.[244] They tend to clinically present with more comorbidities and higher overall frailty.[200,201,203,245] Brain damage (described as Post Operative Cognitive Decline) after surgery and anaesthesia, which ranges from 25-80% is a growing concern in seniors (POCD) generates a significant burden for society - financially and socially.[200] Additionally, most seniors require surgery and general anaesthesia during the rest of their lives. The resulting increase in overall healthcare spending, along with the decrease in the number of younger, working age population to pay for it, is driving the demand for more outcome-based advances in the medical field. [83,198,199,201]

Systems for the delivery of general anaesthesia with anaesthetic vapours rely on CO_2 absorbers. These chemically bind and remove CO_2 from the exhaled gas mixture in order to allow for rebreathing of the contained anaesthetic vapours. Since these vapours are expensive and harmful to the environment, the retention of these anaesthetic vapours for rebreathing is desired.[50,125,211] However, chemical CO_2 absorbers used in a rebreathing circuit produce harmful compounds in conjunction with the use of vapours. These compounds have been shown to be neuro and nephrotoxic, and are therefore not desired to accumulate in the circuit.[39–42,45,70,70,186,187,246]

Therefore, a constant supra physiological fresh gas flow to dilute the rebreathed gas mixture is required, leading to significant losses of the unused anaesthetic vapours to the environment.[247]

An alternative approach to CO_2 absorbers is to use membranes for selective gas separation. Dense PMP membranes have been shown to be capable of efficiently removing

CO_2 and retaining the anaesthetic vapours in a gas mixture (Chapter V). Further, membrane separation per se does not produce any harmful substances (Chapter IV). Therefore, employing membrane technology instead of chemical absorption would eliminate the need to maintain excessively large dilution rates, thereby also avoiding the loss of anaesthetic vapours to the environment.

The primary objective of this study is to design and optimize a membrane system for the separation of CO_2 from anaesthesia circuits. Both experimental and computational techniques were used to synthesize various designs and decide between alternatives. Given the application of interest, the design problem is tightly constrained. To be practical for the use in anaesthesia rebreathing systems, the following constraints have been developed for the operation of the device:

- Less than 1 mBar resistance at 30 Lpm feed flow (ISO[248])
- Long term humidity resistant
- Maximum of 25 Lpm sweep gas (maximum scavenging systems can handle)
- Maintain a retentate concentration of ≤ 0.5 vol% CO_2 at a feed flow of 5 Lpm and 5 vol%; retentate/inspired levels above 0.5 % CO_2 typically alert the anesthesiologist of CO_2 absorber desiccation and the necessity to replace it
- Length of the device ≤ 155 mm
- Feed and retentate connector on the same face (industry standard)
- No active system components to induce vacuum or pressure (common regulatory requirement)
- Membrane shall not have activated components actively supporting gas transport (activation components typically decrease lifetime of a membrane)

The purpose of this application is the elimination of chemical processes. Therefore, the membrane system must be optimized through manipulation of partial pressures and flow regimes inside the module using a given membrane.

C.VII - 2 DESIGN CONSIDERATIONS

This section discusses some of the advantages and disadvantages associated with different types of hollow fiber membrane module configurations. The purpose is to review applicable configurations, and ultimately design a configuration that is both suitable for the application and most likely to fit the design constraints identified in the introduction.

C.VII - 2.1 Parallel Contactor Principles

Parallel flow contactors utilize co-current or counter-current flow regimes described in more detail below. They are relatively easy and inexpensive to manufacture and are widely used in liquid membrane separations and gas-liquid membrane contactors. Common applications include microfiltration, ultrafiltration and dialysis.

The terminology that has been adopted in this paper is as follows: The gas stream to be separated that enters the membrane system is referred to as the "feed" and the gas that exits the membrane on the same side of the membrane as the feed is referred to as the "retentate" (shell side). Conversely, the gas that enters the system on the opposite side of the membrane as the feed is referred to as the "sweep" and the gas that exits the membrane on the same side of the membrane as the sweep is referred to as the "permeate" (lumen side). The purpose of the sweep gas is to maintain a partial pressure driving force to facilitate transfer of some chemicals (CO_2 in this case) across the membrane. Gas flows in membrane systems using a sweep gas can be configured to approximately follow one of two idealized flow patterns (see Fig. VII-1.) or a flow pattern somewhere in between (see next section).

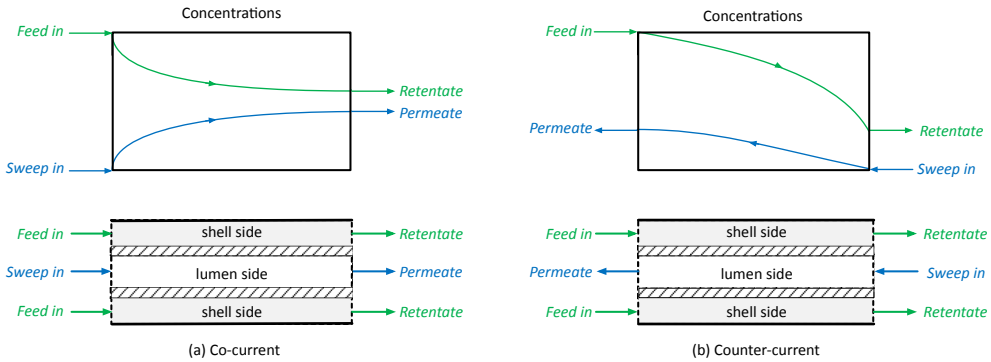

Fig. VII-1. Idealized flow patterns in membrane modules: (a) co-current and (b) counter-current along with the corresponding concentration gradients

In this specific application, a gas mixture containing the CO_2 enters the feed side. CO_2 passes through the membrane to the permeate side leaving the retentate with a reduced CO_2 concentration compared to the feed. If the feed and the sweep gas flow in the same direction, the flow configuration is called co-current (Fig. VII-1.a). Conversely, if the feed and the sweep gas flow in the opposite direction, the flow configuration is called counter-current (Fig. VII-1.b). While co-current systems only allow for the outlet concentrations to approach each other, counter-current systems allow for a higher permeate than retentate concentration.[249]

Counter-current configurations maintain a higher average mass transfer driving force (partial pressure difference) along the length of the membrane module and are therefore typically preferred. Shamsabadi *et al.* showed that counter-current and co-current flow patterns show similar membrane area requirements to achieve the same retentate CO_2 concentration when used with very high sweep gas flows. [249] This higher sweep gas flow rate is required in the co-current case in order to maintain $y_{iR} < y_{iP}$, where y_{iR} is the concentration of the gas component i on the retentate and i_P the concentration on the permeate side. Since the quantity of i that must be transferred to the sweep gas is fixed by the feed concentration, a high sweep flow rate would be required. Conversely, in the counter-current configuration the exiting retentate stream is in contact with the entering sweep gas, which normally has a negligible

concentration of *i*. As a result, y_{iP} can approach the concentration of *i* in the entering feed, without losing a partial pressure gradient, hence a much lower sweep gas flow rate can achieve the same y_{iR} as in a co-current setup.

In reality, the maximum sweep gas flow rate is limited in practice. The large gas volume must be forced through a limited cross-sectional area of the membrane fibers, causing a significant pressure drop, leading to a backpressure across the membrane. This backpressure would significantly reduce the mass transfer driving force. In practice, the effect of very high sweep gas flow rates is typically limited by an increasing pressure drop, cancelling the benefits of the higher flow rate. The added cost associated with using more sweep gas and exhaust handling of the permeate mixture is also of significant importance. In addition to approaching a counter-current flow wherever possible, membrane systems typically rely on compressor and/or vacuum systems in order to increase the partial pressure difference. This allows for achieving a small y_{iR} without having to use excessive sweep gas volumes. However, as noted in the constraints defined in the introduction, for the practical application of membranes in anaesthesia rebreathing circuits, such modifications would not be advisable for patient safety reasons.

When considering this design for gas separation, a low shell side (feed side) mass transfer efficiency is observed compared to liquids. This is due to shell side channelling and bypassing, specifically for gas phase flows. Also, since the modules are usually relatively long and narrow, the tube side pressure drop is often quite high.[250,251] These limitations render the application of parallel contactors inefficient for gas separations.

C.VII - 2.2 Cross-Flow Contactor Principles

In order to avoid the inefficiencies for gas separation using parallel membrane modules, the feed flow can be arranged perpendicular to the fiber direction. Such an arrangement is referred to as cross-flow. A schematic representation of the separation performance in a cross-flow hollow fiber membrane module is shown in Fig. VII-2. As can be observed, the efficiency of a cross-flow module is between that of co-current and counter-current arrangements.

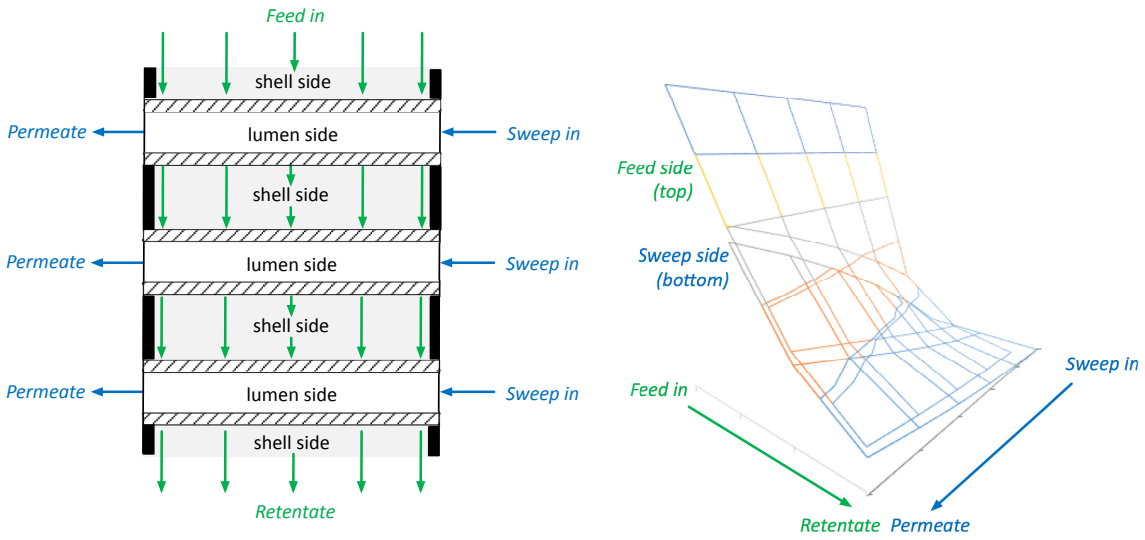

Fig. VII-2 Schematic representation of a basic cross-flow hollow fiber membrane contactor and exemplary sweep and feed side concentrations. For representation purposes, the concentrations have been presented as lines. The permeate and retentate concentrations on the vertical axis mix at the module outlet.

In cross-flow modules, the feed flow is directed perpendicular to membrane direction on the shell side to permit the cross-flow over the outside of the fibers. The advantage of this configuration is good flow distribution and therefore good mass transfer efficiency compared to co-current configurations, and low feed gas resistance. While parallel flow modules work well when liquid phase flow is supported by capillary forces evenly distributing the liquid phase to all fiber surfaces, even where the membranes touch each other, gas phase flows will achieve better overall contact with the fiber surfaces and avoid dead zones when used in a cross-flow design than in a parallel flow design.

Vladisavljević and Mitrović have investigated pressure drops through stacked sheets of hollow fibers that are arranged perpendicular to the flow path, finding that the resistances of the module system was 2.6–4 times higher than the friction resistance of the fibers.[252] Unfortunately, the investigation did not include an analysis of the mass transfer efficiencies.[253]

A similar hollow fiber arrangement, albeit using a circular cross-section, has been employed by Kneifel *et al.* for the dehumidification of air. [254] They did determine, that the pressure drop through the system was relatively independent of the fiber arrangement and instead depended primarily on the number of hollow fiber frames and the gas velocity. This is relevant to this design because it means it is possible to select the fiber arrangement based on the ability to reliably space them without much concern for variation in system performance.

In this specific application, the feed mixture is a gas mixture. Traditional counter-current module setups have the hollow fibers in parallel, resulting in fiber-to-fiber contact. Even when spacers are used, the fiber-to-fiber contact results in a lot of the membrane surface not being accessible to the gas flow. While this is not a problem for liquids, where capillary forces ensure good surface contact with the membrane even in these areas, in this application gases will bypass these higher resistance areas. Hence a different setup has to be explored. Theory predicts that a cross-flow setup, which provides a low pressure drop, would be desirable in this application.

C.VII - 3 CUSTOM APPLICATION MODULE DESIGN

A cylindrical design was developed for this application. This design allows the application of cross-flow, resulting in even resistance and residence time throughout the module. Furthermore, it is possible for the retentate to return concentrically to the feed entering the unit, as demanded by the constraints of this application (C.VII - 1, Fig. VII-3).

The proposed design is based on cross-wound fiber mats[255] wrapped around a hollow, perforated core. The fibers run alongside the hollow core and the fiber ends are embedded in a disk shaped glue line one either end, separating the feed from the sweep flow Fig. VII-3.

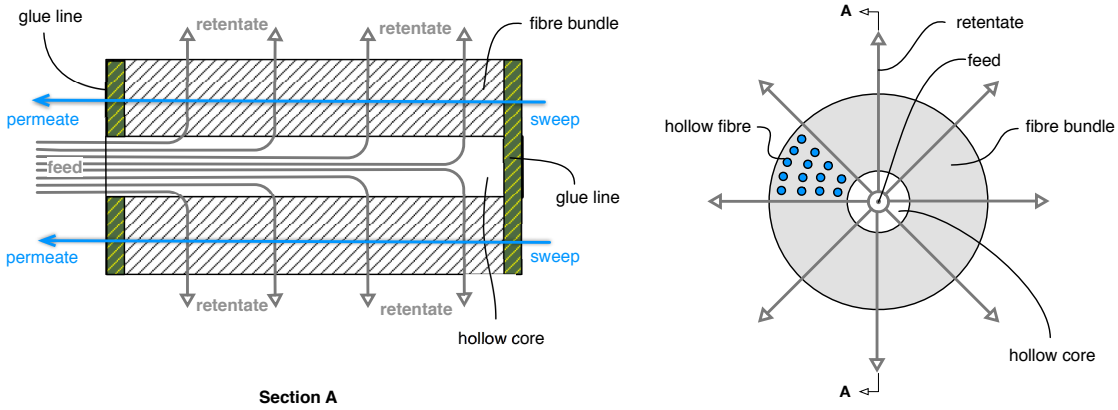

Fig. VII-3. Schematic of the cross-flow module design as side view (left) and cross section (right). The feed enters the fiber bundle and flows radially to the outside, contacting the outside surface of the hollow fibers. The lumen of the hollow fibers is supplied with a sweep flow in order to maintain the partial pressure gradient.

Two identical cylindrical modules were supplied by 3M, Membranes Business Unit in Wuppertal, Germany (3M) to custom specifications. The required surface area was estimated with initial simulations[256] and the modules defined at a length of 120 mm, with an outer diameter of 100 mm. The hollow core was sized to fit the diameter of standard ventilation hoses at an outer diameter of 22 mm, resulting in an inside surface area of 2.4 m^2. An exploded view of the testing container for these modules, along with cross sectional views showing the flow paths for the feed and sweep gas in the assembled unit, is shown in Fig. VII-4. The custom container was manufactured using SLS Rapid Prototyping (Stratasys Ltd., Eden Prairie, Minnesota, USA) with a clear coat to make the container gas tight. To allow for easy disassembly, the membrane module was wrapped around a custom machined perforated hollow core and potted into machined PVC rings each holding an O-ring (Buna-N, 3 mm, McMaster Carr, Elmhurst, Illinois, USA) in a groove on either end of the module, providing

a seal against the faces in the container. The O-rings were installed using high vacuum grease (Dow Corning, Auburn MI, USA).

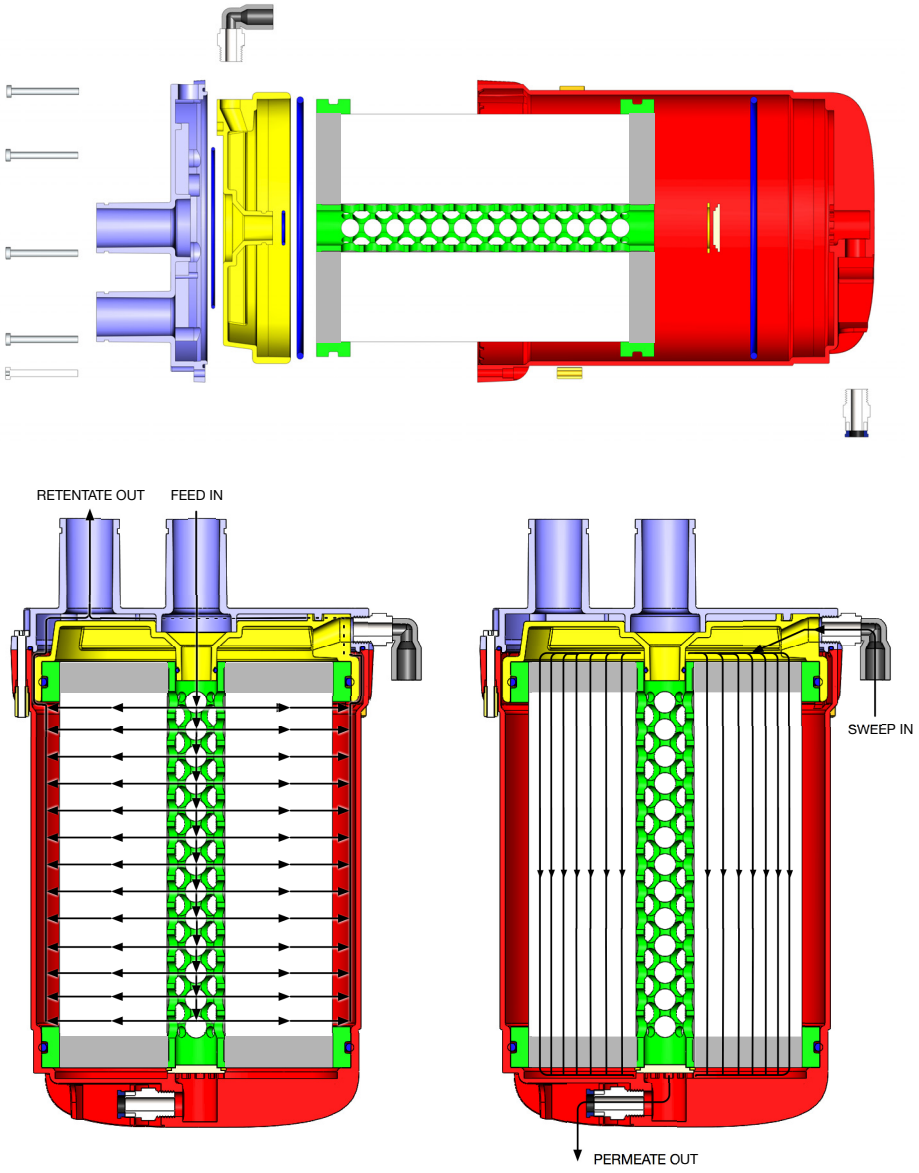

Fig. VII-4. Membrane module with container. Top: Exploded View; Bottom Left: Sweep Gas Flow Pattern; Bottom Right: Feed Gas Flow Pattern. The feed flow enters through the core (green) and then transverse trough the membrane bundle (white), and out as retentate through the side channel between the housing (red) and fibre bundle. The sweep flow is directed through the hollow membrane tubes from top to bottom exiting as permeate.

C.VII - 4 MODULE RESISTANCE

To confirm that the module design described above satisfies the backpressure design constraint, the pressure drop through the assembled membrane module was tested for a variety of flow rates.

C.VII - 4.1 Material and Methods

The application modules were connected to a compressed air source controlled by a rotameter (Scott Speciality Gases, Plumsteadville, PA, USA). Flow rates of 1.5, 3, 6, 9, 10, 20 and 30 $L \cdot min^{-1}$ were supplied to the unit and the pressure was measured using a T-junction at the inlet of the unit using a Datex Ohmeda Patient Monitor with calibrated blood pressure transducer. The outlet of each unit was open to atmosphere (Fig. VII-5).

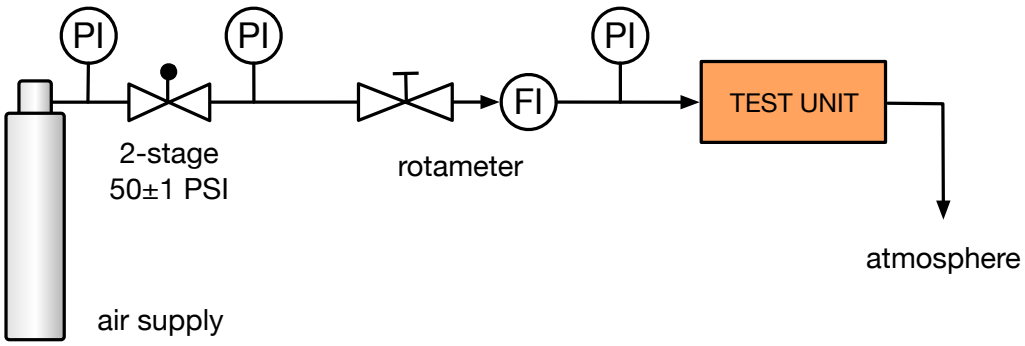

Fig. VII-5. Schematic of the test setup to determine resistance

Two GE Medisorb™ CO_2 absorbers (GE Healthcare, Chicago, USA) and two viral and bacterial respiratory filters (DAR™, Covidien, Dublin, Ireland), both components typically employed in anaesthesia circuits, were included in this experiment. Each test was repeated three times.

C.VII - 4.2 Results

The application module and Medisorb CO_2 absorber showed no measurable back pressure with a measurement sensitivity of 1 mmHg (1.36 mmH_2O) for a mean of six repeated measurements. In comparison, a standard component of the ventilation circuit, a bacterial and viral filter, showed a pressure of up to 1 mmHg at a flow rate of 30 Lpm.

It can therefore be concluded that the cylindrical design of the module using a cross-flow approach allows for large membrane surface areas, while not significantly increasing the resistance for airflow in the system at flow rates up to 30 Lpm. The results show that this design passes the design constraints for backpressure and even provides lower resistance than a typical bacterial and viral filter applied in anaesthesia machines.

C.VII - 5 MASS TRANSFER OPTIMIZATION

To minimize membrane cost and to maintain the size constraints for the system, it is necessary to optimize mass transfer efficiency within the system. In this case, mass transfer efficiency does not refer to improved transfer efficiency across concentration boundary layers that are formed on the inside and outside surface of the membrane fibers. Simple order-of-magnitude calculations have already revealed that the resistance of these boundary layers is negligible compared to the membrane itself. Instead, the focus is on the optimization of the local contacting of the feed and sweep streams to maintain maximum partial pressure differences across the membrane in the module. Both experimental and computational studies were performed to investigate the impact of variations in the module configuration.

C.VII - 5.1 Materials and Methods

Theory predicts that two units in series (i.e. a two-pass cross-flow system) would increase the sweep gas efficiency in the low CO_2 concentration areas of the feed flow.[257] Using

the sweep flow in more than one pass through the membranes allows for the sweep to accumulate little CO_2 on the first pass exposed to the already low concentration retentate. When the sweep passes through the whole module at once, the accumulation of CO_2 would lead to an elimination of the driving force due to concentration equilibrium towards the end of the sweep pass. A new membrane housing was therefore manufactured with O-rings located on the lower cut surface of the fiber bundle, allowing for the sweep gas to take two passes through segments of the module (deep blue in Fig. VII-6).

