From the Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine
Karolinska Institutet, Stockholm, Sweden

BODY POSTURE AND GRAVITY

AS DETERMINANTS OF LUNG PERFUSION AND VENTILATION

Malin Ax

Stockholm 2019

Published by Karolinska Institutet.

ISBN 978-91-7831-400-3
Printed by Eprint AB 2019

BODY POSTURE AND GRAVITY AS DETERMINANTS OF LUNG PERFUSION AND VENTILATION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Torsten Gordhsalen, Norrbacka S2:02, Karolinska Universitetssjukhuset Solna.
Fredagen den tjugosjätte april 2019, kl. 09.00.

By

Malin Ax, M.D.

Principal Supervisor:
Associate Professor Johan Petersson
Karolinska Institutet
Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine

Co-supervisors:
Associate Professor Margareta Mure
Karolinska Institutet
Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine

Associate Professor Alejandro Sánchez-Crespo
Karolinska Institutet
Department of Oncology-Pathology

Professor Sten G. E. Lindahl
Karolinska Institutet
Department of Physiology and Pharmacology
Section for Anesthesiology and Intensive Care Medicine

Opponent:
Professor Sten Walther
Linköpings Universitet
Department of Medical and Health Sciences

Examination Board:
Professor Göran Hedenstierna
Uppsala Universitet
Department of Medical Sciences

Associate Professor Maria Eriksson
Karolinska Institutet
Department of Molecular Medicine and Surgery

Associate Professor Anders Ahlsson
Karolinska Institutet
Department of Molecular Medicine and Surgery

TILL MORMOR OCH FARFAR

ABSTRACT

Normal lung gas exchange depends on an intimate match between regional ventilation and regional blood flow in the lungs. The beneficial effect of the prone posture in acute respiratory failure is well documented but the mechanisms involved are not completely understood. The overall aim of this thesis was to gain further knowledge about the influence of gravity and body posture on the distributions of ventilation (V) and lung blood flow (Q) in healthy humans. In the studies included in this thesis, regional lung blood flow was marked with intravenous injection of macroaggregates of albumin labelled with ^{113m}In or ^{99m}Tc, while ventilation was marked with Technegas (^{99m}Tc). The radiotracers remain fixed in the lungs after administration. The distribution of the radiotracers, thus representing the distribution of V and Q at the time of administration, was mapped with quantitative single photon emission computed tomography (SPECT).

In **Study I**, we compared regional lung blood flow and ventilation in supine and prone anesthetized and mechanically ventilated healthy humans, with and without PEEP (10 cm H_2O). Half of the subjects were studied supine, the other half prone. All subjects were studied twice; once with, and once without PEEP. We found that in supine subjects, PEEP caused similar redistributions of both perfusion and ventilation towards dependent lung regions with little changes in V/Q ratios. In prone subjects on the other hand, the addition of PEEP caused a much greater redistribution of perfusion compared to ventilation towards dependent lung regions, leading to an increased V/Q mismatch. With PEEP, the vertical ventilation-to-perfusion gradient was similar between supine and prone postures. However, without PEEP the gradient was less in prone than in supine posture. These results lead us to the conclusion that PEEP should be titrated differently according to the actual body posture.

In **Study II**, the influence of gravity on regional lung blood flow in the upright and head-down posture was evaluated. For each subject, one radiotracer was administered while standing upright and the other in the head-down posture using a tilt table. A shift from upright to the head-down posture resulted in a clear redistribution of blood flow from basal to apical regions of the lung. The results further demonstrated that lung structure, and not gravity, is the major determinant of regional lung blood flow in the upright and head-down posture.