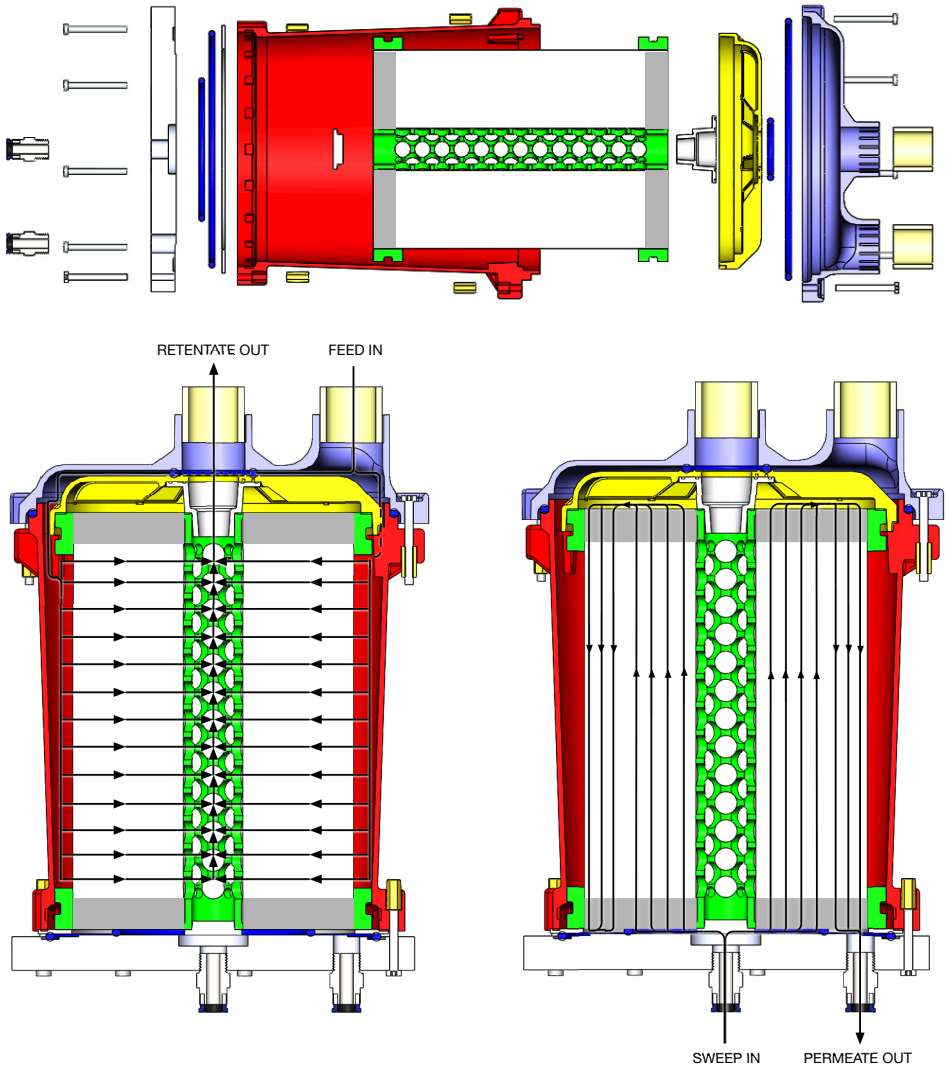

Fig. VII-6. Modified application module with O-ring for double pass (deep blue). These force, the sweep gas up through one section of the membrane module and to return to the remainder of the fibers

The O-rings force the sweep flow to pass up through part of the fiber bundle on one side of the O-ring (pass 1) and to return on the other side through the second part of the fiber bundle (pass 2), as the top cut surface of the membrane module is sealed tight against an inner cap (see Fig. VII-6). This effectively creates a two-pass cross-flow series arrangement within one fiber bundle. Three different sizes of O-rings were used to force the sweep gas through different membrane areas for the first and second pass as shown in Table 7, the contact of the O-ring creates some dead area.

Table 7. List of different O-ring sizes used and the area distribution for the first and second pass as well as the dead area created by the O-ring contact.

O-ring #	O-ring ID	O-ring OD	Area Pass 1	Area Pass 2	Area Dead
1	35 mm	42 mm	8%	86%	6%
2	50 mm	57 mm	22%	70%	8%
3	66 mm	73 mm	42%	48%	10%

C.VII - 5.2 Simulations using COMSOL Multiphysics

A comprehensive two-dimensional, axisymmetric model was built in Multiphysics (Comsol Inc., Burlington, MA, USA) to predict membrane module performance and to permit visualization of the concentration profiles within the module. Visualization is especially important in early-stage, qualitative system optimization because it permits rapid identification of inefficiencies. A full description of the Multiphysics model is beyond the scope of this paper. However, to summarize, our model employed previously measured membrane permeation characteristics and is pending publication.[256,258] Using the COMSOL finite element method solver, the momentum equations were solved to approximate local velocities, and species and continuity equations at the element boundaries were solved to determine the concentration distribution of CO_2. The model can be used for both dynamic and steady-state simulations, but only steady-state simulation results are presented in this paper.

The goal of the simulations was to optimize CO_2 permeation in order to comply with the constraints described above. In addition, achieving even distribution of the CO_2 concentration along the length of the membrane module. This avoids concentration breakthrough and maintains the CO_2 driving force at low retentate concentrations.

C.VII - 5.3 Results of the Simulation

Simulation results for the membrane module with a single sweep pass (no O-ring) are shown for a variety of feed and sweep flow rates in Fig. VII-7. High CO_2 concentrations in the feed gas (near 5%) are displayed in red, and low concentrations are shown in blue.

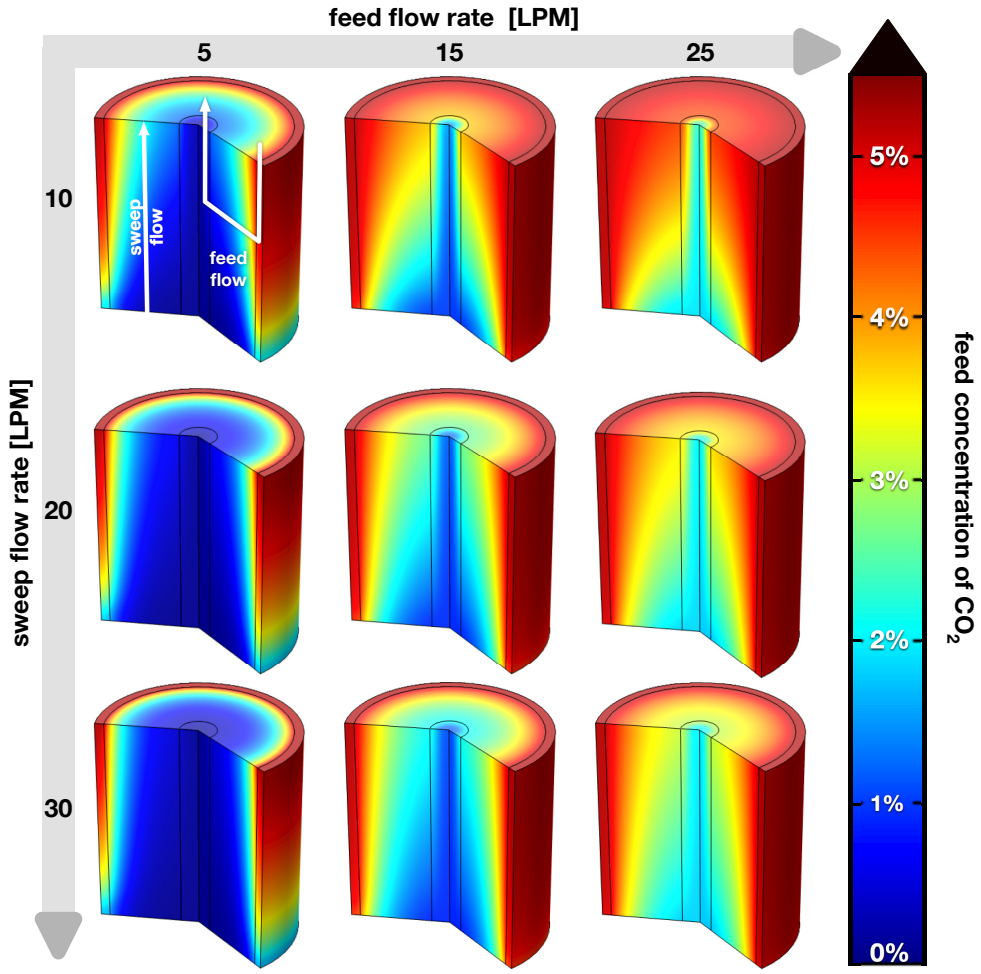

Fig. VII-7. Comsol simulation showing the high CO_2 concentration breakthrough (red) on top of the unit at higher flow rates, where the sweep gas is enriched with CO_2 and therefore the concentration gradient suffers.

At all flow rates an uneven concentration distribution in each concentric shell layer can be observed, leading to high CO_2 breakthroughs at a feed flow rate of 15 Lpm with 10 Lpm sweep flow and at 25 Lpm with all sweep flow rates. The breakthrough can be observed on top of the unit, where the sweep gas is enriched with CO_2, lowering the concentration difference and therefore lowering the driving force for removing CO_2.

For the double sweep pass experiments, several O-ring diameters (Table 7) were simulated to find the best ration of fiber bundle sections that achieve an even concentration distribution (Fig. VII-8).

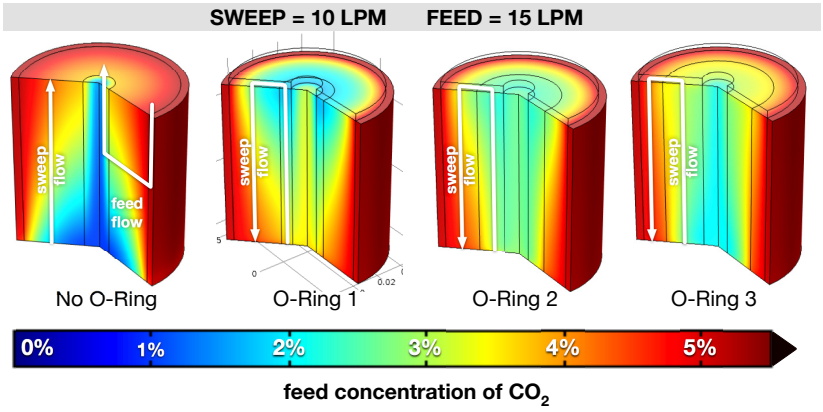

Fig. VII-8. Comparison of different O-ring positions and the resulting concentrations distribution in homogenous radial shell segments. O-ring position 3 results in the most evenly distributed concentrations.

The concentrations are more evenly distributed for O-ring position 3, as the first pass of sweep gas passes with roughly double the flow through the first segment with approximately half of the module's fibers. In this segment, the CO_2 concentration is already substantially decreased, as the initial high concentration allows for high mass transport efficiency. Furthermore, the relatively small CO_2 amounts accumulated in the sweep flow on the first pass due to the already decreased retentate concentration, do not significantly decrease the driving force to the low concentration retentate. A double pass sweep flow therefore results in a more even distribution of concentrations across the length of the module and results in a

lower residual CO_2 concentration in the retentate. O-ring 3, which splits the membrane area in two even segments for the first and second sweep pass, was chosen as the best configuration. In order to confirm that O-ring position 3 improved the concentration distribution, the simulation was repeated with several flow rates for comparison (Fig. VII-9).

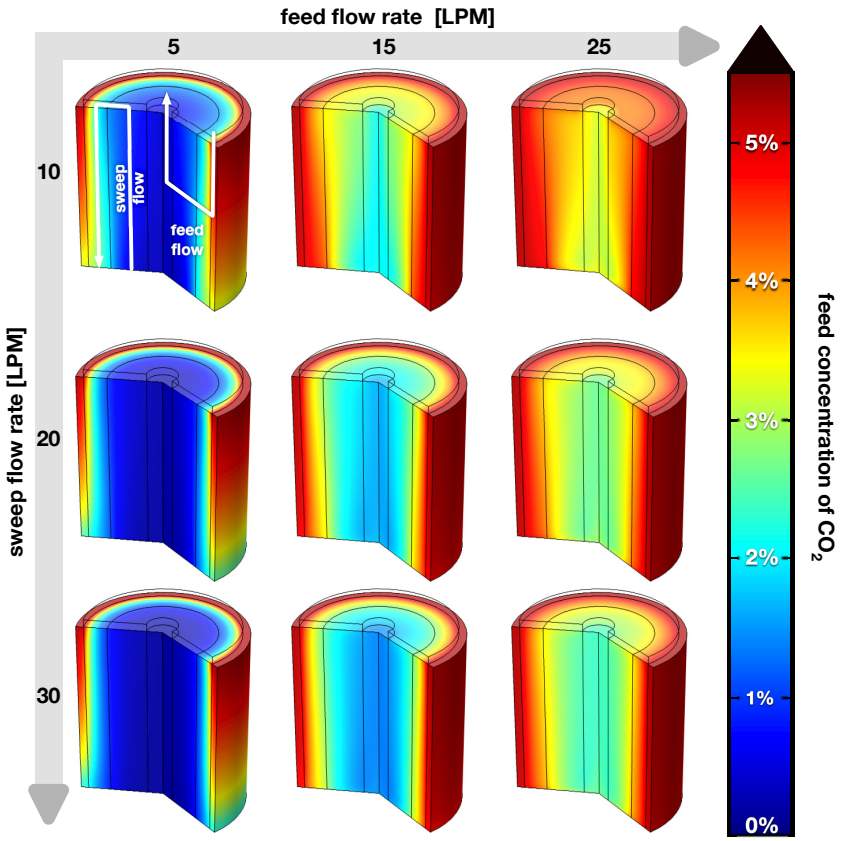

Fig. VII-9. The use of an O-ring that separates the membrane surface area into equal parts, eliminates a breakthrough of high concentration CO_2 (red) and homogenous shell segment concentrations are achieved.

The simulation results indicate that the concentration profile is more evenly distributed in all flow scenarios using O-ring position 3. The numerical results from the simulations are pending manuscript submission.[256] They indicate, as expected, a reduced CO_2 concentration in the retentate stream.

C.VII - 5.4 Results of the Experimental Verification

For verification of the model predictions that an even membrane surface split for a two-pass sweep gas flow improves the removal of CO_2 resulting in a lower residual CO_2 concentration, experimental data was collected using the experimental system with O-ring 3 as described above. Results from six sets of these experiments are shown in Fig. VII-10.

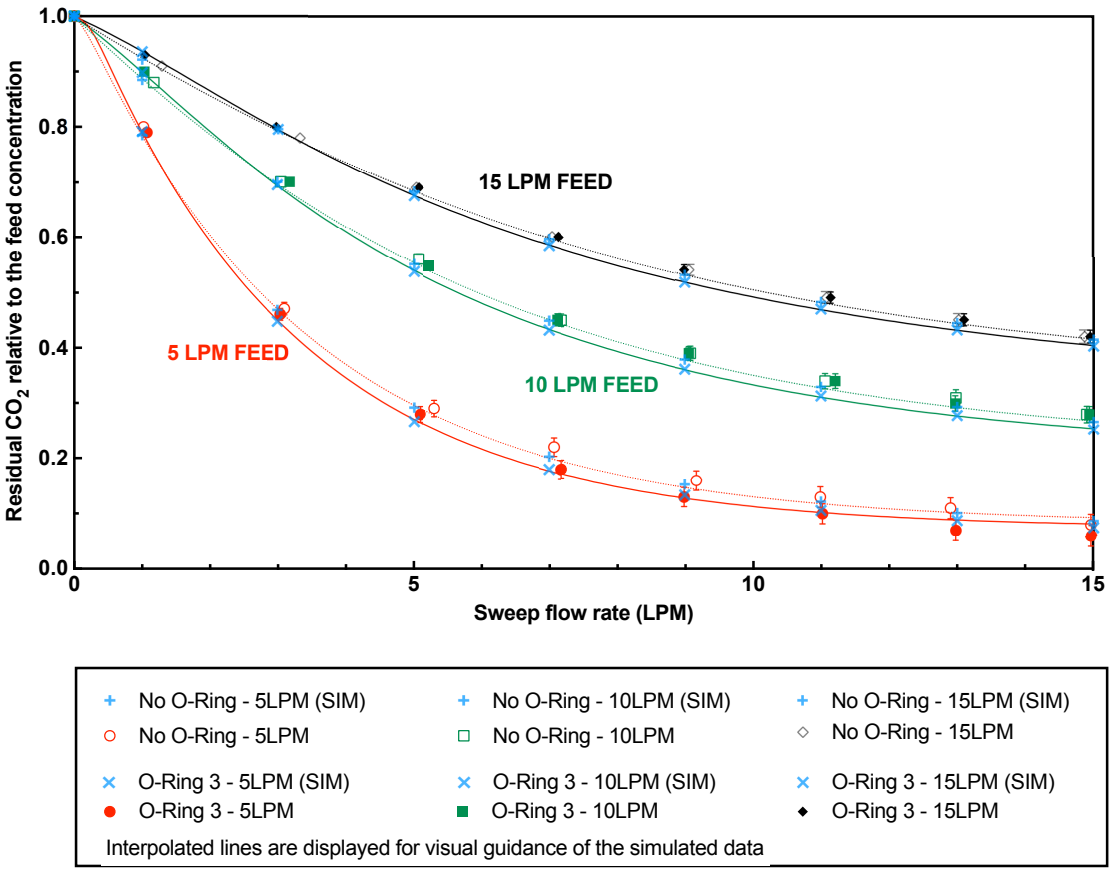

Fig. VII-10. Experimental and simulation results for no O-Ring and O-ring position 3. Residual CO_2 concentrations as ratio to the feed concentration for 5, 10 and 15 Lpm Feed flow rate, comparing the setup with and without the O-ring placed as predicted are shown along with the simulations. Interpolation lines for the simulated data is shown for visual guidance. The O-ring decreases the residual CO_2 at the same sweep flow rate for 5 Lpm Feed particularly for sweep flow rates of 5 lpm and above. Data shown as mean ± SD.

Residual CO_2 concentrations of the gas mixture that would normally be shown as ratio to the feed concentration for 5, 10 and 15 Lpm feed flow rate, comparing the setup with and without the O-ring placed as predicted in our simulations. The O-ring clearly decreases the residual CO_2 at the same sweep flow rate for 5 Lpm feed. However, the concentration

differences only become apparent when the concentration, and therefore the driving force, is reduced to a very low value, therefore it is not apparent for 10 and 15 Lpm feed flow rates in this experimental setup. As explained above, the double pass sweep flow allows for maintained driving force for CO_2 in areas where the retentate has already decreased significantly. When the feed flow exceeds the ability of the membrane area to reduce the concentration to such low levels, the effect of the double pass does not become apparent. This is the case for the 10 and 15 Lpm feed flow rates.

Good agreement between the simulated and experimental data can be observed in the parity plot of Fig. II-11.

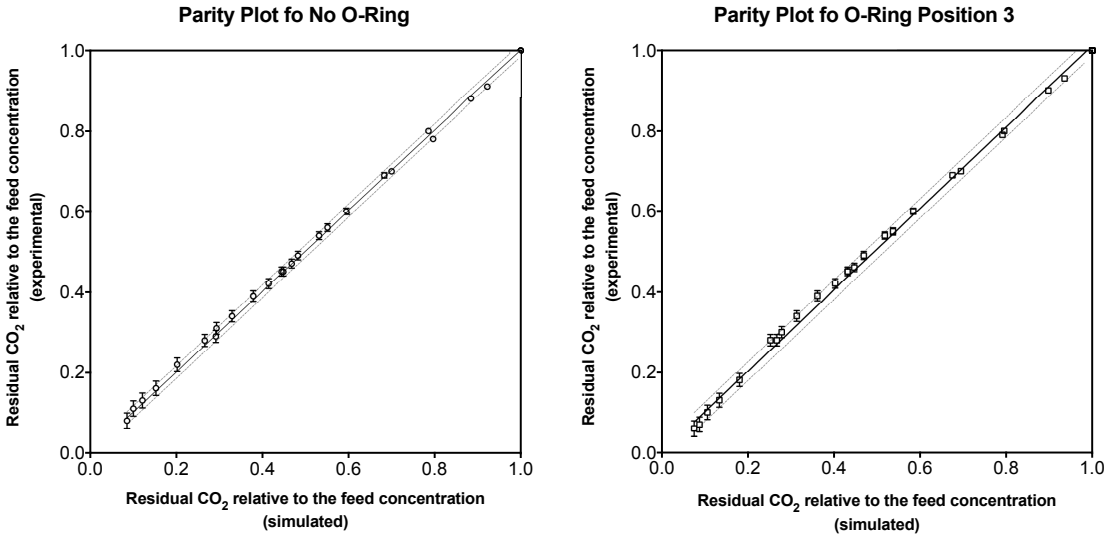

Fig. VII-11. Parity plot of the simulated and experimental data for no O-Ring (left) and O-Ring position 3 (right). The standard deviation of the experimental data is shown along with the 90% prediction interval of the linear regression. Overall, good agreement between simulated and experimental data can be observed.

The residuals of the linear regression in both parity plots from Fig. II-11 can be observed in Fig. II-12.

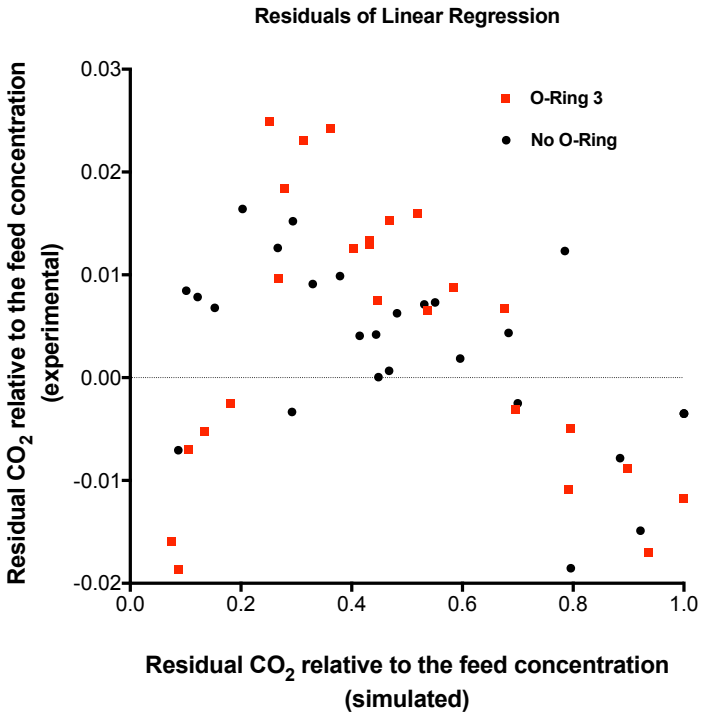

Fig. VII-12. Residuals of the linear regressions in the parity plots of Fig. II-11.

Membrane systems for CO_2 removal have been explored in the past, including the removal of CO_2 from flue gases,[259–262] natural gas,[263–266] and the human body.[267] The majority of industrial systems for CO_2 removal can be generally grouped into (i) liquid-gas, (ii) gas-liquid and (iii) gas separation applications. Either application typically employs counter-current flow arrangements of the membrane. This is possible, as these systems are typically using compressors and/or vacuum systems to overcome resistance and bypassing problems, often in the range of several atmospheres of pressure far above maximum pressures a lung can handle and which would therefore seriously harm or kill a patient in case of a system failure.[268] Gas-liquid systems typically employ absorption media on the sweep side. Portugal *et al.* (2009) describes the use of amino acid salt solutions on the sweep side of a membrane for the removal of CO_2 from a gas mixture.[269] The system requires a large reservoir and a desorption column continuously recycling the solution. These would not be appropriate for anesthetic gas systems

because of the the risk of chemical substances, and compressors or vacuum systems would pose to a patient's lung, apart from the unnecessary added system complexity requirements. Thus such systems do not provide a viable alternative for CO_2 absorbers in anaesthesia circuits.

Passive systems typically achieve very low efficiency in comparison to active systems, hence there has been no comparable design and optimization study for passive gas separation membran modules as the one presented in this thesis, to the author's knowledge. However, passive system oxygenators do employ liquid-gas based membrane systems, for removing CO_2 from the blood during cardiac surgery. While such systems are also passive, i.e. limited to the systemic blood pressure, the removal of CO_2 from a patients expired gas mixture adds an additional compartment to the system. Using membranes for removing CO_2 from the blood via the lung, CO_2 has to diffuse from the blood into the lung, then by diffusion from the exhaled gas mixture into the sweep gas stream, resulting in a total resistance of two membrane systems with the added challenge of dead spaces in the breathing circuit. This creates a challenge as it is necessary maintaining the inspired CO_2 concentration below the alarm level of former chemical CO_2 absorbers in order to allow for adoption by anaesthesiologists in current practice.

C.VII - 6 CONCLUSION

This study described the design and optimization of a membrane system for the separation of CO_2 from anaesthesia circuits. The design process has been tightly constrained by size, operation and safety limitations. Both experimental and computational techniques were used in the design and optimization process. Through review of the membrane process literature, preliminary experiments and simple calculations, this report describes that a cross-flow hollow fiber module is feasible, and would be beneficial for achieving the low pressure resistance required for anesthetic rebreathing devices. This was experimentally confirmed by performing a series of pressure drop measurements on a custom cylindrical cross-flow membrane module.

Successful optimization of mass transfer performance of the custom membrane module was achieved by incorporating O-rings into the unit to permit multiple sweep passes. These O-rings allowed for the reduction of the sweep flow rate as compared to the units that only used one sweep pass. Two-dimensional computer simulations were used to confirm that the use of multiple sweep passes eliminated high concentration breakthroughs of the feed, thereby improving performance. These simulations were also used to decide on the optimal O-ring position, and experimental data confirmed these predictions.

This study was able, for the first time, to design a passive gas separation membrane module with a low pressure drop suitable for anesthesia rebreathing systems. This approach optimized the effectiveness of the sweep flow for a given membrane area, without any active components, and successfully reduced the residual CO_2 concentration, ultimately lowering the inspired CO_2 concentration below the level set in the design constraint. Together these results makes the passive application of membranes for CO_2 absorption in anaesthetic circuits possible.

Chapter VIII IN VIVO VALIDATION – PIG

Validation of membrane separation as safe alternative to current chemical based CO_2 absorbers in anaesthesia circuits in a pig study

F Wilfart, M Schmidt

C.VIII - 1 INTRODUCTION

This chapter aims to verify the performance and safety of a membrane based CO_2 filter developed in this thesis *in vivo* . This CO_2 filter is meant to replace current chemical CO_2 absorbers required for rebreathing circuits in anaesthesia systems.

Historically, membranes have been characterized in bench experiments for their permeation and separation behaviour.[218,270–272] Such experiments allow for the analysis of a large number of samples under controlled conditions instead of assembling large and costly membrane units and testing them in real life conditions. For most industrial applications, the predictions from such characterization experiments provide good predictions for large scale performance, as the final systems typically operate under controlled conditions closely matching the characterization conditions. The operating conditions in industrial applications can be matched closely as they are generated using compressors, vacuum systems and active adsorption and desorption systems.[273–279] Additionally, the chemical compositions (i.e. gas compositions) under operating conditions are typically reproducible on the bench.

In this thesis, a membrane system has been developed. The system employs dense skin PMP membranes to remove CO_2 from anaesthesia rebreathing circuits while retaining the anesthetic vapour.

Anesthesia circuits operate near normobaric conditions ($\leq$ 30cmH^2O), contain high levels of water vapour and the gas composition contains a multitude of metabolic by-products and drugs from the blood stream.[280–284] These intrinsic physiological conditions are given and cannot be altered. It is also not feasible to recreate the gas mixtures encountered under physiological operating conditions on the bench. As these chemicals in the gas mixture can have secondary effects on the performance of a membrane, it is appropriate to use the

membrane system pre-clinically in an animal study to help validate that the system can perform as predicted before it is tested in humans. Pigs provide a convenient large animal model, that has been shown to provide clinically relevant findings for other pre-clinical and research studies in the past.[232,285–289] Pigs also allow for the use of full size operating room equipment, such as an anaesthesia machine, physiological monitoring and cauterization, thus best mimicking the intended environment.

C.VIII - 2 RATIONALE

A true test of the safety and performance of this novel technology *in vivo* is a valuable step before entering clinical studies. Gas mixtures exhaled by humans contain many components not practically feasible to simulate in a bench experiment. Also realistic flow patterns and physiologic conditions of the breathing circuit and lung fluidum are impossible to simulate well in an *ex vivo* experiment.

C.VIII - 3 MATERIAL AND METHODS

After obtaining approval from the local University Committee on Laboratory Animals (UCLA, Protocol Number 13-047**)** and drug exemption from Health Canada, pigs weighing 30 ± 5 kg were intubated and ventilated using an EKU Tangens 2c anaesthesia machine (EKU Elektronik, Leiningen, Germany). Anaesthesia was maintained as balanced anaesthesia using intravenous drugs, as described below, in combination with Sevoflurane. All animals were monitored for blood pressure, oxygen saturation, EKG and ventilation parameters using a Datex Ohmeda Patient monitor (Datex Ohmeda, Bromma, Sweden).

The pigs were pre-medicated with Azaperone (2.2 mg/kg, i.m.) and Atropine (0.1 mg/kg, i.m.). The animals were then masked down with Sevoflurane to facilitate

induction. An ear vein was punctured, an intravenous line placed and anaesthesia was induced with Pentobarbital (10-30 mg/kg, bolus, i.v.) and analgesia with Buprenorphine (0.01-0.05 mg/kg, i.v. bolus) to achieve the loss of coughing reflex before intubation. Pigs were placed in supine position on a temperature controlled heating pad. An ear clip was used for continuous measurement of SpO_2 (pulse oximetry) and electrocardiogram (ECG) to monitor the heart rate (Fig. VIII-1).

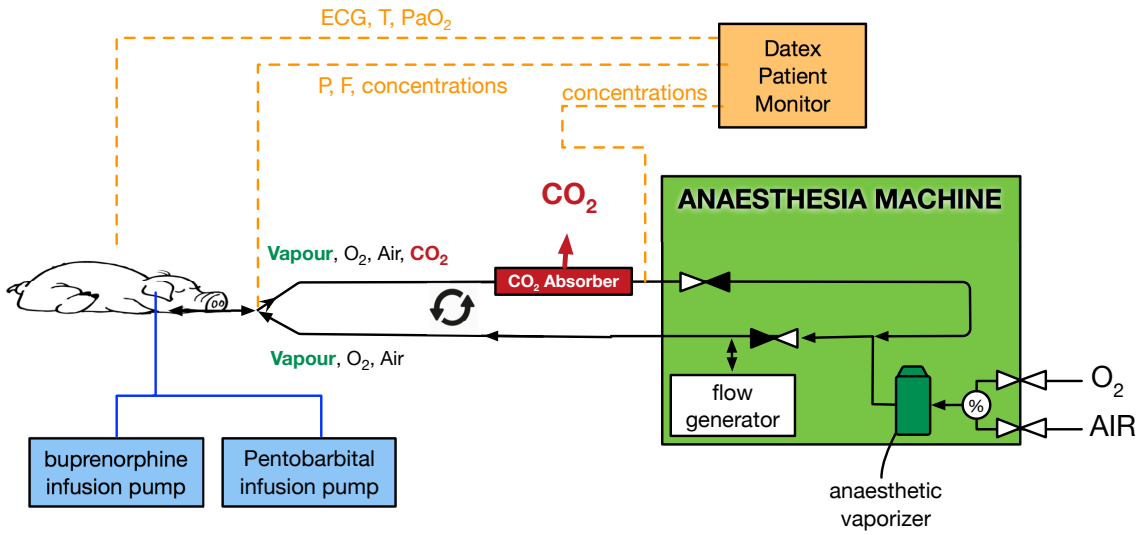

Fig. VIII-1. Schematic of the Experimental Setup

Neuromuscular relaxation was provided by Rocuronium Bromide (0.6 mg/kg) to facilitate intubation, a standard procedure in human patients. The pigs were oro-tracheally intubated with a super safety endotracheal tube and the cuff was inflated to avoid leakage of anaesthetic gases. Mechanical ventilation commenced using a tidal volume of VT = 8-10 mL/kg, an inspired oxygen fraction of inspired oxygen 0.5-1 in air and a positive end-expiratory pressure PEEP of 5 cmH_2O. The respiratory rate was set to keep $PaCO_2$ between 40-50 mmHg and pH 7.3 – 7.5. Neuromuscular relaxation was provided by Rocuronium Bromide (0.6 mg/kg) for ventilation. For maintenance of anaesthesia, Buprenorphine (0.48

μg/kg/h, i.v.) and Sevoflurane were started and continued for the duration of the experimental procedure. Physiologic monitoring included monitoring of the respiratory function (tidal volume, respiratory rate, peak flow, vapour concentrations) and the cardiovascular system (heart rate, arterial systemic vascular pressure). While under general anaesthesia, at the completion of the experimental phase, the animals were sacrificed by administration of potassium chloride (KCI). The concentrated KCl was given rapidly i.v. until rising serum potassium levels result in cardiac arrest.

During ventilation, fresh gas flows (FGF) and the sweep flow rates were varied and the resulting CO_2 levels, system compliance, pressures and flows were recorded for each pig.

C.VIII - 4 RESULTS

Running the membrane module instead of the chemical CO_2 absorber resulted in stabile and safe expiratory and inspiratory CO_2 levels over extended amounts of time and at virtually any sweep gas pressure (Fig. VII-7).

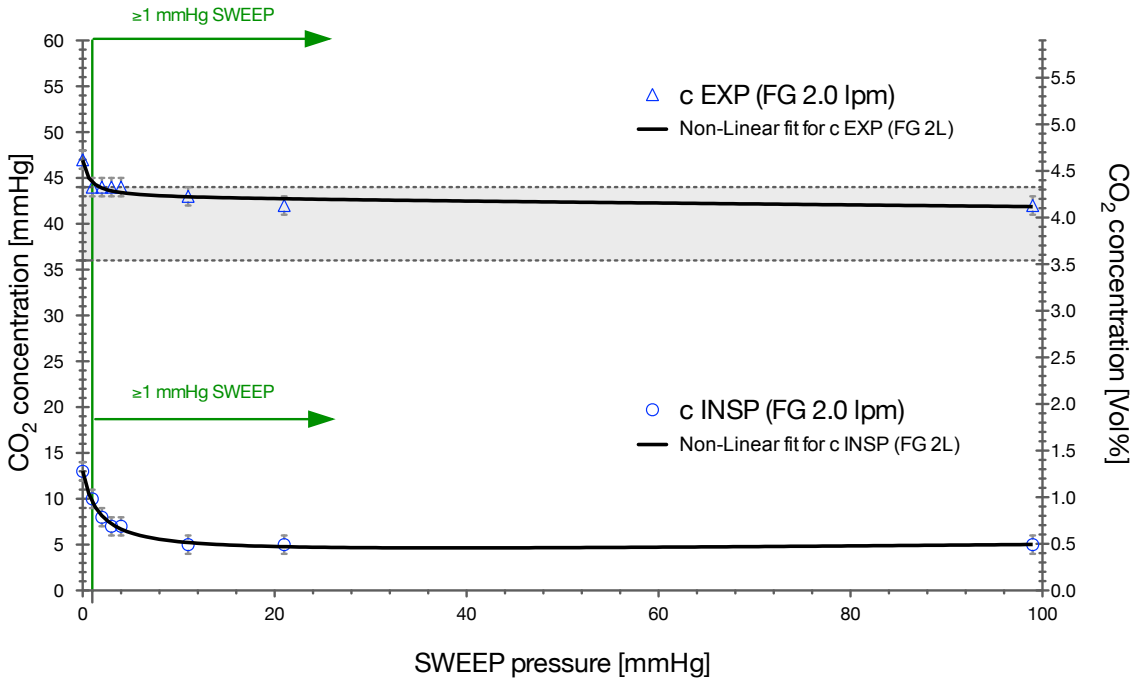

Fig. VIII-2. Inspiratory and expiratory CO_2 are maintained in the target limits of 40 ± 4 mmHG expiratory and 4±4mmHg inspiratory over nearly all sweep pressures.

All other physiological parameters of the pig were kept stabile over the course of the investigation (e.g. hemodynamics, temperature, blood pressure).

During ventilation with 12x600ml tidal volume per minute, resulting in a minute volume of 7.2 Lpm. Different fresh gas flows and mixtures were tested. The end tidal concentration of CO_2 was easily maintained in the range targeted by the anaesthesiologist (Table 8).

Table 8. $EtCO_2$ values for different fresh gas mixtures and flow rates

Fresh Gas [litre × min^{-1}]	**Fresh Gas** [%O_2 in Air]	**Et**CO_2[%] MEAN	STDEV
2	100	5.32	0.15
4	100	5.20	0.05
2	50	5.28	0.15
4	50	5.32	0.04

From the readings from the anesthesia machine (Fig. VIII-3) and patient monitor (Fig. VIII-4), there were no obvious changes observed in flow patterns, circuit compliance, pressures or volumes delivered, and therefore the compliance of the systems did not change from standard values typically observed with standard CO_2 absorbers per the monitor of the anaesthesia machine. Compliance describes a change in volume for any given applied pressure and is typically used to monitor the lung.

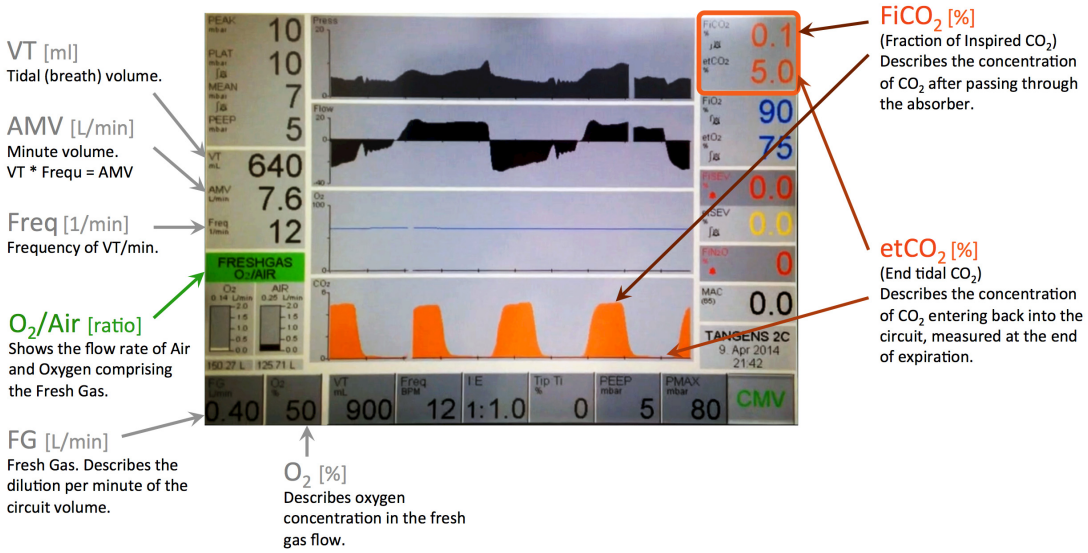

Fig. VIII-3. Anaesthesia machine (Tangens 2c, EKU, Germany) monitoring screen. All parameters are in a physiological range.

Fig. VIII-4. Additional data from a patient monitoring system (Datex Ohmeda, Sweden). From monitoring the output, normal pressure and flow conditions were observed with the membrane module installed (normal pressure and flow conditions would need to be defined in methods).

C.VIII - 5 DISCUSSION

Using a pig model, it was shown that the tested absorber units could keep the expired CO_2 in the safe target range. This means that the membrane based CO_2 filter was able to safely replace the chemical based CO_2 absorber. This is the first time a membrane based CO_2 filter was succesfully used in a large animal study.

These findings are in keeping with the observation that, in extracorporeal membrane oxygenation (ECMO) and cardiac surgery using oxygenators, safe CO_2 levels can be maintained in patients over extended time.[253,292–296] However, these systems do not have the additional lung compartment as they are in direct blood contact, more easily maintaining driving forces and not operating to ventilation standards in respect to CO_2 concentrations, but directly to partial pressures of CO_2 in the blood. No other passive membrane system has been reported in the literature to safely replace a CO_2 absorber *in vivo*. This proof of concept demonstration in a live animal has some limitations. The principle limitation of this experimental setting is that the pigs have lower than human CO_2 production with a relatively limited production rate of CO_2 in a 30 ± 5kg pig. While our CO_2 filter is expected to maintain safe CO_2 levels in the blood, larger membrane areas and sweep flows may be required in order to achieve inspired CO_2 concentrations below the adoption limit of 0.5% CO_2, although the inspired concentration is not safety relevant as long as it is maintained significantly below half the expired concentration.

However, these results provide a proof of concept, and larger designs would be able to accommodate larger CO_2 volumes if needed. Another limitation lies in the gas composition exhaled by a pig, as there are differences in the digestive system and metabolism, and thus it is possible that exhaled human breath may contain molecules that could potentially interfere with CO_2 extraction, although this possibility is quite remote.[297,298]

This experiment serves as proof using a pig model, that membrane separation can be safely employed in a physiological ventilation circuit and therefore minimizes the risk of testing this approach in human patients. Indeed, the results of this study enabled a successful application for the testing of this approach in a clinical study described in the next chapter. However, because the pig ventilation volumes and volumes of exhaled CO_2 are smaller than that of humans, a larger size and other optimizations are needed and are described in the next chapter.

C.VIII - 6 CONCLUSION

This was the first successful application of a passive membrane module in an anaesthetic circuit. This demonstrates, that dense PMP membranes under physiological conditions including humidity, gas mixtures and dynamic flow patterns can maintain safe CO_2 removal performance.

Chapter IX IN VIVO VALIDATION – HUMANS

Clinical validation of membrane separation as safe alternative to current chemical based CO_2 absorbers in anaesthesia circuits

F Wilfart, O Hung, M Schmidt

This thesis chapter describes the clinical testing of the membrane CO_2 filter developed in this thesis as replacement for current chemical CO_2 absorbers after successful bench testing and proof of concept in a preclinical study using pigs, described in previous chapters.

C.IX - 1 INTRODUCTION

This study compares the performance of state of the art chemical absorbers used at the Nova Scotia Health Authority (NSHA) in Halifax, Nova Scotia to the membrane based CO_2 filter developed in this thesis, memsorb℠ . The study was designed such that an independent researcher, Dr. Orlando Hung, MD, FRCPC, oversaw the study while DMF Medical Incorporated supplied the test device to him as sponsor of the study. After approval by the local ethics board, Dr. Hung identified NSHA Anaesthesiologists and residents to be trained on the device and the study coordinator obtained consent from patients, identified on the operating room schedule that day.

Many details from the REB protocol were maintained in this chapter because they are believed to be helpful information for researchers that follow this area of research.

C.IX - 2 BACKGROUND

CO_2 removal is a mandatory part of modern anaesthesia systems. Current chemical absorbers pose problems as the chemical granulate reacts not only with the CO_2 but also the anaesthetic drugs, producing neuro and nephro toxic substances. The proposed CO_2 filter used in this study, memsorb℠, has previously been shown in bench and animal studies described in this thesis, to provide a solution to the problem of neuro and nephro toxin production in anaesthetic circuits by the current CO_2 absorbers that are based on chemical absorption. Memsorb can be easily integrated into any anaesthesia circuit, and can effectively remove CO_2 without reacting with anaesthetic drugs (Chapter IV), thus eliminating the production of the neuro and nephro toxic by-products of current chemical absorbers. Memsorb uses advanced membrane technology to separate gas flows within the circuit,

separating the expensive anaesthetic vapours from the unwanted exhaled CO_2 (Chapter V and Chapter VII). Anaesthetic vapours thus remain in the circuit, while CO_2 is separated and exhausted to the atmosphere, rather than being absorbed through a chemical reaction.

C.IX - 3 SUMMARY OF OBJECTIVES

The purpose of the proposed research pilot trial was to validate previous bench and animal results (Chapter V and Chapter VII) in patients. Therefore, the study was designed to directly compare the CO_2 absorber replacement memsorb℠ with the currently used chemical granulate absorbers used at NSHA in 20 elective surgeries. This study will evaluate that memsorb℠ can maintain safe levels of CO_2, measured at the end of expiration, throughout the duration of anaesthesia in patients of varying weight and lung sizes during different surgical procedures. The primary outcome measure was no significant difference between the expiratory ($EtCO_2$) levels of both groups. $EtCO_2$ is an accepted surrogate measure that assesses the concentration of CO_2 in the blood ($paCO_2$) and therefore the pH.[299,300] This is common practice for anaesthesiologists worldwide, as it avoids the need for repeated invasive blood gas analysis. The $EtCO_2$ is thus considered the most important patient parameter for ventilation besides the oxygen saturation SaO_2.

C.IX - 4 SUBJECT SELECTION

Twenty patients were recruited from the Queen Elizabeth II Health Sciences Centre (QE II HSC) site of NSHA who were undergoing general anaesthesia for an elective surgical procedure. Participants were included on the basis of the operating room in which their surgery was performed.

Inclusion criteria

- American Society of Anaesthesiology Physical Status Class I, II, III (low-medium risk patient)
- English-speaking patients
- Scheduled for elective surgery
- Length of anaesthesia ≥ 60 minutes

Exclusion Criteria

- Pregnant
- American Society of Anaesthesiology Physical Status Class IV (high risk patient)
- Patients scheduled for emergency surgery
- Known respiratory disease, including COPD and severe asthma
- Have elevated pressure in the brain (intra cranial pressure, ICP)

C.IX - 5 METHODS

C.IX - 5.1 Trial design

This was an interventional study comparing $EtCO_2$ levels in patients that used either the CO_2 absorber replacement memsorb℠ or the standard chemical granulate absorber. Participants were assigned to groups based on their willingness to participate using the new device. Patients who did not consent to using the new device were automatically assigned to the control group, and had their observational data collected following their surgery.

The current trial evaluated the equivalence of two techniques for CO_2 removal from anaesthesia circuits. Standard electronic data collection occurred during the induction and maintenance of general anaesthesia throughout the procedure with the hospitals Inovian® anaesthesia database (Draegerwerk, Luebbeck, Germany). Data were exported from the Inovian® database by the database manager of the Department of Anaesthesia.

C.IX - 5.2 Procedure

Participants received the same treatment and anaesthesia per the standard of care at NSHA. The anesthesiologist decides on the specifics of the anaesthetic vapour used and general procedure as per his own and NSHA standards. If a participant was willing to be

included in the test device group, the standard chemical granulate absorber was replaced with a memsorb℠ device. If a participant declined to be included, the regular chemical granulate absorber was used in-line for the procedure.

Due to the technical nature of this trial and our goal of maintaining the highest standard of safety for the patient, the anaesthesiologist was not blinded to the absorber type (chemical absorber or memsorb℠) used during surgery. Additionally, since we were using objective measures that were automatically recorded, i.e. $EtC0_2$, it was not necessary for the anaesthesiologist to be blinded to the group. The key ventilation parameters will be compared between the groups to exclude that memsorb℠ influenced their behaviour.

C.IX - 5.3 Participant Recruitment

Twenty participants, ten per group, were recruited during their preoperative assessment by Anaesthesia on the day of their surgery. Patients were approached to provide informed consent to participate in this research study at the same time they were approached by the anaesthesiologist to provide consent for their general anaesthesia. Because consent was obtained while consent to anaesthesia was being completed, an anaesthesiologist and research coordinator were on hand to answer any questions the patient had. To minimize impact on operating room flow, a single OR was used for recruitment. Ten patients were recruited for the memsorb℠ group, using the Informed Consent Form and ten patients were recruited for the control group, using the Access to Health Information Form. During the course of surgery, any adverse events during the use of memsorb℠ were reported in the Patient Safety Reporting System as mandated by NSHA. Patients in the control group had already consented to have their de-identified data used for research purposes per NSHA guidelines.

Patients were able to withdraw at any time and their information would not be used in the data analysis. The anaesthesia procedure was performed according to the standards of the attending anaesthesiologist. Per the standard anaesthesia practice, each patient was required to meet the NSHA criteria both prior to extubation and prior to transfer to the post-anaesthetic care unit (PACU). No further follow-up was required as we only used intra-operative data. All serious unexpected adverse reactions were required to be reported to Health Canada per Health Canada's Mandatory Problem Reporting guidelines (from Health Canada's Medical Device Regulations). There were no serious adverse events related to patient safety as a result of this study.

C.IX - 5.4 Experimental Design (subject allocation)

Ten (10) procedures requiring general anaesthesia were proposed to be performed using the memsorb℠ device. Metrics from these procedures were compared to those derived from 10 procedures using the current standard of care, which is a chemical granulate based absorber (Table 9).

Table 9. Subject allocation

Independent Variable	**Number of Patients**
chemical granulate absorber	10
memsorb℠ membrane device	10

Due to a lack of reported effect size data related to this technology, a formal power analysis could not be calculated.

C.IX - 5.5 Confidentiality

Data was collected directly from the Inovian® Anaesthesia management system. All trial records on participants were kept strictly confidential and were maintained within NSHA's electronic system. Primary and secondary data points were downloaded directly from the Inovian® OR software and stored as de-identified data. For the purposes of device comparisons there was no requirement that any data points retrieved from Inovian® be linked back to a specific patient identifier. For auditing purposes, or in the event a memsorb℠ participant wished to have their data excluded from the study, each memsorb℠ data set was de-identified using a unique identifier. A master file was kept by the Principal Investigator only, which linked patient name with unique identifier. Trial data is kept for 25 years per NSHA's requirements. De-identified trial data was only made available to the principal investigator and assigned trial personnel as they were identified in this application. Patient participants were not identified in any reports or publications as a result of participation in this trial. Records may be shown to the NSHA Research Ethics Board in the case of an audit.

C.IX - 5.6 Harms

Anaesthesia has been performed with semi-open (without any CO_2 absorber) systems for decades, safely. Therefore, even in the unexpected case of a malfunction of a memsorb℠ device, anaesthesia could be performed safely without ***any*** CO_2 absorption in the circuit using a higher level of fresh gas flow. This can be achieved by opening up the circuit and continuously venting fresh gas. Because of this, there is no additional risk to the patient if the test device, or standard chemical granulate absorber, had not performed as expected. A failure of memsorb℠ would thus be equivalent to the regular exhaustion of current chemical absorbers and therefore reacting to such an incident is standard practice.