In **Study III and IV**, the human centrifuge at Karolinska Institutet was used to determine the distribution of regional ventilation in supine and prone humans exposed to hypergravity. In **Study III**, a technique to map regional ventilation during exposure to hypergravity was developed, using Technegas and SPECT. The results demonstrated a significant redistribution of ventilation from dependent to non-dependent lung regions in both supine and prone subjects exposed to three times normal gravity. We also found that the hypergravity-induced arterial desaturation was less pronounced in the prone posture.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Petersson J, **Ax M**, Frey J, Sánchez-Crespo A, Lindahl S. G. E, Mure M
Positive End-expiratory Pressure Redistributes Regional Blood Flow and Ventilation Differently in Supine and Prone Humans
Anesthesiology 2010; 113:1361–9

II. **Ax M**, Sánchez-Crespo A, Lindahl S. G. E, Mure M, Petersson J
The Influence of Gravity on Regional Lung Blood Flow in Humans – SPECT in the Upright and Head-down Posture
Journal of Applied Physiology 2017; 122:1445-1451

III. **Ax M**, Karlsson L. L, Sánchez-Crespo A, Lindahl S. G. E, Linnarsson D, Mure M, Petersson J
Regional Lung Ventilation in Humans During Hypergravity Studied with Quantitative SPECT
Respiratory Physiology & Neurobiology 2013; 189:558– 564

IV. **Ax M**, Karlsson L. L, Sánchez-Crespo A, Lindahl S. G. E, Linnarsson D, Mure M, Petersson J
Regional Lung Ventilation in Supine and Prone Humans During Hypergravity Studied with Quantitative SPECT
Manuscript

CONTENTS

INTRODUCTION AND BACKGROUND 1
Distribution of regional ventilation at normal gravity 3
Distribution of regional lung perfusion at normal gravity 4
Gas exchange and ventilation-to-perfusion match 5
Anesthesia and mechanical ventilation, and the impact on regional ventilation and lung perfusion 6
Positive end-expiratory pressure and its impact on regional ventilation and lung perfusion 7
Hypergravity and the human centrifuge 9
Distribution of regional ventilation at hypergravity 9
Distribution of regional lung perfusion at hypergravity 10
Gas exchange and ventilation-to-perfusion match at hypergravity 11
Single Photon Emission Computed Tomography 11
AIMS 15
MATERIALS AND METHODS 17
Subjects and Ethics 17
Study protocols 18
Anesthesia (Study I) 20
Tilt table (Study II) 20
The human centrifuge (Study III-IV) 21
SPECT (Study I-IV) 22
SPECT data analysis (Study I-IV) 22
Statistics 24
RESULTS 25
Study I 25
Study II 29
Study III 32
Study IV 35
DISCUSSION 39
Determinants of lung perfusion and ventilation 39
Distribution of ventilation 40
Distribution of perfusion 42
Ventilation-to-perfusion match 44
Other factors influencing regional lung blood flow 47
Limitations 49
Clinical implications - optimizing gas exchange 51
CONCLUSIONS 53
ACKNOWLEDGEMENTS 55
REFERENCES 57

LIST OF ABBREVIATIONS AND DEFINITIONS

ARDS	Acute Respiratory Distress Syndrome
CO	Cardiac Output
CO_2	Carbon Dioxide
CT	Computed Tomography
Density	Weight per unit volume
FRC	Functional Residual Capacity, the volume of air remaining in the lungs at the end of passive expiration in the absence of positive airway pressure
G	Gravity level
HPV	Hypoxic Pulmonary Vasoconstriction
HR	Heart Rate
ND/D	Ratio between Non-Dependent (ND) and Dependent (D)
Hypergravity	Condition where the gravitational force exceeds that on the surface of Earth, i.e. greater than 1 G. 3 G denotes three times normal gravity
NO	Nitric Oxide
Normal gravity	Gravitational force on the surface of Earth, i.e. 1 G
P	Partial pressure
PAP	Pulmonary Artery Pressure
PEEP	Positive End-Expiratory Pressure
Q	Perfusion, i.e. blood flow
SD	Standard Deviation
V	Ventilation
V/Q	Ratio between ventilation (V) and perfusion (Q)
SPECT	Single Photon Emission Computed Tomography
Transpulmonary pressure	The difference between the pressure in the alveoli and the pressure in the pleural space
Voxel	Volume element