C.IX - 5.7 Benefits

There were no direct benefits to patients participating in this trial. However, besides having enlarged the body of knowledge in the field, patients experienced a safer anaesthesia process via elimination of neuro and nephro toxic compounds that arise from chemical CO_2 absorbers when they react with anaesthetic vapours to which they would have otherwise been exposed. Based on the fact that they are associated with increased risks of cell damage and organ dysfunction memsorb may help to reduce POCD after surgery and anesthesia (C.II - 3 and C.III - 3.3), with the highest potential for benefits expected for those patients who are 65+ years old.

C.IX - 5.8 Liability

If the patients became ill or injured as a direct result of having participated in this study, necessary medical treatment was available at no additional cost. Their signed and verbal consent indicated that they understood the information regarding participation in the study and agreed to participate as a subject. In no way did it waive their legal rights nor release the investigator, the research doctor, the study sponsor or involved institutions from their legal and professional responsibilities.

C.IX - 5.9 Disclosure of Any Financial Compensation

There was no financial compensation for the study doctors or the participants.

C.IX - 6 STUDY RESULTS

For both, the control (CTL) and device intervention group (INT), the End Tidal and Inspired CO_2 levels along with the volume related ventilation parameters were analysed. Anesthesiologists used Sevoflurane or Desflurane per standard of care. In the control group, absorbers were used as usual until the anaesthesiologist considered them read to replace. All control group patients were operated using Drägersorb Free (Draegerwerk, Luebbeck, Germany) absorbers. Neither the minute volumes, tidal volumes or ventilation frequency differed significantly between the control (CTL) and device intervention group (INT) as determined using a Kruskal-Wallis test and a significance level of $P<0.05$ (see Fig. IX-1).

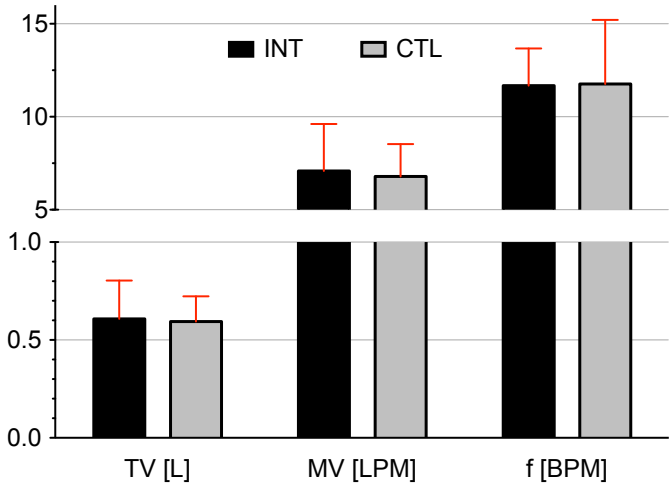

Fig. IX-1 Study results for control (CTL) and device intervention (INT) group the tidal volume (TV), Frequency (f) and Minute Volume (MV) as mean and SD. Units for each group differ and are reported in the group descriptor.

The mean $EtCO_2$ did not differ statistically between the CTL and INT as determined Kruskal-Wallis test and a significance level of $P<0.05$ (Fig. IX-2).

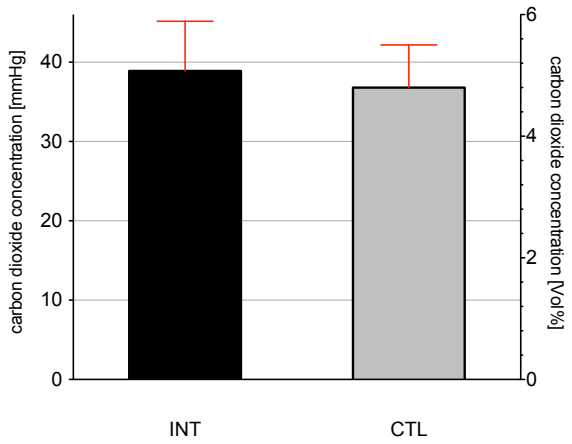

Fig. IX-2. Expired CO_2 concentration of the control (CTL) and intervention (INT) group as mean with standard deviation. The left y-axis shows the concentration in mmHg and the right y-axis in Vol%. There was no significant difference between the means of the two groups as determined Kruskal-Wallis test and a significance level of P<0.05.

The mean $InspCO_2$ did not differ statistically between the groups as determined Kruskal-Wallis test and a significance level of $P<0.05$ (Fig. IX-3). The measurement sensitivity is limited to 1 mmHg. However, concentrations below the sensitivity of the standard monitoring in an operating room is not of interest for a device determined for exactly such environment.

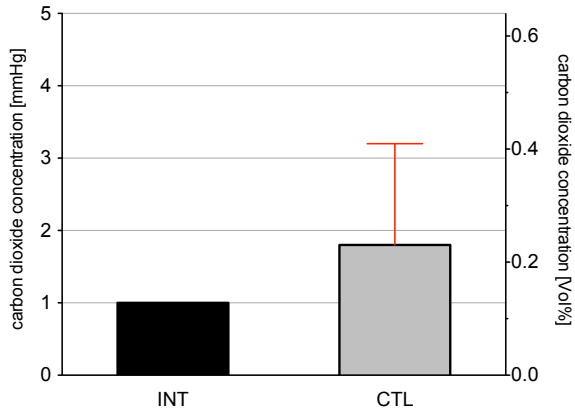

Fig. IX-3. Inspiratory CO_2 concentration of the control (CTL) and intervention (INT) group as mean with standard deviation. No standard deviation was determined for the INT group at a device limited resolution of 1 mmHg. The left y-axis shows the concentration in mmHg and the right y-axis in Vol%. There was no significant difference between the means of the two groups as determined Kruskal-Wallis test and a significance level of P<0.05.

C.IX - 7 DISCUSSION

The data in this study was collected automatically by the Draeger Inovian® database system. The reliability of data acquisition could therefore not be validated. The accuracy of record keeping with the Inovian® system has been an item of controversy.[301,302] This may affect the measurements; however despite the criticism of the data reporting, we do not expect much difference between the control and intervention group arising from this limitation, as the patients were exposed to the same system driven limitations. Any bias in these measures is likely similar in both groups. To confirm that this limitation does not affect the results, a future study could involve running a machine under controlled conditions without a patient and comparing manually recorded data with the data base, but access to an unoccupied ventilator and the weight of a few sample runs could be limited. However, random values in the exported excel file were compared to the database in order to validate the reliability of the exporting procedure into the excel file.

For many years, the impact of tidal volumes has been explored. While each anaesthesiologist can decide freely on the most appropriate tidal volume for a patient, literature generally separates tidal volume into "low" for less than 8 mL/kg, and "high" for more than 12 mL/kg bodyweight.[303–305] For a patient with a bodyweight of 65 kg, the tidal volume would hence range from 520 mL to 780 mL. This is in agreement with the tidal volumes in both groups of the study. Karalapillai found that ventilation frequencies varied from 10 - 12 breaths per minute (b/minute) and Wrigge and Pelosi found a range from 8 - 21 b/minute by comparing several randomized and controlled trials.[303,305] Either finding agrees with the frequencies in both groups of our study. Minute volumes are an indirect measure (calculated as $f * TV$) and they are therefore only shown to make the results easier to interpret.

Inspiratory CO_2 concentrations are not typically discussed in literature, but studies determining the maximum CO_2 capacity of the chemicals in these absorbers have shown the trend of the inspired CO_2 concentration over time. However, a typical level used to indicate it is time to exchange the absorber is 0.5% inspired CO_2. Both groups were below this threshold.

Expired levels of CO_2 are reported as 33.9±2.7 to 35.4±4.2 mmHg for small tidal volumes and large tidal volumes respectively by Bustmante *et al.*[306] This ranges is comparable to our findings in both groups, indicating that our groups were composed of typical subjects and that memsorb℠ did allow for safe CO_2 control.

The assignment to the control and device group could be perceived as study bias. However, patients are not believed to be able to predict their ventilation parameters. No correlation between the patient's prediction of ventilation volumes, CO_2 levels and anesthesiologists behaviour would be realistic. Therefore, no bias regarding the ventilation conditions by a patient's ability to influence group allocation is expected.

C.IX - 8 CONCLUSION

Clinically, using memsorb℠ in 10 patients and comparing CO_2 concentration parameters to 10 patients using state of the art Draegersorb Free® chemical absorbers, no significant difference could be found. Furthermore, no adverse events were recorded during the study. This means that memsorb℠ CO_2 removal equals that of a state of the art CO_2 absorber currently used in this hospital, making it an innovative and safe alternative to state-of-the-art chemical absorbers.

Chapter X DYNAMIC SYSTEM OPTIMIZATION

Optimizing a Membrane System for Carbon Dioxide Removal from Gas Mixtures in Anaesthesia Circuits under Dynamic Conditions

F Wilfart, M Soehl, J Haelssig, D Roach, G Maksym, M Schmidt

Unpublished manuscript

Clinical testing of memsorb, described in the previous chapter, showed equal CO_2 removal performance for memsorb℠ in comparison to current chemical CO_2 absorbers. However, the patient population in this study was small and memsorb℠ has to maintain the inspired CO_2 concentrations below 0.5% for 95% of all patients. Given the challenge of recruiting patients in the high percentile ranges, model predictions were developed for the final sizing memsorb℠. The model was experimentally validated for a median two 95 percentile patient scenarios. Using the validated model, a design curve was developed, showing the trade-off between sweep gas flow rate and required membrane area. Based on the design curve, a final membrane area was selected and the patient scenarios simulated.

C.X - 1 BACKGROUND

The concept of respiration and air dates back to BC. Hippocrates describes the first intubation in his book *Treatise on Air*. Mechanical ventilation in started with Paracelsus in 1550 and better ventilators developed successively until we arrived at a first medical ventilator with Positive End Expiratory Pressure (PEEP) in the late 1960's.[307] Todays medical ventilators have advanced to a "smart" level, adjusting ventilation to achieve specific pressure and volume scenarious.[308]

Patients undergoing general anaesthesia, typically receive drugs that relax their muscles. The relaxation induces respiratory suppression, making mechanical ventilation of these patients necessary. These machines are able to maintain a set tidal volume (*TV*) and respiratory frequency (*f*), delivering a defined gas mixture with oxygen and anaesthetic vapour. Due to cost and environmental reasons, the anaesthetic vapour is rebreathed by the patient after replenishing the metabolized oxygen and chemically binding and removing the metabolic end product CO_2. The total volume delivered each minute is referred to as minute volume (*MV*). The minute volume is defined per Equation 12:

$$MV = f \cdot TV \qquad (12)$$

where *MV* is the Minute Volume [L/min], *f* is the frequency in [1/min] and *TV* is the Tidal Volume [L].

The human body requires a narrow pH range in the blood. The pH is directly dependent on the CO_2 concentration in the blood ($paCO_2$).[309] During mechanical ventilation, the expired concentration of CO_2 at the end of each respiratory cycle ($EtCO_2$) is an accepted surrogate measure for the $paCO_2$, and thus an indicator of pH, eliminating the need for frequent invasive blood gas measurements.[299,300] Therefore, mechanical ventilation is adjusted in order to

maintain a safe $EtCO_2$ level. Fig.X-1 shows a sample screenshot of a typical patient monitoring system displaying the described ventilation parameters.

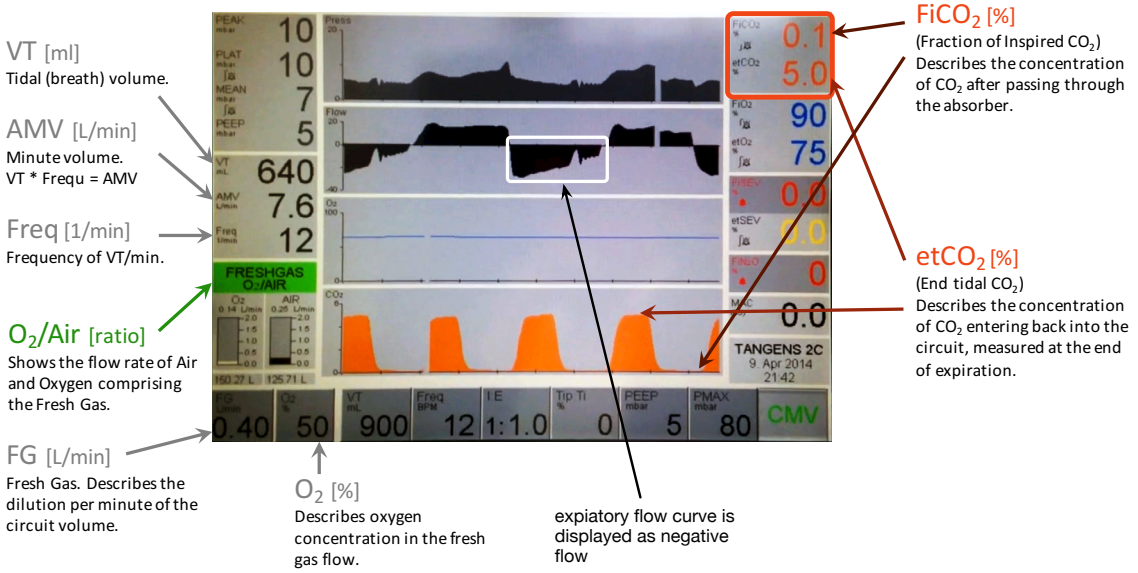

Fig. X-1. Screenshot of the anaesthesia machine monitor with ventilation parameters.

While the $EtCO_2$ reflects the ability to maintain sufficient CO_2 removal, the inspired fraction of CO_2 ($InspCO_2$ or $FiCO_2$) is also displayed. This measure is used to identify the time when the chemical CO_2 absorbent is exhausted and needs to be replaced. Typically, chemical absorbers will scrub the carbon dioxide completely. Once the inspired CO_2 fraction exceeds 0.5 vol%, the anaesthesiologist is notified by the ventilator by an alarm message, and this indicates that it is time to exchange the absorber.

However, when membrane separation is used for CO_2 removal, the rate of transfer through the membrane relies on the concentration difference between the patient gas mixture and the sweep gas on the inside of the membrane fibers, resulting in small $InspCO_2$ concentration remaining in the gas mixture. To avoid giving the anaesthesiologist the

impression, that the CO_2 filter has to be exchanged when memsorb℠ is employed, it is important to keep the majority of patients below an InspCO2 concentration of 0.5 vol%.

Hypothesis: The surface area and sweep flow rate necessary for a membrane separation based CO_2 removal system able to maintain the $InspCO_2$ in anaesthesia circuits below 0.5 vol% for 95 % of patient ventilation scenarios can be optimized using a dynamic mathematical model. This model is able to predict a final surface area and sweep flow rate.

C.X - 2 MATERIALS AND METHODS

A lung simulator (ASL 5000, IngMar Medical, Pittsburgh, PA, USA) was operated with PNEUMA, a respiratory simulation software developed by the University of Southern California.[310] The software allows the definition of lung characteristics like compliance as well as the resistance of the airways. The motor driven cylinder in the simulator is capable of a tidal volume up to 3.1 liters, and is connected through a viral filter to a y-piece. At this y-piece the inspiratory and expiratory tube from and to the anaesthesia machine (EKU Elektronik, Leiningen, Germany) are joined (Fig. X-2).

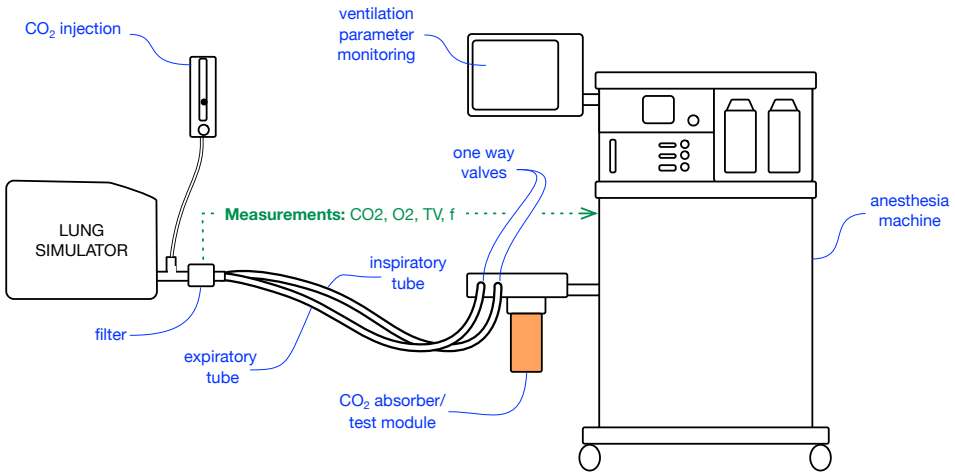

Fig. X-2 Schematic showing the connection of the anaesthesia machine to the lung simulator, including a viral filter and CO_2 injection and a CO_2 absorber in the designated mounting bracket. The absorber will be removed and the test module placed in the expiratory arm.

In between the filter and the lung simulator, an injection port allows the delivery predetermined volumes of CO_2 in order to simulate the metabolic rate of the patient case. At the viral filter (DAR™, Covidien, Dublin, Ireland), the sampling tube from the anaesthesia machine was connected, allowing the machine to continuously measure CO_2 and O_2 concentrations, and hence determine the inspiratory ($FiCO_2$) and end expiratory ($EtCO_2$) concentration of CO_2. The anaesthesia machine displayed all relevant ventilation parameters on a monitor. The CO_2 absorber mounted in the expiratory arm at the anaesthesia machine was replaced by the test module. The test module was supplied with oxygen as a sweep gas (not shown). Fig. X-3 shows a schematic diagram of the experimental setup.

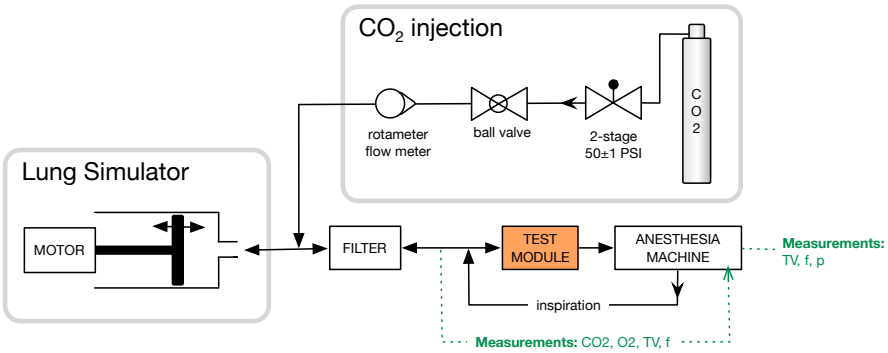

Fig. X-3. Schematic setup of the anaesthesia ventilator, lung simulator, CO_2 injection and test module in the expiratory arm

The *TV*, *f* and $EtCO_2$ was set on the ventilator for each case patient, while the lung simulator was set to typical compliance and resistance. Screenshots of the monitor were taken in order to record the resulting curves and parameters after the system reached steady state.

C.X - 2.1 Modeling

A mathematical model was developed using Simulink® (MathWorks®, Natick, MA, United States). The previously developed "tanks-in-series" model [256] has been developed to include the ability to predict dynamic responses to ventilation paramters.[311]

As input for the model, 95th percentile patient cases were defined as described in the following section in order to reflect average and extreme cases of both flow and CO_2 concentrations.

The modeling was based on a membrane permeance one standard deviation below the reported mean of the manufacturing variability of the membrane.[256,258] For validation purposes, data was collected using the double pass module described in C.VII - 3.

C.X - 2.1.1 Ventilator and Lung Model

A single compartment lung model was chosen to represent the respiratory system of different subject scenarios. The model consists of a resistance (R_{rs}) that represents a single Newtonian resistive tube and an elastance (E_{rs}) that represents the stored elastic energy largely from surface tension, but also from tissue stretching and some gas compression. E_{rs} is known to be the inverse of the respiratory system's compliance (C_{rs}). The airway opening pressure (P_{awo}) that is caused by the mechanical ventilator's applied pressure generates a flow Q_v that is shaped depending on R_{rs} and E_{rs}.[312] The model was built using Simulink® to represent the respiratory system.[311]

One common lung model was used for all patient scenarios with a single lung compartment compliance (E_{rs}) of 30 mL/cmH_2O and a resistance (R_{rs}) of 10 cmH_2O/L/s resulting in a total system compliance of 54.7 to 60.2 mL/cmH_2O for the defined patient cases. This total compliance range is in agreement with a range of 29.4 to 80.8 mL/cmH_2O in

literature.[313] The resistance would be considered on the high side from a perspective of lung parameters compared to 2.3 to 10.7 $cmH_2O/L/s$,[313] but it should be considered that typical resistance from the tubus is not given in this setup and was therefore compounded into the airway resistance.

C.X - 2.1.2 Membrane System Model

The ventilator and lung model developed above was connected to the membrane system model (Fig. X-4).

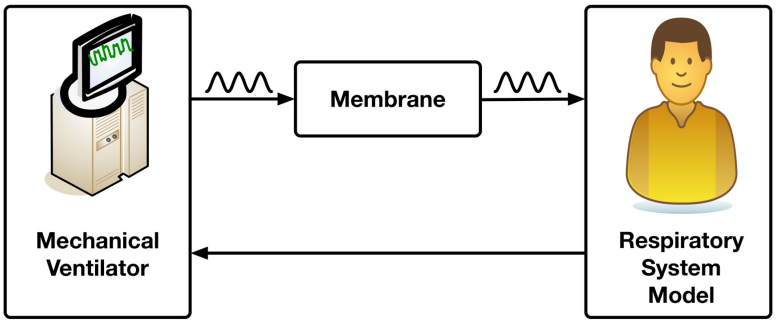

Fig. X-4. Schematic of the Ventilator and Lung model and its connection the membrane system model

The membrane system model was developed by sub-dividing the membrane module into discrete, completely-mixed sub-sections (Fig. X-5). This approach is similar to the "tanks-in-series" approach that is commonly employed in chemical reaction engineering, and it is also representative of a coarse grid finite volume discretization of the conservation equations.

The model was derived by writing both total and component material balance equations for both the permeate and retentate sides of each sub-section. The balance equations were coupled using the local permeation rates, which were predicted using the permeance values that were determined from the mini-module experiments (Chapter V).[258]

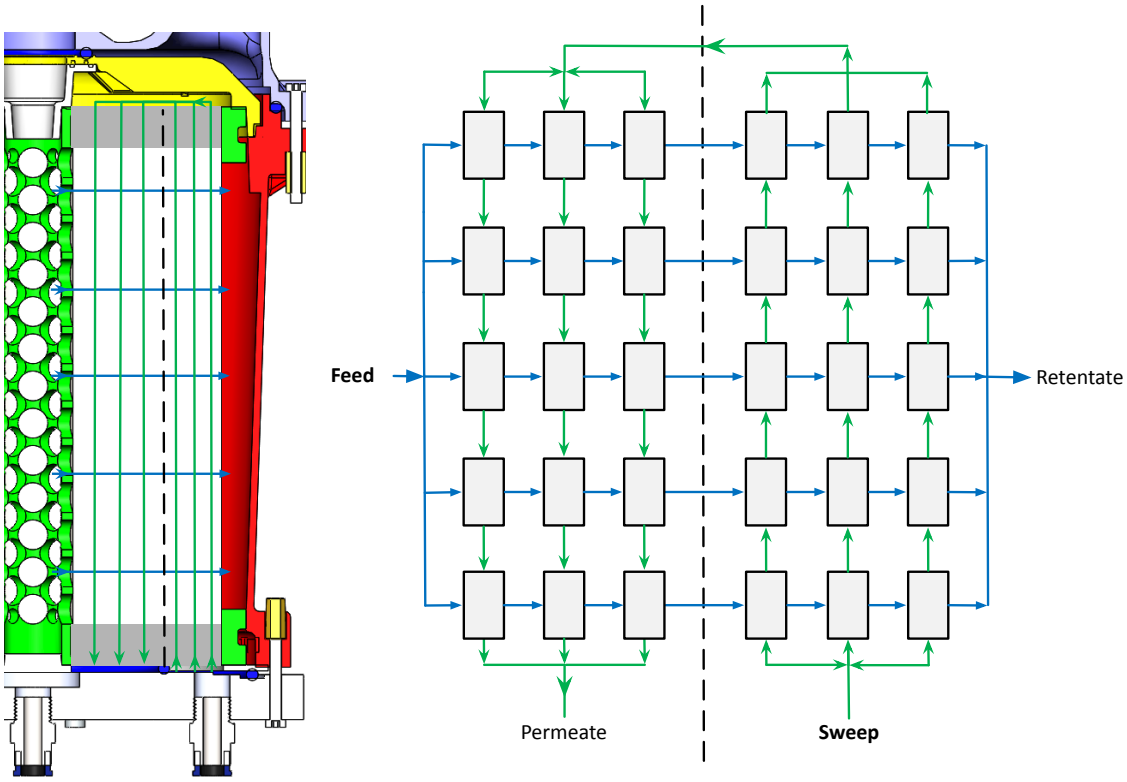

Fig. X-5. (LEFT) Cross section of the modules used for experimental validation with schematic feed (blue) and sweep (green) flows (C.VII - 3). (RIGHT)Schematic of discrete module subdivisions for a multiple pass arrangement.