INTRODUCTION AND BACKGROUND

“But the gods, foreknowing that the palpitation of the heart in the expectation of danger and the swelling and excitement of passion was caused by fire, formed and implanted as a supporter to the heart the lung, which was, in the first place, soft and bloodless, and also had within hollows like the pores of a sponge, in order that by receiving the breath and the drink, it might give coolness and the power of respiration and alleviate the heat. Wherefore they cut the air-channels leading to the lung, and placed the lung about the heart as a soft spring, that, when passion was rife within, the heart, beating against a yielding body, might be cooled and suffer less, and might thus become more ready to join with passion in the service of reason.“

Timaeus by Plato, 360 B.C. Translated by Benjamin Jowett

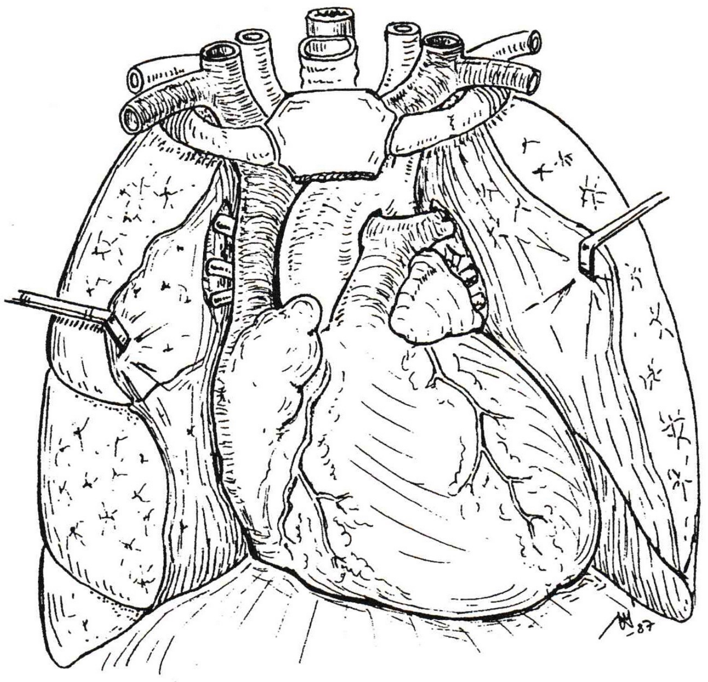


Figure 1. The heart and lungs. Published with the kind permission from the Illustrator Rhagnar Myrhage, Orthopedic Surgeon and Associate Professor of Anatomy

Already B.C. men, and most certainly women alike, were intrigued by the work and function of the heart and lungs. Over the millenniums, the explanations and suggestions have been as colorful as diverse, and sprung from scientific, religious or philosophical views. Since then, the knowledge about the complex relation between ventilation and lung blood flow, i.e. the ventilation-to-perfusion (V/Q) match, has evolved tremendously along with new techniques for measurement. Many of the old truths still hold true, although modified.

Working bedside with patients with severe respiratory or cardiac failure demands a deep understanding of the normal physiology as well as pathophysiology of the cardiopulmonary system. However, a never-ending curiosity about *how it actually works* makes research and clinical work alike even more exciting. The studies in this thesis are all conducted with healthy volunteers. Nevertheless, the intention has always been to gain knowledge that hopefully will lead to a deeper understanding of the mechanisms behind V/Q match, and how to treat patients with respiratory failure in an optimal way.