As shown in Fig. X-5, for all sub-sections that are not connected to the pure feed or pure sweep, the inlet conditions are defined by the outlet conditions from the previous sub-section. The entire system therefore becomes tightly coupled. The number of discrete sub-sections required in both the feed and the sweep directions was determined by comparing the simulation results to curves from residence time distribution studies that were performed using an inert gas tracer.[311] The dynamic material balance equations and flux relationships form a coupled system of differential and algebraic equations (DAE). The dynamic model was implemented in Simulink®, to allow easy coupling to the ventilator and lung models. The model was solved using MATLAB's® implicit multistep ode15s solver.

C.X - 2.2 Patient Cases

Given the dynamic nature of the ventilation flow rates, and difficulties recruiting patients close to a 95%ile of ventilation parameters, a dynamic mathematical model will be employed to determine the final size and sweep flow of the unit. After approval by the local ethics board, all available ventilation data from 2013-2014 at the Nova Scotia Health Authority (NSHA) were analyzed in order to define median and 95%ile patients. Data were taken from the Inovian® anaesthesia database (Draegerwerk, Luebbeck, Germany) and the data transfer from the Inovian® system to the excel data file was validated by the database manager of the Department of Anaesthesia by comparing random datum points in the exported excel file to the database.

As described above, the MV is adjusted by the anaesthesiologist in order to keep the $EtCO_2$ in a safe range. The 95%ile of MV is determined and the resulting 95%ile dataset is analyzed for the 95%ile of TV and $EtCO_2$.

C.X - 3 RESULTS

This ventilator and lung model described above was given inputs for tidal volume, ventilation frequency, peak pressures, and lung compliance and resistance, to output a realistic flow and pressure curve.[311] The output of this model was then used as input for the membrane system model described above.[311] Fig. X-6 shows the combined model output including flow and the inspiratory and expiratory CO_2 concentrations from the two modules.

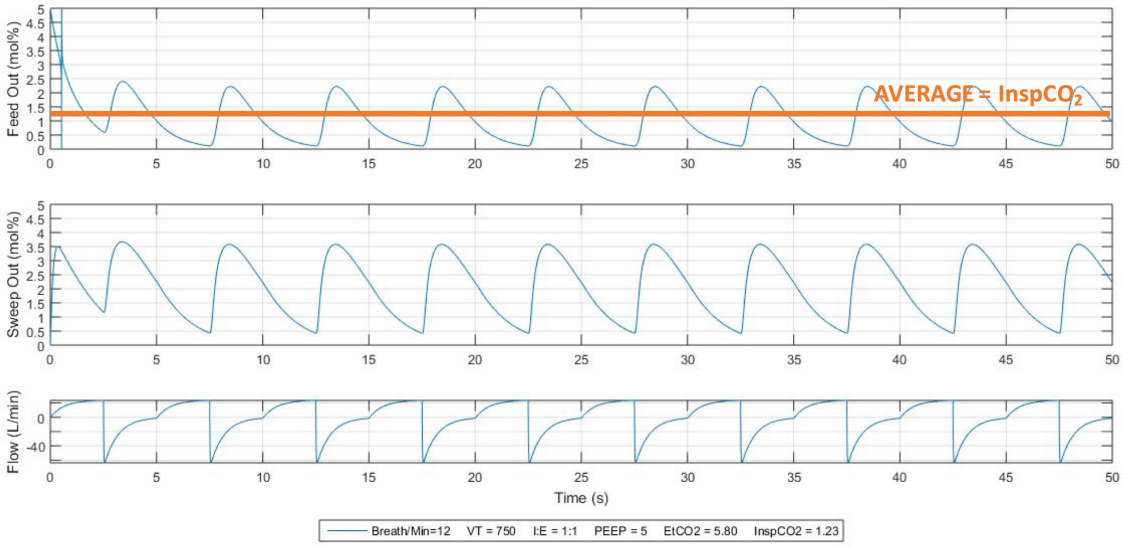

Fig. X-6. Screenshot of the patient monitor for VT = 750 mL, Frequency = 12, $EtCO_2$ = 5.8%. Orange line represents the mixed feed output = $inspCO_2$.

The expired and inspired concentration of CO_2 was then experimentally confirmed. Fig. X-7 shows a screenshot of the corresponding experimental data.

*Fig. X-7. Sample screenshot of the ventilation parameter read out for 12 * 750ml and 5.8% $EtCO_2$.*

Three (3) patient cases were determined from the dataset obtained from the Inovian® system for 2013 and 2014, described above. Using the parameters for these three patient cases, the simulation and experimental results were recorded (Table 10). The tidal volumes set on the anesthesia machines do sometimes vary slightly from the actual volume delivered by up to 50 mL.

Table 10. Patient cases statistically determined from the 2013 -2014 dataset from the Nova Scotia Health Authority and corresponding simulation (SIM) and experimental (EXP) data.

			$EtCO_2$ [Vol%]		$InspCO_2$ [Vol%]	
Patient Case	**TV [mL]**	**F [b/minute]**	**EXP**	**SIM**	**EXP**	**SIM**
Median Patient	725	8	5.8	5.8	1.1	1.07
95%ile Patient	775	12	5.8	5.8	1.3	1.23
95%ile Patient	930	10	4.8	4.8	1.0	1.03

A good fit between simulated and experimental data could be observed.

In addition to the simulations and experiments performed to validate the model, a variety of simulations were performed to determine the most appropriate size for a full-scale module. For this purpose, the model was used to determine the surface area required to adjust the higher of the two 95%ile cases for an InspCO_2 of 0.45±0.05. This procedure was repeated for several sweep flow rates and resulted in the design curve shown in Fig. X-8.

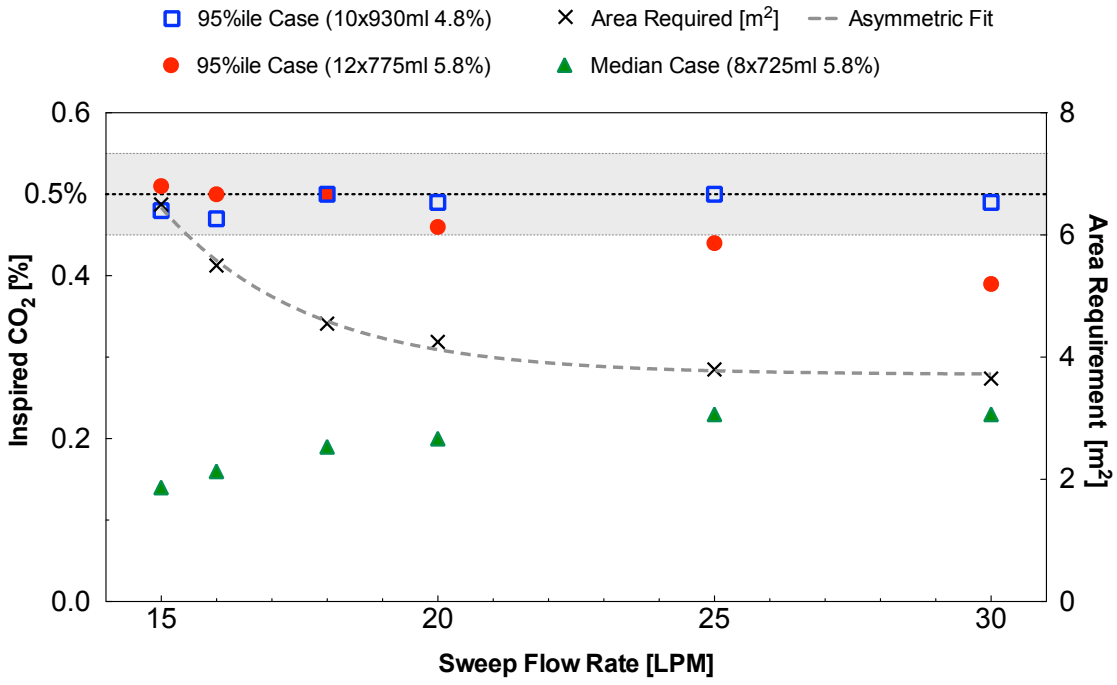

Fig. X-8 *Design Curve with three key findings: (i) dominant 95%ile at Inspired CO_2 of 0.45±0.05 % (left y-axis, horizontal black dashed line) and (ii) the respective required area (right y-axis, dashed grey line, asymmetric fit with 5 ambiguous parameters) along with (iii) the respective median patient data. All data are shown as function of the sweep flow rate in liters per minute.*

Plotting only the area as function of sweep flow rate, it can be observed that it is an inverse relationship (Asymmetric LogEC50 fit with 5 ambiguous parameters and r^2=0.9945) and the rate of decrease in area requirements drops less at higher sweep flow rates, with only marginal differences above a sweep flow rate of 20 Lpm.

Using this membrane area, it was then possible to predict the expected inspired CO_2 concentrations for the three patient cases at a variety of sweep flow rates. The resulting predictions of inspired CO_2 concentration as a function of sweep flow rate for the three patient cases is shown in Fig. X-9.

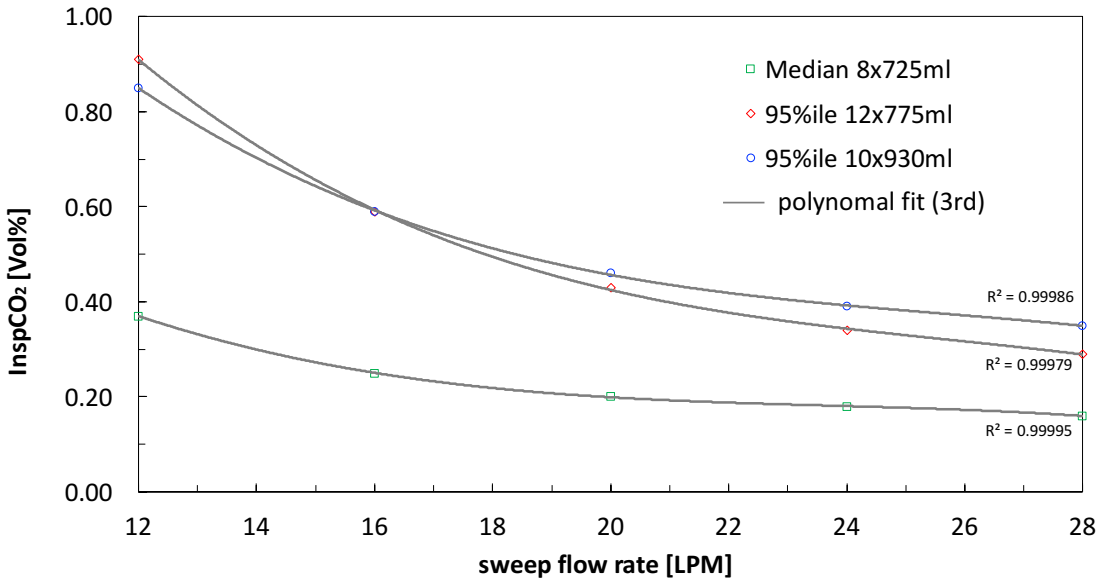

Fig. X-9. Computed performance for a 4.6sqm module and the three patient cases. 3rd order polynomial fits where provided to guide the eye

From the results, it appears that a membrane with an area of approximately 4.6 m^2 should maintain the inspired CO_2 concentration below 0.45 ± 0.05% for the 95%ile patient cases, provided that a sufficient sweep flow rate above 15 Lpm is supplied. This provides a membrane surface that is larger than required for most patients, but robust against changes in sweep flow rate. The trade-off between sweep gas flow and the inspired concentration of CO_2 is most prominent at high CO_2 loads and high minute volumes, where sufficient sweep is necessary to avoid a decrease in driving force caused by the large amounts of CO_2 permeated to the sweep side.

C.X - 4 DISCUSSION

The data in this study were exported from the Draeger Inovian® database system. This method is the standard data collection process that serves for regulation of real patient cases in all medical and legal aspects. While not designed for research, we accept its reliability even though the reliability of the automated data acquisition could therefore not be validated. As described in Chapter 9, accurate record keeping with the Inovian® system has been discussed controversially.[301,302] However, given the large dataset, collection of data under more controlled or validated conditions was not possible, and with a large data set, effects of random recording errors would not be significant. Since averages are calculated from the total duration of recording, not of ventilation, this could be affected by artefact readings at the beginning and end of cases when the patient is not connected yet or already extubated. These limitations may mask temporary extremes in either of the recordings, but the error this would cause on the average parameter data is likely small, and likely smaller than the safety margin contained in the conservative membrane permeability that was used for modeling.

As discussed in Chapter IV, typical tidal volumes are in the range of 8 – 12 ml/kg bodyweight.[303–305] Karalapillai found that ventilation frequencies varied from 10-12 b/minute and Wrigge and Pelosi found a range from 8-21 b/minute by comparing several randomized and controlled trials.[303,305] Expired levels of CO_2 were reported as 31.2 to 39.6 mmHg by Bustmante *et al.*[306] Generally, the literature data does not discredit the median patient cases, however there was no literature found describing 95%ile patient data to be compared with the analysis presented in this study.

C.X - 5 CONCLUSION

Using existing ventilation data distributions from a large sample of patients, as input for a dynamic ventilator model, a final membrane area was determined. This membrane system was predicted to maintain inspired CO_2 levels below the determined threshold of 0.5% in 95% of patient cases. While a smaller size of memsorb® has already shown to maintain safe expired CO_2 levels in a clinical study with typical patients (Chapter IX), the predicted final size is expected to maintain the inspired CO_2 levels in the comfort level of anaesthesiologists, for more than 95% of the population thus should help, supporting the effective adoption in the marketplace, ultimately achieving the goal of providing safer, more environmentally friendly anaesthesia, saving cost of anaesthetic vapours. These predictions have to be validated by further testing a prototype with the model specifications simulated here in a clinical study with a larger patient cohort.

Chapter XI CONCLUSION

This chapter provides summary of the content and achievements of this thesis, conclusions of the findings, as well as a selection of my journal articles and presentations relevant to this thesis.

C.XI - 1 THESIS SUMMARY

Society faces rising costs in healthcare systems throughout the developed world. Additionally, a stagnating younger working age population means increasing pressure on fewer people to carry the cost. A growing group of elderly, and therefore more frail patients require surgery. In recent years, brain damage after surgery and anaesthesia has been discovered with incidences in a range of 25 to 80%. This brain damage is known as Post Operative Cognitive Decline (POCD), a multifactorial and generally permanent problem. This contributes to the burden on society, financially and socially.

Most surgeries are performed under general anaesthesia; in a majority of cases involving anaesthetic vapours. The safety of these anaesthetic vapours has been discussed since their discovery and they have been compared to an alternative general anaesthesia approach using Total Intravenous Anaesthesia (TIVA). No conclusive evidence has been found as to which is the safer approach. However, given the intraoperative physiological stability, ability to adjust depth of anaesthesia quickly and fast wakeup times, the typical choice is most often vapours.

These vapours are delivered in a rebreathing circuit to reduce cost and therefore require the removal of the metabolic end product, CO_2 through the use of an absorber. The chemicals in these absorbers are known, since their first application in anaesthesia in 1920, to react with the anaesthetic vapours and produce harmful substances that are known to be toxic to the kidney and brain. While no direct causality between these substances and POCD has been established, the evidence of harm to the kidney and brain along with brand new evidence linking neurological cellular damage to POCD, make it desirable to address this problem. A safer CO_2 filter will therefore contribute to safer anaesthesia, and in turn lead to better outcomes and reduced health care costs, which was reviewed in Chapters I and II.

CO_2 absorbers are required for the safe and efficient use of anaesthetic vapours in rebreathing circuits. Comparing literature findings regarding the safety of anaesthetic vapours and TIVA, it could be shown that vapours are and will be a comparably safe and relevant choice of anaesthetic, warranting the need for an innovative and safe CO_2 absorber, allowing for better outcomes and reduced cost as described in Chapter III.

Analyzing the need for CO_2 removal in anaesthesia led to the conclusion that PMP dense skin membranes would be a great technology for the safe and efficient removal of CO_2 from anaesthetic rebreathing circuits, retaining anaesthetic vapours. The main contribution of this thesis was the demonstration that these membranes can be modified and used for this purpose. The main purpose of using membranes instead of chemical absorbents lies in the hypothesis that these membranes do not produce any harmful substances when used with anaesthetic vapours, providing safer anaesthesia delivery. It was shown in a "worst case scenario" of anaesthetic vapour exposure based bench setup, that no volatile substances are created. This makes these membranes a valid and safe choice to replace chemical CO_2 absorbents (Chapter IV).

It was demonstrated, that dense skin PMP membranes can be used to separate CO_2 from these anaesthetic vapours. Using a unique approach, a custom membrane was characterized and optimized for CO_2 transport in balance with selectivity near operating conditions, ultimately facilitating the recovery of CO_2 while retaining the anaesthetic vapours in the circuit (Chapter V).

The fact that these membranes do not allow anaesthetic vapours to pass through and that they are used in some oxygenators makes for a clinically relevant observation. Some hospitals desire the use of anaesthetic vapours during cardiac surgery on the cardiopulmonary

bypass (CPB). During these surgeries, the CPB takes over the function of the heart, maintaining blood circulation. As there is no blood flow through the lungs during the use of a CPB, a membrane-based oxygenator is used to deliver oxygen to the patient and remove CO_2. TIVA is typically used to provide anaesthesia. Given the desirable properties of anaesthetic vapours, some hospitals have been delivering anaesthetic vapours to these oxygenators in order to deliver them to the patient's blood. Using a bench setup, it was shown that oxygenators using dense skin PMP membranes severely restrict the vapour delivered to the patient, wasting the majority of anaesthetic vapours and hence causing excessive and unnecessary costs. Furthermore, despite best efforts, these oxygenators, for safety reasons, are not capable of reliably delivering all of the anaesthetic vapour passing through the oxygenator to a scavenging system, exposing operating room personnel to occupational hazards (eg birth defects, etc.) (Chapter VI).

Other systems that use compressors, vacuums and alcolotic liquids have been explored but are prohibitively complex and costly. Furthermore, they are a risk to patient safety due to the very high or low pressures and chemical hazards. Using a unique approach, a passive membrane system was designed. This system was based on hollow fiber dense skin PMP membranes and optimized to achieve maximum CO_2 removal performance with minimal sweep flow rates. The optimization achieved residual CO_2 concentrations low enough to make this solution valid for anaesthesia systems while not increasing the resistance of the rebreathing circuit (Chapter VII).

The composition of a gas mixture exhaled by humans contains a multitude of substances produced by the metabolism and high levels of water vapour. When breathing openly, these substances, due to their low concentration, are diluted so much by the large surrounding air

volume that they are not detectable when air is inhaled from the same large volume (i.e. a room). When patients are ventilated using rebreathing circuits, these substances accumulate over time and, dependent on the fresh gas flow rate diluting the circuit content, can reach dangerous levels. Membranes can change their permeation and selectivity properties in presence of other gases and water. As representative physiological gas mixtures are virtually impossible to achieve in a bench setup, nor can models account for the actual behavior, *in vivo* experiments are important in order to confirm, that modules made from dense skin PMP membranes operate as predicted from simulations and bench experiments.

Before moving into human patients, a preclinical study in animals is a good way to minimize risk and also test the developed prototype within controlled parameters, and provides an *in vivo* proof of concept. Pigs provide a good animal model for a pre-clinical study in the field of anaesthesia, as they allow for the use of standard operating room equipment and have a comparable metabolism and blood composition. It was shown that a dense skin PMP membrane-based module operates under physiological conditions as predicted and allows for stabile long-term anaesthesia using anaesthetic vapours (Chapter VIII).

After confirming the basic functionality, a clinical pilot-study was designed comparing 10 patients using state of the art chemical CO_2 absorbers with 10 patients using the membrane-based module. It was demonstrated that the $EtCO_2$ did not differ between the two groups and that stable long-term anaesthesia was achieved in both groups (Chapter IV).

While safety is the most important aspect of this novel membrane based solution that has to be considered, the system also has to be designed such that it will be adopted into operating rooms. Without widespread adoption, the system would not be able to actually improve patient outcomes, save money and protect the environment. Chemical CO_2 absorbers

wear out every 1-3 days and need to be replaced in order to maintain safe $EtCO_2$ levels. Anaesthesiologists are trained to monitor the inspired fraction of CO_2, replacing the absorber when it reaches around 0.5%. As monitoring the inspired fraction of CO_2 is a warning sign for all anaesthesiologists and some machines even have alarms set on the machines, it is an important design criterion to keep 95% of all patients below this limit, although the device would be safe even above these levels. In order to be able to predict the module's response to patient scenarios and therefore to be able to properly predict the final size, a mathematical model has been developed, that can simulate performance based on typical ventilation (Chapter X).

C.XI - 2 THESIS CONCLUSION

In conclusion, despite many other technological advances in anaesthesia and in gas separation, none have been demonstrated to be useful in the removal of the remnants of the patient's metabolism in the anaesthetic process. The method invented by Draeger in 1925 for removing CO_2 out of an anaesthetic circuit via the use of soda lime persists today because limited research to advance existing technology has shown nothing else viable. While there have been small advances in improving the types of gas and gas mixtures and in understanding the flow rates and in removing the particulates, bacteria and viruses in the anaesthetic circuit- at their core all still rely on the same absorbent system that is approaching 100 years old.

The membrane system described in this thesis is the first major development and the first system to not rely on soda lime (or similar substances) and the associated chemical reaction to remove the CO_2.

As importantly, this system addresses the most three pressing problems associated with anaesthesia in the medical system today; safety, financial efficiency and good environmental stewardship.

The described innovative and revolutionary membrane system provides immediate and meaningful relief from the financial pressures that health care systems are experiencing. It does this directly by dramatically reducing the volume of expensive anaesthetic vapours required in each operation by reducing the fresh gas flow into the anaesthetic circuit to the amount physiologically needed. The control of pollution by dilution becomes unnecessary. Ultra-low flow, in the sense of metabolic anaesthesia, becomes a reality without the known downsides that have persisted until now. It provides a safer anaesthesia result for the patient by removing the toxic degradation products caused by the chemical absorber and by accumulating harmful metabolic byproducts generated by the patient. It is anticipated that this will have a positive impact on the incidence of POCD in the elderly. The follow-on effect of cost increases to the system, driven by the cognitive impairment of patients post operatively, is significant. This will further assist with the reduction of overall costs in the health care system.

More broadly, the dramatic reduction of environment-polluting halogenated gasses escaping unused into the atmosphere will benefit the entirety of the planet and all of its inhabitants, including people. It is not only the avoidance of their release, but also the reduction in the harms associated with their production, transportation and disposal that will benefit the world.

The introduction of memsorb℠ into the market will mark a turning point in the delivery of anaesthesia.

C.XI - 3 FUTURE OUTLOOK

As the membrane is further refined and developed, its potential future uses are many and unexplored. It may be possible to filter for other, unknown and as yet not understood metabolic byproducts and open the way for new vapour application systems that do not rely on vapourizers anymore but on direct injection into the membrane system.

As a next step, memsorb℠ with a final size as predicted in Chapter X has been approved by Health Canada and NSHA Ethics to be tested in a 6 month trial and least 400 patients. Three main scientific questions will be addressed:

(1) Validating the model predictions in Chapter X for CO_2 levels and vapour retention.

(2) Gas sampling in order to compare the concentrations of by-products in a control group using chemical absorbers and a device group using memsorb℠.

(3) Validating that memsorb℠ is not accumulating patient's metabolic by-products (i.e. methane) where chemical absorbers do.

(4) Validating that memsorb significantly reduces the combined vapour loss from (i) absorption in the chemical absorbers and (ii) the dilution necessary due to the by-products of CO_2 absorbers.

C.XI - 4 CONTRIBUTIONS ARISING FROM THIS THESIS

C.XI - 4.1 Statement of Original Contributions

In all chapters of this thesis, I was the lead investigator, responsible for all major areas of concept formation, data collection and analysis, as well as manuscript composition. Megan Soehl, as part of her master's thesis, implemented and ran the mathematical models. Without the guidance of Prof. Dr. med. M. Schmidt, this thesis would not have been successful. For further details on the author's contributions to each manuscript, please refer to Appendix C – Statement of Contribution. The following briefly lists the original contributions I have made described within this thesis.

- After reviewing the relevant literature, I presented the need for increased safety in anesthesia and for cost savings and reduction of environmental impact. (Chapter II)
- After reviewing the relevant literature, I described the continued need for anaesthetic vapors, hence CO_2 absorbers in anaesthesia. (Chapter III)
- Based on published evidence for a potential selectivity of anesthetic vapours, I demonstrated the selectivity for anaesthetic vapours of dense PMP membranes by characterizing oxygenators in a physiological bench setup I designed using human blood,. This overcame the limitations of prior studies that used liquids with different solubilities for these anaesthetic vapours (Chapter IV). This led to my investigations of PMP membranes for the application of removing CO_2 in anaesthesia circuits. This is the first time PMP membranes have been optimized for gas separation of anaesthetic vapours. This was a significant first step towards replacing chemical CO_2 absorbers in anaesthesia circuits and increasing safety, financial efficiency and environmental stewardship described in Chapter V.

- I demonstrated that PMP membranes do not produce harmful volatile byproducts when contacting anaesthetic vapours, hence eliminating the toxic degradation products caused by the chemical absorber (Chapter VI). There is some early evidence that these byproducts are linked to POCD, and therefore these membranes are expected to have a positive impact on the incidence of POCD in the elderly. The follow-on effect of cost increases to the system driven by the cognitive impairment of patients post operatively would be significant, further assisting with the reduction of overall costs in the health care system. Furthermore, it would dramatically reduce the environment-polluting halogenated anaesthetic vapours escaping unused into the atmosphere, benefiting the entirety of the planet and all of its inhabitants, including people.

- I developed a novel passive system based on PMP membranes and I optimized the system with the help of simulations executed by collaborators (Chapter VII).

- In the context of pig and human studies, I could demonstrate that the novel, passive, membrane-based CO2 filter can maintain CO2 levels in a target range considered safe by the practicing anesthesiologist (Chapter VIII and IV).

- By analysing the NSHA patient population from 2013 and 2014 for the definition of a 95 percentile minute volume and tidal volume, I was able to use them as input for a co-developed dynamic model to predict a final design for the CO_2 filter. This final design optimizes cost and size while keeping within the design constraints, and would make the delivery of anesthesia safer. The final design is currently ready for long term testing in a clinical study (Chapter X).

C.XI - 4.2 Relevant Journal Articles

Are anaesthetic vapours a safe choice for elderly patients or are CO_2 absorbers irrelevant for future anaesthesia? **F Wilfart**, M Schmidt, *Unpublished Manuscript.*

Characterization of dense PMP membranes for the separation of carbon dioxide from anaesthetic vapours in low pressure applications. **F Wilfart**, M Soehl, N Kilcup, J Haelssig, *Unpublished Manuscript.*

Delivery of Vapours on Cardiopulmonary Bypass using Different Oxygenator Membranes. **F Wilfart**, A McFadgen, B Kent, K Gardiner, M Schmidt, *Biomed Eng. (NY) 2011:265–70*

Design of a membrane System for Carbon Dioxide Removal from Gas Mixtures under Normobaric Conditions in Anaesthesia Circuits. **F Wilfart**, M Soehl, N Kilcup, D Roach, M Schmidt, G Maksym, J Haelssig, *Unpublished Manuscript.*

Optimizing a Membrane System for Carbon Dioxide Removal from Gas Mixtures in Anaesthesia Circuits under Dynamic Conditions. **F Wilfart**, M Soehl, J Haelssig, D Roach, G Maksym, M Schmidt, *Unpublished Manuscript.*

C.XI - 4.3 Relevant Patents

An anaesthetic circuit having a hollow fiber membrane. DC Roach, M Schmidt, F Wilfart, *PCT/CA2013/001080*

C.XI - 4.4 Relevant Posters and Podium Presentations

F Wilfart, D Roach, J Haelssig, O Hung, M Schmidt, *Membrane separation as novel solution for co2 removal in anaesthesia - clinical data*, Anaesthesia Research Day, Halifax, NS, 2015 *PODIUM*

Wilfart F, Roach D, Haelssig J, Schmidt M, *Membrane Separation as Novel Solution for CO_2 Removal in Anaesthesia Circuits*, BMES, San Antonio, TX, 2014 *PODIUM*

Wilfart F, Roach D, Haelssig J, Soehl M, Schmidt M, *Membrane separation as novel solution for CO_2 removal in anaesthesia circuits*, Anaesthesia Research Day, Halifax, NS, 2014 *PODIUM*

Wilfart F, Haelssig J, Soehl M, Schmidt M, Roach D, Haelssig J, Schmidt M, *Characterization of polymer membranes*, Biomedical Engineering Research Day, Halifax, NS, 2014 *PODIUM*

Wilfart F, *Development and Assessment of a New Solution for Carbon Dioxide Removal from Anaesthesia Loop*, School of Biomedical Engineering Research Day, Halifax, NS, 2013 *PODIUM*

Wilfart F, McFadgen A, Kent B, Gardiner K, Schmidt M, *Evaluation of the performance of different oxygenators on the cardiopulmonary bypass*, School of Biomedical Engineering Research Day, 2012 *PODIUM*

Wilfart F, Gardiner K, Kent B, Schmidt M, *Usage of Organ Protective Vapours on the CPB in Children*, Dalhousie University Cardiac Research Day, 2012 *POSTER*

Wilfart F, McFadgen A, Kent B, Gardiner K, Schmidt M K. *Delivery of vapours on cardiopulmonary bypass using different oxygenator membranes*. Proceedings of the IASTED International Conference Biomedical Engineering (Biomed 2011): 265-270, 2011 PODIUM

Wilfart F, McFadgen A, Kent B, Gardiner K, Schmidt M, *Usage of organ protective vapours on the CPB in elderly patients*, Cardiac Research Day, Dalhousie University, Halifax 2011 *PODIUM*

Wilfart F, McFadgen A, Kent B, Gardiner K, Schmidt M, *Usage of organ protective vapours on the CPB in elderly patients*, Anaesthesia Research Day, Dalhousie University, Halifax 2011 *PODIUM*

F Wilfart, K Gardiner, B Kent, A McFadgen, M Schmidt, *Usage of organ protective vapours on the CPB in elderly patients*, FICCDAT: CMBEC 34, Toronto, Canada, 2011 *PODIUM*

Wilfart F, McFadgen A, Kent B., Gardiner K, Schmidt M., *Delivery of vapours on cardiopulmonary bypass using different oxygenator membranes*, IASTED International Conf. on Biomedical Engineering, Innsbruck, Austria, 2011 *PODIUM*

Wilfart F, McFadgen A, Kent B, Gardiner K, Schmidt M, *Delivery of vapours on cardiopulmonary bypass using different oxygenator membranes*, Biomedical Engineering, 2011 *PODIUM*

BIBLIOGRAPHY

1. Eger 2nd EI, Brandstater B, Saidman LJ, Regan MJ, Severinghaus JW, Munson ES. Equipotent alveolar concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon and nitrous oxide in the dog. Anesthesiology 1965;26:771–7.
2. Clinical Anesthesia. Lippincott Williams & Wilkins, 2009.
3. Whalen FX, Bacon DR, Smith HM. Inhaled anesthetics: An historical overview. Best Pract Res Clin Anaesthesiol 2005;19:323–30.
4. Long CW. An Account of the First Use of Sulphuric Ether by Inhalation as an Anaesthetic in Surgical Operations. South Med Surg Journ 1949;35:275–7.
5. Greene NM. A consideration of factors in the discovery of anesthesia and their effects on its development. Anesthesiology 1971;35:515–22.
6. Henderson VE, Smith AHR. Propylene impurities - hexenes and hexanes. J Pharmacol Exp Ther 1936:319–27.
7. Lucas GHW, Henderson VE. A New Anaesthetic Gas: Cyclopropane. Can Med Assoc J 1929:173–5.
8. J. A. Stiles, W. B. Neff EAR, Waters RM. Cyclopropane as an Anesthetic Agent: A Preliminary Clinical Report. Anesth Analg 1934:56–60.
9. Wawersik J. The history of anesthesia apparatus: basic principles. Anaesthesist 1982;31:541–8.
10. Wawersik J. History of anesthesia in Germany. J Clin Anesth 1991;3:235–44.
11. Wawersik J. History of chloroform anesthesia. Anaesthesiol Reanim 1997;22:144–52.
12. Calverley RK. Fluorinated Anesthetics. I. The Early Years 1932-1946. Surv Anesthesiol 1986;30:170–2.
13. Robbins BH. Preliminary studies of the anesthetic activity of fluorinated hydrocarbons. J Pharmacol Exp Ther 1946;86:197–204.
14. Calverley RK. Fluorinated Anesthetics. II. Fluroxene. Surv Anesthesiol 1987;31:126–9.
15. Suckling CW, Virtue RW. Some Chemical and Physical Factors in the Development of Fluothane. Surv Anesthesiol 1959;3:19.
16. Oyama T, Kotrly K, Barboriak J, Henschel EO. Nephrotoxic effect of methoxyflurane anesthesia. A case report. Der Anaesthesist 25, 37–8 (1976).
17. Mazze RI. Methoxyflurane nephropathy. Environ Health Perspect 1976;Vol.15:111–9.
18. Bergstrand A, Collste L, Franksson C. Methoxyflurane and renal injury. Lakartidningen 1971;68:3323–46.
19. Brunson JG, Eckman PL, Campbell JB. Increasing Prevalence of Unexplained Liver Necrosis. N Engl J Med 1957:52–6.

20. Dobkin AB, Nishioka K, Gengaje DB, Kim DS, Evers W, Israel JS. Ethrane (Compound 347) anesthesia: a clinical and laboratory review of 700 cases. Anesth Analg 1969;48:477–94.

21. A U 3476860. Halomethyl fluoroisopropyl ethers as anesthetic agents. 1966.

22. Stevens WC. New Halogenated Anesthetics: Enflurane and Isofluranerane. West J Med 1970:47.

23. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: a new inhalational anesthetic agent. Anesth Analg 1975;54:758–66.

24. Young J, Apfelbaum JL. Inhalational Anesthetics: Desflurane and Sevoflurane. Rev Lit Arts Am 1995;8180.

25. Prielipp RC. An anesthesiologist's perspective on inhaled anesthesia decision-making. Am J Health Syst Pharm 2010;67:S13–20.

26. Brown Burnell Jr. Sevoflurane: Introduction and Overview. Anesth Analg 1995.

27. Ishizawa Y. General Anesthetic Gases and the Global Environment. Anesth Analg 2011;112:213–7.

28. Hanne P, Marx T, Musati S, Santo M, Suwa K, Morita S. Xenon: uptake and costs. Int Anesthesiol Clin 2001;39:43.

29. Vecil M, Stefano CDI, Saltarini M, Monte ADE. Low flow, minimal flow and closed circuit system inhalational anesthesia in modern clinical practice. Signa Vitae 2008;3 Suppl 1:S33–6.

30. Butler TC. Theories of general anesthesia. J Pharmacol Exp Ther 1950;98:121–60.

31. Lee W, Kim M, Kang S, Kim S, Lee J. Type of anaesthesia and patient quality of recovery: a randomized trial comparing propofol-remifentanil total i.v. anaesthesia with desflurane anaesthesia. Br J Anaesth 2015;114:663–8.

32. Eger EI. Characteristics of anesthetic agents used for induction and maintenance of general anesthesia. Am J Health Syst Pharm 2004;61.

33. Lauta E, Abbinante C, Gaudio A Del, Aloj F, Fanelli M, Vivo P de, Tommasino C, Fiore T. Emergence times are similar with sevoflurane and total intravenous anesthesia: results of a multicenter RCT of patients scheduled for elective supratentorial craniotomy. J Neurosurg Anesthesiol 2010;22:110–8.

34. Tonner PH. Balanced anaesthesia today. Best Pract Res Clin Anaesthesiol 2005;19:475–84.

35. Przybylo HJ, Tarbell SE, Stevenson GW. Mask fear in children presenting for anesthesia: Aversion, phobia, or both? Paediatr Anaesth 2005;15:366–70.

36. U.S. Congress Office of Technology Asessment. Improved Technologies and Practice. In: Industrial Energy Efficiency. DIANE Publishing, 1993:88.

37. How much carbon dioxide is produced per kilowatthour when generating electricity with fossil fuels? - FAQ - U.S. Energy Information Administration (EIA). Available at: https://www.eia.gov/tools/faqs/faq.cfm?id=74&t=11. Accessed April 26, 2016.

38. Allam RJ. Improved oxygen production technologies. Energy Procedia 2009;1:461–70.

39. Stabernack CR, Eger EI, Warnken UH, Fürster H, Hanks DK, Ferrell LD, Förster H. Sevoflurane degradation by carbon dioxide absorbents may produce more than one nephrotoxic compound in rats. Can J Anesth 2003;50:249–52.

40. Konat GW, Kofke WA, Miric S. Toxicity of compound A to C6 rat glioma cells. Metab Brain Dis 2003;18:11–5.

41. Li YC, Zhang YN, LIU SJ, ZHOU YM, Wang CS, Gong YL, LI EY. Degradation products of different water content sevoflurane in carbon dioxide absorbents by gas chromatography-mass spectrometry analysis. Chin Med J (Engl) 2011;124:1050–4.

42. Bito H, IKEDA K. Degradation products of sevoflurane during low-flow anaesthesia. Br J Anaesth 1995;74:56–9.

43. Cunningham DD, Huang S, Webster J, Mayoral J, Grabenkort RW. Sevoflurane degradation to compound A in anaesthesia breathing systems. Br J Anaesth 1996;77:537–43.

44. Keller, Callan, Prokocimer, Delgado-Herra, Friedman, Hoffman, Wooding, Cusick K. Inhalation Toxicity Study of a Haloalkene Degradamt of Sevoflurnae, Compound A (pife), in Sprague-Dawley Rats. Anesthesiology.

45. Struys M, Bouche M, Rolly G, Vandevivere Y, Dyzers D, Goeteyn W, Versichelen L, Bocxlaer J Van, Mortier E. Production of compound A and carbon monoxide in circle systems: an in vitro comparison of two carbon dioxide absorbents. Anaesthesia 2004;59:584–9.

46. Marini F, Bellugi I, Gambi D, Pacenti M, Dugheri S, Focardi L, Tulli G. Compound A, formaldehyde and methanol concentrations during low-flow sevoflurane anaesthesia: comparison of three carbon dioxide absorbers. Acta Anaesthesiol Scand 2007;51:625–32.

47. Keijzer C, Perez RSGM, Lange JJ de. Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. Acta Anaesthesiol Scand 2007;51:31–7.

48. Rappold T, Laflam A, Hori D, Brown C, Brandt J, Mintz CD, Sieber F, Gottschalk A, Yenokyan G, Everett A, Hogue CW. Evidence of an association between brain cellular injury and cognitive decline after non-cardiac surgery. Br J Anaesth 2016;116:83–9.

49. Ekbom K, Assareh H, Anderson RE, Jakobsson JG. The effects of fresh gas flow on the amount of sevoflurane vaporized during 1 minimum alveolar concentration anaesthesia for day surgery: a clinical study. Acta Anaesthesiol Scand 2007;51:290–3.

50. Doolke A. The effects of lowering fresh gas flow during sevoflurane anaesthesia: a clinical study in patients having elective knee arthroscopy. Ambul Surg 2001;9:95–8.

51. Ryan SM, Nielsen CJ. Global warming potential of inhaled anesthetics: application to clinical use. Anesth Analg 2010;111:92–8.

52. Langbein T, Sonntag H, Trapp D, Hoffmann A, Walms W, Röth E-P, Mörs V, Zellner R. Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. Br J Anaesth 2000;84:534–6.

53. Bosenberg M. Anaesthetic gases : environmental impact and alternatives. South African J Anaesth … 2011;17:345–8.

54. Ishizawa Y. Special article: general anesthetic gases and the global environment. Anesth Analg 2011;112:213–7.

55. Berry J. Volatile Anesthetic Reclamation: It's About Time (and Temperature)!

56. Office of Transportation and Air Quality. Average Annual Emissions and Fuel Consumption for Gasoline-Fueled Passenger Cars and Light Trucks -- Emission Facts., 2008.

57. Fatheree RS, Leighton BL. Acute respiratory distress syndrome after an exothermic Baralyme-sevoflurane reaction. Anesthesiology 2004;101:531–3.

58. Wu J, Previte JP, Adler E, Myers T, Ball J, Gunter JB. Spontaneous Ignition, Explosion, and Fire with Sevoflurane and Barium Hydroxide Lime. Anesthesiology 2004;101:534–7.

59. Castro BA, Freedman A, Craig WL, Lynch C. Explosion within an Anesthesia Machine: Baralyme®, High Fresh Gas Flows and Sevoflurane Concentration. Anesthesiology 2004;101:537–9.

60. Woehlck HJ. Sleeping with uncertainty: anesthetics and desiccated absorbent. Anesthesiology 2004;101:276–8.

61. Yamakage M, Takahashi K, Takahashi M, Satoh J-I, Namiki a. Performance of four carbon dioxide absorbents in experimental and clinical settings. Anaesthesia 2009;64:287–92.

62. Kuhns JF. SODA LIME. :1–9.

63. Morio M, Fujii K, Satoh N, Imai M, Kawakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, others. Reaction of Sevoflurane and its degradation products with soda lime - toxicity of the byproducts. Anesthesiology 1992;77:1155.

64. Lu Y, Wu X, Dong Y, Xu Z, Zhang Y, Xie Z. Anesthetic sevoflurane causes neurotoxicity differently in neonatal naïve and Alzheimer disease transgenic mice. Anesthesiology 2010;112:1404–16.

65. Perouansky M, Hemmings H. Neurotoxicity of General Anesthetics: Cause for Concern?[Editorial]. Anesthesiology 2009;111:1365–71.

66. Stratmann G. Neurotoxicity of Anesthetic Drugs in the Developing Brain. Anesth Analg 2011;113:1170–9.

67. Keijzer C, Perez RSGM, Lange JJ De. Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. Acta Anaesthesiol Scand 2007;51:31–7.

68. Keijzer C. Interactions of inhalational anesthetics and carbon dioxide absorbents Measurements of carbon monoxide and compound A in an anesthetic circuit. 2007.

69. Bouche MP, Bocxlaer JF Van, Rolly G, Versichelen LF, Struys MM, Mortier E, Leenheer a P De. Quantitative determination of vapor-phase compound A in sevoflurane anesthesia using gas chromatography-mass spectrometry. Clin Chem 2001;47:281–91.

70. Eger EI, Koblin DD, Bowland T, Ionescu P, Laster MJ, Fang Z, Gong D, Sonner J, Weiskopf RB. Nephrotoxicity of Sevoflurane Versus Desflurane Anesthesia in Volunteers. Surv Anesthesiol 1998;42:132.

71. Zhang C, Li C, Xu Z, Zhao S, Li P, Cao J, Mi W. The effect of surgical and psychological stress on learning and memory function in aged C57BL/6 mice. Neuroscience 2016.

72. Hovens IB, Leeuwen BL Van, Mariani MA, Kraneveld AD, Schoemaker RG. Postoperative cognitive dysfunction and neuroinflammation; Cardiac surgery and abdominal surgery are not the same. 2016.

73. Woehlck HJ, Dunning M, Gandhi S, Chang D. Indirect Detection of Intraoperative Carbon monoxide exposure by mass spectrometry during isoflurane anesthesia. Anesthesiology 1995:213–7.

74. Kobayashi S, Bito H, Morita K, Katoh T, Sato S. Amsorb Plus and Drägersorb Free, two new-generation carbon dioxide absorbents that produce a low compound A concentration while providing sufficient CO2 absorption capacity in simulated sevoflurane anesthesia. J Anesth 2004;18:277–81.

75. W. R. Grace & CO. Sodasorb Manual., 1993.

76. Sodasorb. Manual of CO2 absorption. 1993:17–17.

77. Kummar P, Korula G, Kumar S, Saravanan P. Unusual Cause of Leak in Datex Aisys. Anesth Analg 2009;109:1350.

78. Bryson G, Wyand A. Evidence-based clinical update: general anesthesia and the risk of delirium and postoperative cognitive dysfunction. Can J Anesth 2006;53:669.

79. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic Management and One-Year Mortality After Noncardiac Surgery. Anesth Analg 2005;100:4–10.

80. Lewis MC, Nevo I, Paniagua M a, Ben-Ari a, Pretto E, Eisdorfer S, Davidson E, Matot I, Eisdorfer C. Uncomplicated general anesthesia in the elderly results in cognitive decline: does cognitive decline predict morbidity and mortality? Med Hypotheses 2007;68:484–92.

81. Rasmussen LS. Postoperative cognitive dysfunction: Incidence and prevention. Best Pract Res Clin Anaesthesiol 2006;20:315–30.

82. Silverstein JH, Steinmetz J, Reichenberg A, Harvey PD, Rasmussen LS. Postoperative cognitive dysfunction in patients with preoperative cognitive impairment: which domains are most vulnerable? Anesthesiology 2007;106:431–5.

83. Etzioni D a, Liu JH, Maggard M a, Ko CY. The aging population and its impact on the surgery workforce. Ann Surg 2003;238:170–7.

84. Saving the Heart Can Sometimes Mean Losing the Memory - NYTimes.com. Available at: http://www.nytimes.com/2000/09/19/science/saving-the-heart-can-sometimes-mean-losing-the-memory.html?pagewanted=all. Accessed March 15, 2016.

85. Monk TG, Meiler S, MAyfield J, Head A. Can We Alter Long-Term Outcome ? The Role of Inflammation and Immunity in the Perioperative Period (Part II). Reg Anesth 2004;19:1–16.

86. Zuccherelli L. "Killing Me Softly?" South African J Anaesth Analg 2007;13:5–10.

87. IARS. SmartTots Releases Consensus Statement Regarding Anesthesia Safety in Children. Available at: http://www.smarttots.org/media/smarttots-releases-consensus-statement-regarding-anesthesia-safety-in-children. Accessed December 18, 2012.

88. Fane T. Membrane separations - 100 years of achievements and challenges. 2008.

89. Lonsdale HK. The growth of membrane technology. J Memb Sci 1982;10:81–181.

90. Strathmann H, Giorno L, Drioli E. Introduction. In: An Introduction to Membrane and Science Technology., 2006:3–13.

91. Car A, Stropnik C, Yave W, Peinemann K-V. Tailor-made Polymeric Membranes based on Segmented Block Copolymers for CO 2 Separation. Adv Funct Mater 2008;18:2815–23.

92. Prasser C, Zelenka M, Gruber M, Philipp a, Keyser a, Wiesenack C. Elimination of sevoflurane is reduced in plasma-tight compared to conventional membrane oxygenators. Eur J Anaesthesiol 2008;25:152–7.

93. Wilfart FM, McFadgen A, Kent B, Gardiner K, Schmidt MK. Delivery of Vapors on Cardiopulmonary Bypass using Different Oxygenator Membranes. Biomed Eng (NY) 2011:265–70.

94. Wijmans JG, Baker RW. The solution-diffusion model : a review. 1995;107:1–21.

95. Heintz A, Stephan W. A generalized solution diffusion-model of the pervaporation process through composite membranes. J Memb Sci 1994;89:153–69.

96. Riecke M. Process and device for separating carbon dioxide from a breathing gas mixture by means of a fixed site carrier membrane. 2008.

97. Graham T. LV . On the absorption and dialytic separation of gases by colloid septa. 1866;32:401–20.

98. Kruczek B, Lashkari S. Challenges in Microflow Measurements. In: Urquiza DG, ed. Flow Measurement. InTech, 2012.

99. Yampolskii Y. Polymeric Gas Separation Membranes. Chem Eng Sci 2012;45:3298–311.

100. Baker RW. Vapor and Gas Separation by Membranes. In: Advanced Membrane Technology and Applications., 2008:559–80.

101. Morisato A. Synthesis and gas permeation properties of poly(4-methyl-2-pentyne). J Memb Sci 1996;121:243–50.

102. Robeson LM. The upper bound revisited. J Memb Sci 2008;320:390–400.

103. Rowe BW, Robeson LM, Freeman BD, Paul DR. Influence of temperature on the upper bound: Theoretical considerations and comparison with experimental results. J Memb Sci 2010;360:58–69.

104. Lin H, Yavari M. Upper bound of polymeric membranes for mixed-gas CO 2 / CH 4 separations. J Memb Sci 2015;475:101–9.

105. Thompson GH, Murray, J. M., Fee JPH. Absorption of carbon dioxide and anaesthetic gases by zeolite 5A. In: Royal Academy of Medicine in Ireland.Vol 165., 1996:306–306.

106. Sanchez-Lainez J, Zornoza B, Mayoral A, Berenguer-Murcia Á, Cazorla-Amorós D, Tellez C, Coronas J. Beyond the H2/CO2 upper bound: one-step crystallization and separation of nano-sized ZIF-11 by centrifugation and its application in mixed matrix membranes. J Mater Chem A 2015;7:6549–56.

107. Ulldemolins M, Martín-Loeches I, Llauradó-Serra M, Fernández J, Vaquer S, Rodríguez A, Pontes C, Calvo G, Torres A, Soy D. Piperacillin population pharmacokinetics in critically ill patients with multiple organ dysfunction syndrome receiving continuous venovenous haemodiafiltration: effect of type of dialysis membrane on dosing requirements. J Antimicrob Chemother 2016:dkv503 – .

108. Baxter Corp. Isoflurane (Forane). 2012:1–7.

109. Baxter. Desflurane. 2011.

110. Piramal Critical Care. Sevoflurane. 2011.

111. Abbvie. SEVORANE AF Product Monograph. 2014:1–36.

112. Meyer H. Zur theorie der alkoholnarkose. Naunyn Schmiedebergs Arch Pharmacol 1899.

113. Overtone C. Studien über die Narkose. Fischer, Jena 1901.

114. Pike LJ. Rafts defined: a report on the Keystone Symposium on Lipid Rafts and Cell Function. J Lipid Res 2006;47:1597–8.

115. Meyer H. Zur Theorie der Alkoholnarkose - 3. Mitteilung: Der Einfluss wechselnder Temperatur auf Wirkungsstärke und Teilungscoefficient der Narcotica. Arch für Exp Pathol und Pharmakologie 1901;46:338–46.

116. Missner A, Pohl P. 110 years of the Meyer-Overton rule: predicting membrane permeability of gases and other small compounds. Chemphyschem 2009;10:1405–14.

117. Robin G, Altamirano F, Esteve E, Pessah IN, Allen PD, Lopez JR. Na+/H+ Exchange Blockers Reveal the Existence of a Skeletal Muscle Ca2+/H+ Exchanger, which is Altered in Malignant Hyperthermia Muscle Cells. Biophys J 2015;108:504a.

118. AbbVie. Product monograph: Isoflurane., 2011.

119. Baxter. Desflurane. 2010:1–19.

120. Knolle E, Heinze G, Gilly H. Small carbon monoxide formation in absorbents does not correlate with small carbon dioxide absorption. Anesth Analg 2002;95:650–5, table of contents.

121. Doi. Airway irritation volatile anesthetics humans. 1993:122–6.

122. Tanaka S, Tsuchida H, Nakabayashi K, Seki S, Namiki a. The effects of sevoflurane, isoflurane, halothane, and enflurane on hemodynamic responses during an inhaled induction of anesthesia via a mask in humans. Anesth Analg 1996;82:821–6.

123. Eshima RW, Maurer A, King T, Lin B-K, Heavner JE, Bogetz MS, Kaye AD. A comparison of airway responses during desflurane and sevoflurane administration via a laryngeal mask airway for maintenance of anesthesia. Anesth Analg 2003;96:701–5, table of contents.

124. Kapoor M, Vakamudi M. Desflurane - Revisited. J Anaesthesiol Clin Pharmacol 2012;28:92.

125. Sakai EM, Connolly LA, Klauck JA. Inhalation Anesthesiology and Volatile Liquid Anesthetics: Focus on Isoflurane, Desflurane, and Sevoflurane. Pharmacotherapy 2005;25.

126. Iijima T, Nakamura Z, Iwao Y, Sankawa H. The epileptogenic properties of the volatile anesthetics sevoflurane and isoflurane in patients with epilepsy. Anesth Analg 2000;91:989–95.

127. Fukuda H, Hirabayashi Y, Shimizu R, Saitoh K, Mitsuhata H. Sevoflurane is equivalent to isoflurane for attenuating bupivacaine-induced arrhythmias and seizures in rats. Anesth Analg 1996;83:570–3.

128. Hoerauf KH, Koller C, Taeger K, Hobbhahn J. Occupational exposure to sevoflurane and nitrous oxide in operating room personnel. Int Arch Occup Environ Health 1997;69:134–8.

129. Marx T, Schmidt M, Schirmer U, Reinelt H. Pollution of the environment and the workplace with anesthetic gases. Int Anesthesiol Clin 2001;39:15–27.

130. Hoerauf K, Harth M, Wild K, Hobbhahn J. Occupational exposure to desflurane and isoflurane during cardiopulmonary bypass: is the gas outlet of the membrane oxygenator an operating theatre pollution hazard? Br J Anaesth 1997;78:378–80.

131. Stephan Mierdl Christian Byhahn, MD, Ulf Abdel-Rahman, MD, Georg Matheis, MD, and Klaus Westphal, MD MD, Mierdl S, Byhahn C, Abdel-Rahman U, Matheis G, Westphal K. Occupational Exposure to Inhalational Anesthetics During Cardiac Surgery on cardiopulmonary bypass. Ann Thorac Surg 2003:1924–7.

132. Flack LA. Nurse exposure to waste anesthetic gases in a post anesthesia care unit. 2006.

133. Summer G, Lirk P, Hoerauf K, Riccabona U, Bodrogi F, Raifer H, Deibl M, Rieder J, Schobersberger W. Sevoflurane in Exhaled Air of Operating Room Personnel. Crit Care Med 2003:1070–3.

134. Ishikawa S, Ishikawa H, Shindo T, Yoshida T, Shimoyama Y, Satomi T, Fujii S, Hamamoto Y, Iino M, Fukao A. Effects of occupational environmental controls and work management on chromosomal damage in dental technicians in Japan. Int J Hyg Environ Health 2013;216:100–7.

135. Wiesner G, Schiewe-Langgartner F, Lindner R, Gruber M. Increased formation of sister chromatid exchanges, but not of micronuclei, in anaesthetists exposed to low levels of sevoflurane. Anaesthesia 2008;63:861–4.

136. Szyfter K, Szulc R, Mikstacki A, Stachecki I, Rydzanicz M, Jałoszyński P. Genotoxicity of inhalation anaesthetics: DNA lesions generated by sevoflurane in vitro and in vivo. J Appl Genet 2004;45:369–74.

137. El-Ebiary A, Abuelfadl A, Sarhan N, Othman M. Assessment of genotoxicity risk in operation room personnel by the alkaline comet assay. Hum Exp Toxicol 2012;32:563–70.

138. Xu X, Pan C, Hu J, Liu X, Li Y, Wang H, Chen Y, Dong H, Dai T, Xu L. Effects of isoflurane inhalation on the male reproductive system in rats. Environ Toxicol Pharmacol 2012;34:688–93.

139. Eger EI. Fetal injury and abortion associated with occupational exposure to inhaled anesthetics. AANA J 1991;59:309–12.

140. Vouriot A, Gauchard GC, Chau N, Nadif R, Mur J-M, Perrin PP. Chronic Exposure to Anesthetic Gases Affects Balance Control in Operating Room Personnel. Neurotoxicology 2005;26:193–8.

141. Weiskopf RB, Eger EI, Ionescu P, Yasuda N, Cahalan MK, Freire B, Peterson N, Lockhart SH, Rampil IJ, Laster M. Desflurane does not produce hepatic or renal injury in human volunteers. Anesth Analg 1992;74:570–4.

142. Sulbaek Andersen MP, Nielsen OJ, Wallington TJ, Karpichev B, Sander SP. Medical intelligence article: assessing the impact on global climate from general anesthetic gases. Anesth Analg 2012;114:1081–5.

143. Tsuchiya M, Takahashi M, Tomoda M, Ueda W, Hirakawa M. Halothane impairs the bioenergetic functions of isolated rat liver mitochondria. Toxicol Appl Pharmacol 1990;104:466–75.

144. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, Frosch MP, Crosby G, Tanzi RE. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid ??-protein level in vivo. Ann Neurol 2008;64:618–27.

145. Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, Eckenhoff RG, Eckenhoff MF. Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. Neurobiol Aging 2008;29:1002–10.

146. Zhang Y, Xu Z, Wang H, Dong Y, Shi HN, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. Ann Neurol 2012;71:687–98.

147. Zhang Y, Dong Y, Xu Z, Xie Z. Propofol and magnesium attenuate isofluraneinduced caspase-3 activation via inhibiting mitochondrial permeability transition pore. Med Gas Res 2012;2:20.

148. Wang H, Xu Z, Feng C, Wang Y, Jia X, Wu A, Yue Y. Changes of learning and memory in aged rats after isoflurane inhalational anaesthesia correlated with hippocampal acetylcholine level. Ann Fr Anesth Reanim 2012;31:e61–6.

149. Wu X, Lu Y, Dong Y, Zhang G, Zhang Y, Xu Z, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-alpha, IL-6, and IL-1alpha. Neurobiol Aging 2012;33:1364–78.

150. Lin D, Zuo Z. Isoflurane induces hippocampal cell injury and cognitive impairments in adult rats. Neuropharmacology 2011;61:1354–9.

151. Liu J, Peijun Wang, Xiaoqing Zhang, Wei Zhang GG. Effects of different concentration and duration time of isoflurane on acute and long-term neurocognitive function of young adult C57BL/6 mouse. Int J Clin Exp Pathol 2014;7:5828–36.

152. Culley DJ, Baxter MG, Crosby C a., Yukhananov R, Crosby G. Impaired acquisition of spatial memory 2 weeks after isoflurane and isoflurane-nitrous oxide anesthesia in aged rats. Anesth Analg 2004;99:1393–7.

153. Culley DJ, Loguinov A, Yukhananov R, Crosby G. General anesthesia does not reduce life expectancy in aged rats. Anesth Analg 2005;102:956–9.

154. Kalenka A. Isoflurane anesthesia elicits protein pattern changes in rat hippocampus. J Neurosurg Anesthesiol 2010;22:144.

155. Zhou ZW, Shu Y, Li M, Guo X, Pac-Soo C, Maze M, Ma D. The glutaminergic, GABAergic, dopaminergic but not cholinergic neurons are susceptible to anaesthesia-induced cell death in the rat developing brain. Neuroscience 2011;174:64–70.

156. Callaway JK, Jones NC, Royse CF. Isoflurane induces cognitive deficits in the Morris water maze task in rats. Eur J Anaesthesiol 2012;29:239–45.

157. Zhang F, Zhu Z, Liu D, Zhang C, Gong Q, Zhu Y. Emulsified isoflurane anesthesia decreases brain‐derived neurotrophic factor expression and induces cognitive dysfunction in adult rats. Exp Ther Med 2014:471–7.

158. Callaway JK, Jones NC, Royse AG, Royse CF. Sevoflurane Anesthesia Does Not Impair Acquisition Learning or Memory in the Morris Water Maze in Young Adult and Aged Rats. Anesthesiology 2012;117:1091–101.

159. Ren X, Wang Z, Ma H, Zuo Z. Sevoflurane postconditioning provides neuroprotection against brain hypoxia-ischemia in neonatal rats. Neurol Sci 2014:1401–4.

160. Zhang F, Feng X, Zeng Q, Wang B, Wilhelmsen K, Li Q, Cao X, Yu B. Sevoflurane induced amnesia inhibits hippocampal Arc expression partially through 5-hydroxytryptamine-7 receptors in the bilateral basolateral amygdala in rats. Neurosci Lett 2014;562:13–8.

161. Callaway JK, Jones NC, Royse AG, Royse CF. Memory Impairment in Rats after Desflurane Anesthesia is Age and Dose Dependent. 2015;44:995–1005.

162. Hinkelbein J, Feldmann RE, Kalenka A. Time-dependent alterations of cerebral proteins following short-term normobaric hyperoxia. Mol Cell Biochem 2010;339:9–21.

163. Culley DJ, Raghavan S V., Waly M, Baxter MG, Yukhananov R, Deth RC, Crosby G. Nitrous oxide decreases cortical methionine synthase transiently but produces lasting memory impairment in aged rats. Anesth Analg 2007;105:83–8.

164. Lee IH, Culley DJ, Baxter MG, Xie Z, Tanzi RE, Crosby G. Spatial memory is intact in aged rats after propofol anesthesia. Anesth Analg 2008;107:1211–5.

165. Feldmann RE, Maurer MH, Hunzinger C, Lewicka S, Buergers HF, Kalenka A, Hinkelbein J, Broemme JO, Seidler GH, Martin E, Plaschke K. Reduction in rat phosphatidylethanolamine binding protein-1 (PEBP1) after chronic corticosterone treatment may be paralleled by cognitive impairment: a first study. Stress 2008;11:134–47.

166. Xie Z, Dong Y, Maeda U, Moir RD, Xia W, Culley DJ, Crosby G, Tanzi RE. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. J Neurosci 2007;27:1247–54.

167. Zhang G, Dong Y, Zhang B, Ichinose F, Wu X, Culley DJ, Crosby G, Tanzi RE, Xie Z. Isoflurane-induced caspase-3 activation is dependent on cytosolic calcium and can be attenuated by memantine. J Neurosci 2008;28:4551–60.

168. Zhang Y, Dong Y, Wu X, Lu Y, Xu Z, Knapp A, Yue Y, Xu T, Xie Z. The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. J Biol Chem 2010;285:4025–37.

169. Xu, Z., Dong, Y., Wu, X., Zhang, J., McAuliffe, S., Pan, C., … Xie Z. The Potential Dual Effects of Anesthetic Isoflurane on Aβ- Induced Apoptosis. Curr Alzheimer Res 2011;8:741–52.

170. Zhang B, Dong Y, Zhang G, Moir RD, Xia W, Yue Y, Tian M, Culley DJ, Crosby G, Tanzi RE, Xie Z. The Inhalation Anesthetic Desflurane Induces Caspase Activation and Increases Amyloid β-Protein Levels under Hypoxic Conditions. J Biol Chem 2008;283:11866–75.

171. Zhang L, Zhang J, Dong Y, Swain C a, Zhang Y, Xie Z. The potential dual effects of sevoflurane on AKT/GSK3β signaling pathway. Med Gas Res 2014;4:5.

172. Rundshagen I. Postoperative cognitive dysfunction. Dtsch Arztebl Int 2014;111:119–25.

173. Tachibana S, Hayase T, Osuda M, Kazuma S, Yamakage M. Recovery of postoperative cognitive function in elderly patients after a long duration of desflurane anesthesia: a pilot study. J Anesth 2015:3–6.

174. Ding F, Zheng L, Luo T. Desflurane anesthesia and postoperative cognitive function. J Anesth 2015:2002.

175. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, Jolles J, Papaioannou A, Abildstrom H, Silverstein JH, Bonal J a, Raeder J, Nielsen IK, Korttila K, Munoz L, Dodds C, Hanning CD, Moller JT. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47:260.

176. Farag E, Chelune GJ, Schubert A, Mascha EJ. Is depth of anesthesia, as assessed by the Bispectral Index, related to postoperative cognitive dysfunction and recovery? Anesth Analg 2006;103:633–40.

177. Monk TG, Weldon BC, Garvan CW, Dede DE, Aa MT van der, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008;108:18–30.

178. Xie Z, Moir RD, Romano DM, Tesco G, Kovacs DM, Tanzi RE. Hypocapnia Induces Caspase-3 Activation and Increases Aß Production. Neurodegener Dis 2004;1:29–37.

179. Xie Z, Tanzi RE. Alzheimer's disease and post-operative cognitive dysfunction. Exp Gerontol 2006;41:346–59.

180. Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, Crosby G, Tanzi RE. Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. J Gerontol A Biol Sci Med Sci 2006;61:1300–6.

181. Hubert JP, Kiernan PD, Welch JS, ReMine WH, Beahrs OH. The surgical management of bleeding stress ulcers. Ann Surg 1980;191:672–9.

182. Mauney FM, Ebert PA, Sabiston DC. Postoperative myocardial infarction: a study of predisposing factors, diagnosis and mortality in a high risk group of surgical patients. Ann Surg 1970;172:497–503.

183. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, Vallet B, Vincent J-L, Hoeft A, Rhodes A. Mortality after surgery in Europe: a 7 day cohort study. Lancet (London, England) 2012;380:1059–65.

184. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis 2015;10:93.

185. Hall A, Leuwer M. Side Effects of Drugs Annual 32 - A worldwide yearly survey of new data and trends in adverse drug reactions and interactions. Elsevier, 2010.

186. Kharasch ED, Schroeder JL, Bammler T, Beyer R, Srinouanprachanh S. Gene expression profiling of nephrotoxicity from the sevoflurane degradation product fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl Ether ("Compound A") in Rats. Toxicol Sci 2006;90:419–31.

187. Kharasch ED, Schroeder JL, Sheffels P, Liggitt HD. Influence of sevoflurane on the metabolism and renal effects of compound A in rats. Anesthesiology 2005;103:1183–8.

188. Laster MJ, Eger EI. Temperatures in soda lime during degradation of desflurane, isoflurane, and sevoflurane by desiccated soda lime. Anesth Analg 2005;101:753–7, table of contents.

189. Liebert AD, Chow RT, Bicknell BT, Varigos E. Neuroprotective Effects Against POCD by Photobiomodulation: Evidence from Assembly/ Disassembly of the Cytoskeleton. J Exp Neurosci 2016.

190. Silbert B, Evered L, Scott DA. Cognitive decline in the elderly: is anaesthesia implicated? Best Pract Res Anaesthesiol 2011;25:379–93.

191. Monk TG. Perioperative Care and the Prevention of Delirium. 2014.

192. TIPS - Membrana GmbH Solutions for Healthcare and Industrial Filration. Available at: http://www.membrana.com/technology/manufacturing/tips. Accessed March 15, 2016.

193. 510(k) Summary for Novalung GmbH, K072362. 2007. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf7/K072362.pdf. Accessed March 16, 2016.

194. Schlack W, Biermann E, Graf B, Kazmaier S, Obermayer A, Werner C, Zink W, Züchner K, Dietrich W, Schirmer U. Volatile Anästhetika während extrakorporaler Zirkulation bei herzchirurgischen Eingriffen. Anaesthesiol Intensivmed 2006;47:482–9.

195. The Vacuum Technology Book. Pfeiffer Vacuum GmbH, 2009.

196. Elokhin V a., Ershov TD, Levshankov a. I, Nikolaev VI, Elizarov a. Y. Application of a mass spectrometer as a capnograph. Tech Phys 2010;55:1814–6.

197. Gothard J, Busst C, Branthwaite MA, Davies NJH, Denison DM. Applications of respiratory mass spectrometry to intensive care. … 1980;35:890–5.

198. National Center for Health S. Health, United States. Heal United States, 2014 With Spec Featur Adults Aged 55-64 2015.

199. Health expenditure, total (% of GDP). Available at: http://data.worldbank.org/indicator/SH.XPD.TOTL.ZS/countries/1W-US-CA-EU?order=wbapi_data_value_2013 wbapi_data_value wbapi_data_value-last&sort=asc&display=graph. Accessed February 28, 2016.

200. Lubitz J, Cai L, Kramarow E, Lentzner H. Health, life expectancy, and health care spending among the elderly. N Engl J Med 2003;349:1048–55.

201. Comans TA, Peel NM, Hubbard RE, Mulligan AD, Gray LC, Scuffham PA. The increase in healthcare costs associated with frailty in older people discharged to a post-acute transition care program. Age Ageing 2016:afv196.

202. Promoting Safe and Effective Drugs for 100 Years.

203. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical Risk Factors, Morbidity, and Mortality in Elderly Patients. J Am Coll Surg 2006;203:865–77.

204. Turner AJ, Nikolova S, Sutton M. The effect of living alone on the costs and benefits of surgery amongst older people. Soc Sci Med 2016;150:95–103.

205. Leung JM, Tsai TL, Sands LP. Preoperative Frailty in Older Surgical Patients Is Associated with Early Postoperative Delirium. Anesth Analg 2011;112:1199–201.

206. Feiss P, Demontoux MH, Colin D. Anesthetic gas and vapor saving with minimal flow anesthesia. Acta Anaesthesiol Belg 1990;41:249–51.

207. Cotter SM, Petros AJ, Dore CJ, Barber ND, White DC. Low-flow anaesthesia. Practice, cost implications and acceptability. Anaesthesia 1991;46:1009–12.

208. Bengtson JP, Sonander H, Stenqvist O. Comparison of costs of different anaesthetic techniques. Acta Anaesthesiol Scand 1988;32:33–5.

209. Ishizawa Y. General anesthetic gases and the global environment. Anesth Analg 2011;112:213–7.

210. Forster P, Ramaswamy V, Artaxo P, Berntsen T, Betts R, Fahey DW, Haywood J, Lean J, Lowe DC, Myhre G, Nganga J, Prinn R, Raga G, Schulz M, Dorland R Van. Changes in Atmospheric Constituents and in Radiative Forcing. Chapter 2. 2007.

211. Feldman JM. Managing fresh gas flow to reduce environmental contamination. Anesth Analg 2012;114:1093–101.

212. Wiesenack C, Wiesner G, Keyl C, Gruber M, Philipp A, Ritzka M, Prasser C, Taeger K. In vivo uptake and elimination of isoflurane by different membrane oxygenators during cardiopulmonary bypass. Anesthesiology 2002;97:133–8.

213. Mauviel G, Berthiaud J, Vallieres C, Roizard D, Favre E. Dense membrane permeation: From the limitations of the permeability concept back to the solution-diffusion model. J Memb Sci 2005;266:62–7.

214. Li J-L, Chen B-H. Review of CO2 absorption using chemical solvents in hollow fiber membrane contactors. Sep Purif Technol 2005;41:109–22.

215. Kruczek B, Frisch H, Chapanian R. Analytical solution for the effective time lag of a membrane in a permeate tube collector in which Knudsen flow regime exists. J Memb Sci 2005;256:57–63.

216. Kruczek B, Shemshaki F, Lashkari S, Chapanian R, Frisch HL. Effect of a resistance-free tank on the resistance to gas transport in high vacuum tube. J Memb Sci 2006;280:29–36.

217. Chapanian R, Shemshaki F, Kruczek B. Flow rate measurement errors in vacuum tubes: Effect of gas resistance to accumulation. Can J Chem Eng 2008;86:711–8.

218. Lashkari S. Fundamental Aspects of Membrane Characterization by Constant Volume and Constant Pressure Techniques. 2008.

219. Foster S. Multiple Concentration Determination. 2012.

220. Czichos H, Saito T, Smith LR. Permeation and Diffusion. In: Springer Handbook of Materials Measurement Methods. Springer Berlin Heidelberg, 2006:371–97.

221. Forane (isoflurane). 2013.

222. Suprane (desflurane). 2013.

223. Sevoflurane. 2015.

224. Robeson LM. Correlation of separation factor versus permeability for polymeric membranes. J Memb Sci 1991;62:165–85.

225. Pinnau I, Toy LG. Transport of organic vapors through poly(1-trimethylsilyl-1-propyne). J Memb Sci 1996;116:199–209.

226. Morisato A, Pinnau I. Synthesis and gas permeation properties of poly(4-methyl-2-pentyne). J Memb Sci 1996;121:243–50.

227. Toy LG, Nagai K, Freeman BD, Pinnau I, He Z, Masuda T, Teraguchi M, Yampolskii YP. Pure-gas and vapor permeation and sorption properties of poly[1-phenyl-2-[p-(trimethylsilyl)phenyl]acetylene] (PTMSDPA). Macromolecules 2000;33:2516–24.

228. Morisato a, Shen HC, Sankar SS, Freeman BD, Pinnau I, Casillas CG. Polymer characterization and gas permeability of poly(1-trimethylsilyl-1-propyne) [PTMSP], poly(1-phenyl-1-propyne) [PPP], and PTMSP/PPP blends. J Polym Sci Part B Polym Phys 1996;34:2209–22.

229. Robeson LM. The upper bound revisited. J Memb Sci 2008;320:390–400.

230. Rowe BW, Robeson LM, Freeman BD, Paul DR. Influence of temperature on the upper bound theoretical considerations and comparisons with experimental results. J Memb Sci 2010;360:58–69.

231. Robeson LM. Polymer membranes for gas separation. Curr Oppinion Solid State Mater Sci 2000;4:549–52.

232. Schirmer U, Reinelt H, Erber M, Schmidt M, Marx T. Xenon washout during in-vitro extracorporeal circulation using different oxygenators. J Clin Monit Comput 2002;17:211–5.

233. Medos Medizintechnik AG. Available at: http://www.medos-ag.com/home. Accessed September 13, 2010.

234. Savageau JA, Stanton BA, Jenkins CD, Frater RW. Neuropsychological dysfunction following elective cardiac operation. II. A six-month reassessment. J Thorac Cardiovasc Surg 1982;84:595–600.

235. Shaw PJ, Bates D, Cartlidge NE, French JM, Heaviside D, Julian DG, Shaw DA. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. Stroke 1987;18:700–7.

236. Oakes DA, Mangano CTM. Cardiopulmonary bypass in 2009: Achieving and circulating best practices. Anesth Analg 2009;108:1368–70.

237. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C, others. ADVERSE CEREBRAL OUTCOMES AFTER CORONARY BYPASS SURGERY. N Engl J Med 1996;335:1857–64.

238. Mangano DT. Cardiovascular morbidity and CABG surgery--a perspective: epidemiology, costs, and potential therapeutic solutions. J Card Surg 1995;10:366–8.

239. Shaw PJ, Bates D, Cartlidge NE, French JM, Heaviside D, Julian DG, Shaw DA. Early intellectual dysfunction following coronary bypass surgery. Q J Med 1986;58:59.

240. Sotaniemi KA. Cerebral outcome after extracorporeal circulation: Comparison between prospective and retrospective evaluations. Arch Neurol 1983:75–7.

241. Erdös G, Tzanova I, Schirmer U, Ender J. Neuromonitoring and neuroprotection in cardiac anaesthesia. Nationwide survey conducted by the Cardiac Anaesthesia Working Group of the German Society of Anaesthesiology and Intensive Care Medicine. Anaesthesist 2009;58:247–58.

242. A. Philipp, C. Wiesenack, M. Ritzka, M. Foltan, H. Schienagel, FX Schmid DB. Narkosegastransfer via Membranoxygenator: Eine Untersuchung an mikroporösen und dichten Membranen. Kardiotechnik 2002:1–4.

243. Hert SG De, Linden PJ Van der, Cromheecke S, Meeus R, Nelis A, Van R V, Broecke PW ten, Blier IG De, Stockman BA, Rodrigus IE. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 2004;101:299–310.

244. United States Census Bureau. Annual Estimates of the Resident Population: April 1, 2010 to July 1, 2014 more information 2014 Population Estimates. Am Fact Finder 2014:1–11.

245. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. J Pain Symptom Manage 2011;41:1073–93.

246. Eger EI, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB. Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 1997;85:1154–63.

247. ULTANE (sevoflurane). Available at: http://www.ultane.com/. Accessed June 27, 2013.

248. ISO 16900-13:2015 - Respiratory protective devices -- Methods of test and test equipment -- Part 13: RPD using regenerated breathable gas and special application mining escape RPD: Consolidated test for gas concentration, temperature, humidity, work of br. Available at: http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=62076. Accessed March 16, 2016.

249. Shamsabadi AA, Kargari A, Farshadpour F, Laki S. Mathematical Modeling of CO 2 / CH 4 Separation by Hollow Fiber Membrane Module Using Finite Difference Method. Technology 2012:19–29.

250. Peng Z-G, Lee S-H, Zhou T, Shieh J-J, Chung T-S. A study on pilot-scale degassing by polypropylene (PP) hollow fiber membrane contactors. Desalination 2008;234:316–22.

251. Mansourizadeh a, Ismail a F. Hollow fiber gas-liquid membrane contactors for acid gas capture: a review. J Hazard Mater 2009;171:38–53.

252. Vladisavljevic G, Mitrovic M. Pressure drops and hydraulic resistances in a three-phase hollow fiber membrane contactor with frame elements. Chem Eng Process … 2001;40:3–11.

253. Nagase K, Kohori F, Sakai K. Oxygen transfer performance of a membrane oxygenator composed of crossed and parallel hollow fibers. Biochem Eng J 2005;24:105–13.

254. Kneifel K, Nowak S, Albrecht W, Hilke R, Just R, Peinemann K. Hollow fiber membrane contactor for air humidity control: Modules and membranes. J Memb Sci 2006;276:241–51.

255. Baurmeister U. US 4,940,617. 1990.

256. Soehl M, Wilfart F, Haelssig J. Development of a Mathematical Model for the Optimization of Hollow Fibre Membrane Modules. Unpublished Manuscript. J Memb Sci.

257. Ismail AF, Yaacob N. Performance of treated and untreated asymmetric polysulfone hollow fiber membrane in series and cascade module configurations for CO2/CH 4 gas separation system. J Memb Sci 2006;275:151–65.

258. Wilfart F, Soehl M, Kilcup N, Haelssig J. Characterization of dense PMP membranes for the separation of carbon dioxide from anaesthetic vapours in low pressure applications. Unpublished Manuscript. J Memb Sci.

259. Hussain A, Hägg M-B. A feasibility study of CO2 capture from flue gas by a facilitated transport membrane. J Memb Sci 2010;359:140–8.

260. Powell CE, Qiao GG. Polymeric CO2/N2 gas separation membranes for the capture of carbon dioxide from power plant flue gases. J Memb Sci 2006;279:1–49.

261. Yang H, Fan S, Lang X, Wang Y, Nie J. Economic Comparison of Three Gas Separation Technologies for CO2 Capture from Power Plant Flue Gas. Chinese J Chem Eng 2011;19:615–20.

262. Belaissaoui B, Cabot G, Cabot M-S, Willson D, Favre E. An energetic analysis of CO2 capture on a gas turbine combining flue gas recirculation and membrane separation. Energy 2012;38:167–75.

263. Adewole JK, Ahmad AL, Ismail S, Leo CP. Current challenges in membrane separation of CO2 from natural gas: A review. Int J Greenh Gas Control 2013;17:46–65.

264. Ahmad F, Lau KK, Shariff AM, Murshid G. Process simulation and optimal design of membrane separation system for CO2 capture from natural gas. Comput Chem Eng 2012;36:119–28.

265. Xiao Y, Low BT, Hosseini SS, Chung TS, Paul DR. The strategies of molecular architecture and modification of polyimide-based membranes for CO2 removal from natural gas-A review. Prog Polym Sci 2009;34:561–80.

266. Watanabe H. CO2 removal from synthetic natural gas for city gas use. J Memb Sci 1999;154:121–6.

267. J D S Gaylor Bioengineering Unit S Hickey Department of Anaesthesia, Royal Infirmary, Glasgow, G Bell Department of Chemical and Process Engineering, University of Strathclyde, Glasgow and J M Pei Bioengineering Unit, University of Strathclyde, Glasgow U of SG. Membrane oxygenators: influence of design on performance.

268. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L. Lung stress and strain during mechanical ventilation: Any safe threshold? Am J Respir Crit Care Med 2011;183:1354–62.

269. Portugal a. F, Magalhães FD, Mendes a. Carbon dioxide removal from anaesthetic gas circuits using hollow fiber membrane contactors with amino acid salt solutions. J Memb Sci 2009;339:275–86.

270. Bernstein R, Kaufman Y, Freger V. Membrane characterization. Encycl Membr Sci Technol 2013:41.

271. Lashkari S, Kruczek B. Effect of resistance to gas accumulation in multi-tank receivers on membrane characterization by the time lag method. Analytical approach for optimization of the receiver. J Memb Sci 2010;360:442–53.

272. Wang R, Liu S., Lin T., Chung T. Characterization of hollow fiber membranes in a permeator using binary gas mixtures. Chem Eng Sci 2002;57:967–76.

273. Kc K, Cy F, Matsuura T. Membrane Characterisation. Water Wastewater Treat Technol Encycl Life Support Syst (EOLSS), Dev under Auspices UNESCO.

274. Olajossy A, Gawdzik A, Budner Z, Dula J. Methane separation from coal mine methane gas by vacuum pressure swing adsorption. Fuel Energy Abstr 2004;45:171.

275. Yahaya G, Ajaji A, Tammana V, Bahamdan A. Gas Permeability Measurement Methods in Membrane-Based Gas Separations: Analysis of Transport Properties of Pure Gases Through Dense Polymeric Membranes. North Am Membr Soc 2013.

276. Vallieres C, Favre E. Vacuum versus sweeping gas operation for binary mixtures separation by dense membrane processes. J Memb Sci 2004;244:17–23.

277. Zhao L, Riensche E, Blum L, Stolten D. Multi-stage gas separation membrane processes used in post-combustion capture: Energetic and economic analyses. J Memb Sci 2010;359:160–72.

278. Agrawal R, Xu J. Gas separation membrane cascades II. Two-compressor cascades. J Memb Sci 1996;112:129–46.

279. Takata S, Sugimoto H, Kosuge S. Gas separation by means of the Knudsen compressor. Eur J Mech B/Fluids 2007;26:155–81.

280. Buszewski B, Kęsy M, Ligor T. Human exhaled air analytics: biomarkers of diseases. Biomedical 2007;566:553–66.

281. Corradi M, Mutti A. Exhaled breath analysis: from occupational to respiratory medicine. Acta Biomed 2005;76 Suppl 2:20–9.

282. Beck O, Stephanson N, Sandqvist S, Franck J. Detection of drugs of abuse in exhaled breath from users following recovery from intoxication. J Anal Toxicol 2012;36:638–46.

283. Harrison GR, Critchley ADJ, Mayhew CA, Thompson JM. Real-time breath monitoring of propofol and its volatile metabolites during surgery using a novel mass spectrometric technique: A feasibility study. Br J Anaesth 2003;91:797–9.

284. Miekisch W, Fuchs P, Kamysek S, Neumann C, Schubert JK. Assessment of propofol concentrations in human breath and blood by means of HS-SPME-GC-MS. Clin Chim Acta 2008;395:32–7.

285. Cook DJ, Anderson RE, Michenfelder JD, Oliver Jr WC, Orszulak TA, Daly RC, Bryce RD. Cerebral blood flow during cardiac operations: comparison of Kety-Schmidt and xenon-133 clearance methods. Ann Thorac Surg 1995;59:614–20.

286. Schmidt M, Marx T, Glöggl E, Reinelt H, Schirmer U. Xenon Attenuates Cerebral Damage after Ischemia in Pigs. Anesthesiology 2005;102:929–36.

287. Whitaker EE, Bissonnette B, Miller AD, Koppert TL, Tobias JD, Pierson CR, Christofi FL. A novel, clinically relevant use of a piglet model to study the effects of anesthetics on the developing brain. Clin Transl Med 2016;5:2.

288. Lee KCL, Palacios Jimenez C, Alibhai H, Chang YM, Leckie PJ, Baker LA, Stanzani G, Priestnall SL, Mookerjee RP, Jalan R, Davies NA. A reproducible, clinically relevant, intensively managed, pig model of acute liver failure for testing of therapies aimed to prolong survival. Liver Int 2013;33:544–51.

289. Brant M. Wagener, M.D., Ph.D., Jean-Francois Pittet MD V. A More Clinically Relevant Model of Ventilator-associated Pneumonia? Anesthesiology 2014;120:1075–7.

290. Cong H, Radosz M, Towler B, Shen Y. Polymer–inorganic nanocomposite membranes for gas separation. Sep Purif Technol 2007;55:281–91.

291. Hu X. Membrane separation processes. Adv Physio-Chemical Treat Process 1989:124–83.

292. Makdisi G, Wang I-W. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis 2015;7:E166–76.

293. Marasco SF, Lukas G, McDonald M, McMillan J, Ihle B. Review of ECMO (Extra Corporeal Membrane Oxygenation) Support in Critically Ill Adult Patients. Hear Lung Circ 2008;17.

294. Peek GJ, Sosnowski a W. Extra-corporeal membrane oxygenation for paediatric respiratory failure. Br Med Bull 1997;53:745–56.

295. Wickramasinghe SR, Han B. Microporous membrane blood oxygenators. In: Handbook of Membrane Separation., 2009:671–89.

296. Kim WG, Lim C, Moon HJ, Kim YJ. Comparative analysis of alpha-stat and pH-stat strategies with a membrane oxygenator during deep hypothermic circulatory arrest in young pigs. Artif Organs 2000;24:908–12.

297. Saalfrank A, Flisikowska T, Flisikowski K, Eser S, Wolf E, Saur D, Schnieke A. The pig as a model for human cancer. Eur J Cancer 2014;50:S172.

298. Varel VH, Yen JT. Microbial perspective on fiber utilization by swine. J Anim Sci 75:2715–22.

299. Patil JJ, Maloney DG. Measurement of pulse oximetry, capnography and pH. Anaesth Intensive Care Med 2014;15:522–5.

300. Trill G, Planta M von, Kette F. ETCO2 monitoring during low flow states: clinical aims and limits. Resuscitation 1994;27:1–8.

301. DAVIS TC. Anesthesia recordkeeping: Accuracy of recall with computerized and manual entry recordkeeping. 2012;26.

302. Davis TC, Green JA, Colquhoun A, Hage BL, Biddle C. Anesthesia recordkeeping: Accuracy of recall with computerized and manual entry recordkeeping. J Clin Monit Comput 2012;26:163–9.

303. Wrigge H, Pelosi P. Tidal volume in patients with normal lungs during general anesthesia: lower the better? Anesthesiology 2011;114:1011–3.

304. Pelosi P, Abreu MG de. Tidal Volumes during General Anesthesia: Size Does Matter! Anesthesiology 2012;116:985–6.

305. Karalapillai D, Weinberg L, Galtieri J, Glassford N, Eastwood G, Darvall J, Geertsema J, Bangia R, Fitzgerald J, Phan T, OHallaran L, Cocciante A, Watson S, Story D, Bellomo R. Current ventilation practice during general anaesthesia: a prospective audit in Melbourne, Australia. BMC Anesthesiol 2014;14:85.

306. Fernandez-Bustamante A, Wood CL, Tran Z V, Moine P. Intraoperative ventilation: incidence and risk factors for receiving large tidal volumes during general anesthesia. BMC Anesthesiol 2011;11:22.

307. Kotur PF. Mechanical Ventilation-Past, Present and Future. 430 Indian J Anaesth 2004;48:430–2.

308. Kacmarek RM. The mechanical ventilator: past, present, and future. Respir Care 2011;56:1170–80.

309. Cheng W, Hartmann JF, Cameron DE, Griffiths EM, Kirsch JR, Traystman RJ. Cerebral blood flow during cardiopulmonary bypass: influence of temperature and pH management strategy. Ann Thorac Surg 1995;59:880–6.

310. PNEUMA | BMSR Biomedical Simulations Resource | USC. Available at: https://bmsr.usc.edu/software/pneuma/. Accessed March 17, 2016.

311. Soehl M, Wilfart W, Hanafi H, Jaelssig J. Model of dynamic responses of membrane systems in ventilation circuits. Unpublished Manuscript. J Memb Sci.

312. Alamdari HH, Posada L, Bhatawadekar SA, Brown JA, Maksym GN. A resonance-mode piezoelectric device for measurement of respiratory mechanics. J Biomed Sci Eng 2013;06:1062–71.

313. Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L. Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. Chest 1996;109:144–51.

APPENDIX A – CALIBRATION SAMPLE PREPARATION

For the calibration of the mass spectrometer used in this thesis, a gas mixture with a defined concentration of gas-phase anaesthetic vapour is required. The anaesthetic vapours were calibrated by manually mixing the compound and then calculating the volume concentration using the ideal gas law (Table 11).

Table 11. Properties of Sevoflurane, Desflurane and Isoflurane as well as the calculation approach for determining the calibration mixture concentration used for the mass spectrometer calibration.

	Sevoflurane	Desflurane	Isoflurane
Molecular Formua	C4H3F7O	C3H2F6O	C3H2ClF5O
Molar Mass (g/mol)	200.05	168.04	184.5
Boling Point (°C)	58.5	22.8	48.5
Vapor Pressure at 20°C (mmHg)	157	669	238
Density at 20°C (g/ml)	1.52	1.45	1.5
MAC in O2	2.05%	6.00%	1.13%
Spectra Peaks (A)	69	51	51
Ideal Volume (L/mol)	24.12	24.12	24.12
	Calculations		
Liquid Vapour Volume (mL)	0.0018	0.0018	0.0014
Liquid Mass (g)	0.0027	0.0026	0.0021
Moles	1.37E-05	1.55E-05	1.14E-05
Gas Volume (mL)	0.33	0.37	0.27
Total Syringe Volume (mL)	30	10	30
Vapor Volume %	**1.0996%**	**3.7463%**	**0.9151%**

Liquid sevoflurane, isoflurane or desflurane were extracted from the storage bottle using a syringe in a fume hood. The defined volume (Liquid Vapour Volume) was injected to another syringe full flushed with oxygen. This second syringe was then agitated to vaporize and attain a uniform concentration for calibration. The calculation of the vapour composition was performed using the ideal gas law. The liquid mass [g] was calculated by multiplying the liquid vapour volume [mL] by the density [g/mL]. Dividing the liquid mass [g] by the molar mass [g/mol], the numbers of moles was calculated. Multiplying the moles with the ideal volume [L/mol], and the gas volume [mL] is calculated and multiplied by 10^3 for conversion to milliliters. Dividing the vapour volume by the syringe volume results in a volume concentration (Table 11).

APPENDIX B – COPYRIGHT PERMISSION LETTER FOR CHAPTER VI

Canadian Secretariat
THE INTERNATIONAL ASSOCIATION OF SCIENCE
AND TECHNOLOGY FOR DEVELOPMENT

IASTED

Building B6, Suite 101, 2509 Dieppe Avenue S.W., Calgary, AB T3E 7J9 Canada
Telephone: 1.403.288.1195 Fax: 1.403.247.6851 Website: www.iasted.org
Email: calgary@iasted.org *(for conferences)* and journals@iasted.org *(for publications)*

March 9, 2016

Dipl.-Ing. (FH) Florentin Wilfart

Dalhousie University, Capital District Health Authority
Queen Elizabeth II HSC, Halifax Infirmary Site
5452A – 1796 Summer Street
Halifax, Nova Scotia B3H 4S7 Canada

Dear Mr. Florentin Wilfart,

IASTED grant you permission to include your paper **723-091** entitled "**DELIVERY OF VAPORS ON CARDIOPULMONARY BYPASS USING DIFFERENT OXYGENATOR MEMBRANES**" in your PhD thesis at Dalhousie University.

If you have any questions, please contact calgary@iasted.org

Thank you,

[redacted]

Ahmed Ali
Conference Manager
IASTED-Secretariat
Building B6, Suite #101,
2509 Dieppe Avenue S.W.
Calgary, AB
Canada T3E 7J9
Telephone: +1 (403) 288-1195
Fax: +1 (403) 247-6851
Website: www.actapress.com

APPENDIX C – STATEMENT OF CONTRIBUTION

DALHOUSIE University

Faculty of Graduate Studies

STUDENT CONTRIBUTION TO MANUSCRIPTS IN THESIS

2 PAGES

NAME:	FLORENTIN MICHAEL WILFART	**STUDENT ID #:**	
DEPARTMENT:	SCHOOL OF BIOMEDICAL ENGINEERING	**PROGRAMME:**	PhD
PHONE:	1 (902) 999-1781	**E-MAIL:**	FLORENTIN.WILFART@DAL.CA

MANUSCRIPT AUTHORS:	WILFART F, SCHMIDT M
MANUSCRIPT TITLE:	ARE ANAESTHETIC VAPOURS A SAFE CHOICE FOR ELDERLY PATIENTS OR ARE CO_2 ABSORBERS IRRELEVANT FOR FUTURE ANAESTHESIA? (**CHAPTER III**)
JOURNAL:	JOURNAL OF GERONTOLOGY: MEDICAL SCIENCES. UNPUBLISHED MANUSCRIPT.
STUDENT CONTRIBUTION:	FLORENTIN WILFART DESIGNED THE LITERATURE REVIEW, DEVELOPED THE METHODOLOGY, COLLECTED THE INFORMATION, PERFORMED THE ANALYSIS, AND WROTE THE MANUSCRIPT. CONCEPTUAL GUIDANCE AND EDITING OF MANUSCRIPT BY MICHAEL SCHMIDT.
SUPERVISOR SIGNATURE:	

MANUSCRIPT AUTHORS:	WILFART F, SOEHL M, KILCUP N, HAELSSIG J
MANUSCRIPT TITLE:	CHARACTERIZATION OF DENSE PMP MEMBRANES FOR THE SEPARATION OF CARBON DIOXIDE FROM ANAESTHETIC VAPOURS IN LOW PRESSURE APPLICATIONS. (**CHAPTER V**)
JOURNAL:	JOURNAL OF MEMBRANE SCIENCE. UNPUBLISHED MANUSCRIPT.
STUDENT CONTRIBUTION:	FLORENTIN WILFART DESIGNED THE STUDY CONCEPT, AND WROTE THE MANUSCRIPT. FLORENTIN WILFART AND MEGAN SOEHL DEVELOPED THE METHODOLOGY AND PERFORMED THE ANALYSIS. MEGAN SOEHL AND NANCY KILCUP COLLECTED DATA. CONCEPTUAL GUIDANCE AND HELP WITH ANALYSIS BY JAN HAELSSIG. ALL AUTHORS EDITED THE MANUSCRIPT AND APPROVED IT FOR PUBLICATION.
SUPERVISOR SIGNATURE:	

MANUSCRIPT AUTHORS:	WILFART F, MCFADGEN A, KENT B, GARDINER K, SCHMIDT M
MANUSCRIPT TITLE:	DELIVERY OF VAPOURS ON CARDIOPULMONARY BYPASS USING DIFFERENT OXYGENATOR MEMBRANES. (**CHAPTER VI**)
JOURNAL:	BIOMED ENG. (NY) 2011:265–70
STUDENT CONTRIBUTION:	FLORENTIN WILFART DESIGNED THE STUDY, DEVELOPED THE METHODOLOGY, PERFORMED THE ANALYSIS, AND WROTE THE MANUSCRIPT. FLORENTIN WILFART AND AINSLEY MCFADGEN COLLECTED THE DATA. ALL AUTHORS EDITED THE MANUSCRIPT AND APPROVED IT FOR PUBLICATION.

SUPERVISOR SIGNATURE:

STUDENT CONTRIBUTION TO MANUSCRIPTS IN THESIS

MANUSCRIPT AUTHORS:	WILFART F, SOEHL M, KILCUP N, ROACH D, SCHMIDT M, MAKSYM G, HAELSSIG J
MANUSCRIPT TITLE:	DESIGN OF A MEMBRANE SYSTEM FOR CARBON DIOXIDE REMOVAL FROM GAS MIXTURES UNDER NORMOBARIC CONDITIONS IN ANAESTHESIA CIRCUITS (**CHAPTER VII**)
JOURNAL:	JOURNAL OF MEMBRANE SCIENCE. UNPUBLISHED MANUSCRIPT.
STUDENT CONTRIBUTION:	FLORENTIN WILFART DESIGNED THE STUDY CONCEPT. FLORENTIN WILFART AND MEGAN SOEHL DEVELOPED THE METHODOLOGY, PERFORMED THE ANALYSIS AND WROTE THE MANUSCRIPT. MEGAN SOEHL AND NANCY KILCUP COLLECTED THE DATA. MEGAN SOEHL AND JAN HAELSSIG DEVELOPED THE MODEL BASED ON THE CONCEPT. CONCEPTUAL GUIDANCE AND HELP WITH ANALYSIS BY JAN HAELSSIG AND MICHAEL SCHMIDT. ALL AUTHORS EDITED THE MANUSCRIPT AND APPROVED IT FOR PUBLICATION.
SUPERVISOR SIGNATURE:	

MANUSCRIPT AUTHORS:	WILFART F, HUNG O, SCHMIDT M
MANUSCRIPT TITLE:	CLINICAL VALIDATION OF MEMBRANE SEPARATION AS SAFE ALTERNATIVE TO CURRENT CHEMICAL BASED CO_2 ABSORBERS IN ANAESTHESIA CIRCUITS. (**CHAPTER IX**)
JOURNAL:	TBD. UNPUBLISHED MANUSCRIPT.
STUDENT CONTRIBUTION:	FLORENTIN WILFART DESIGNED THE STUDY CONCEPT, THE METHODOLOGY, PERFORMED THE ANALYSIS AND WROTE THE MANUSCRIPT. FLORENTIN WILFART RECEIVED THE COLLECTED DATA FROM THE DEPARTMENT OF ANAESTHESIA'S DATABASE MANAGER. CONCEPTUAL GUIDANCE BY ORLANDO HUNG AND MICHAEL SCHMIDT.
SUPERVISOR SIGNATURE:	

MANUSCRIPT AUTHORS:	WILFART F, SOEHL M, HAELSSIG J, ROACH D, MAKSYM G, SCHMIDT M
MANUSCRIPT TITLE:	OPTIMIZING A MEMBRANE SYSTEM FOR CARBON DIOXIDE REMOVAL FROM GAS MIXTURES IN ANAESTHESIA CIRCUITS UNDER DYNAMIC CONDITIONS. (**CHAPTER X**)
JOURNAL:	JOURNAL OF MEMBRANE SCIENCE. UNPUBLISHED MANUSCRIPT.
STUDENT CONTRIBUTION:	FLORENTIN WILFART DESIGNED THE STUDY CONCEPT, THE METHODOLOGY, PERFORMED THE ANALYSIS AND WROTE THE MANUSCRIPT. FLORENTIN WILFART AND HAMED HANAFI COLLECTED THE DATA. HAMED HANAFI DEVELOPED THE VENTILATOR AND LUNG MODEL BASED ON THE CONCEPT. MEGAN SOEHL AND JAN HAELSSIG DEVELOPED THE MEMBRANE SYSTEM MODEL BASED ON THE CONCEPT. CONCEPTUAL GUIDANCE AND HELP WITH ANALYSIS BY JAN HAELSSIG AND MICHAEL SCHMIDT. ALL AUTHORS EDITED THE MANUSCRIPT AND APPROVED IT FOR PUBLICATION.
SUPERVISOR SIGNATURE:	