The understanding of the effects a change in body posture have on lung function goes back almost 200 years. In 1849, Hutchinson demonstrated a reduction in vital capacity with a change from erect to supine posture.[1] Johannes Orth pointed out the possible effect of gravity when discussing the apical localization of adult pulmonary tuberculosis in a publication from 1887;[2] *"…I believe that if the total quantity of blood is reduced and there is incomplete filling of the vessels in the smaller circulation, the apex will be particularly affected, especially if the heart´s action is reduced and the blood pressure is low"*. The potential advantage of prone posture was proposed in 1974, when Bryan[3] speculated that turning anesthetized, paralyzed and mechanically ventilated patients with respiratory failure prone resulted in a better expansion of the dorsal lung region and therefore improved oxygenation. Since then, several studies have demonstrated that a shift from supine to prone posture improves arterial oxygenation in patients with severe respiratory failure.[4-12] In the most severe cases of acute respiratory distress syndrome, ARDS, prone posture has also been shown to reduce mortality.[13] In addition, during mechanical ventilation, other factors such as ventilator settings are important for the distribution of regional ventilation and blood flow and hence for gas exchange.

Our interest in the effect of posture originates in the use of prone positioning for patients with respiratory failure. To further explore the posture-dependent effect of gravity on lung function in a disease model in normal subjects, our group has used a human centrifuge to imitate situations with increased density of the lung tissue, here caused by an increased gravitational force. In some regard exposure to hypergravity resembles the pathophysiology of severe ARDS in that the lung tissue becomes heavier, but there are also many important differences. Nevertheless, these studies on hypergravity fill a gap in the overall understanding of the pulmonary physiology under normal and hypergravity conditions.

Below, the distribution of ventilation and lung blood flow in different body postures and gravitational conditions will be presented as a background to the studies included in the thesis.

Distribution of regional ventilation at normal gravity

In 1949, Fowler published a paper on *"the uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease"*.[14] The heterogeneity in regional ventilation was soon confirmed in humans[15] and dogs,[16] followed by Ball[17] and Milic-Emili et al.,[18] demonstrating a spatial gradient with regional ventilation increasing in the non-dependent to dependent direction. In these and later studies it has been demonstrated that at lung volumes below total lung capacity, alveolar size is greatest in the non-dependent region and decreases down the lung.[18, 19] This is explained by less negative pleural pressure in dependent regions. The difference in expansion at e.g. functional residual capacity (FRC) means that alveoli in dependent regions are more compliant than alveoli in non-dependent regions. At inspiration, the tidal volume is therefore preferentially distributed to dependent regions. The less negative pleural pressure in dependent regions has been attributed to the interaction between the elastic properties of the lung, the weight of the lung, and the thoracic cage configuration.[20]

Studies in humans[18, 21-28] have thus demonstrated greater ventilation in the dependent part of the lung in supine posture. In prone posture, most studies have shown a similar dependent distribution,[21, 22, 26, 29] but also a more uniform distribution of ventilation[24, 30] as well as a similar dorsal distribution of ventilation as in supine posture.[25] There are several potential explanations for these seemingly discordant results, e.g. regional ventilation has been measured both during normal breathing and with special breathing maneuvers and results have been reported using different denominators such as per unit lung volume in a specific situation or per alveoli. Our group has shown that the difference in vertical distribution of ventilation per alveolus is minor with a change from supine to prone posture in humans, compared to the much greater changes in regional ventilation per unit lung volume.[21] The latter also applies to studies on regional perfusion. The more uniform distribution of ventilation demonstrated in prone posture compared to supine has been attributed to the decreased transpulmonary pressure gradient, leading to a more uniform alveolar size, lung compliance, and thus ventilation.[30]

Studies using techniques with high spatial resolution have demonstrated heterogeneity also in horizontal, isogravitational planes that clearly cannot be explained by the influence of gravity. Several studies have concluded that height up the lung, i.e. gravity, only explains a minor part of the heterogeneity in regional ventilation.[26, 31-33] In an animal study, Altemeier et al.[34] showed that ventilation is spatially correlated so that high-ventilation regions are close to other high-ventilation regions and low-ventilation regions near other low-ventilation regions, regardless of posture. This suggests that regional differences in ventilation are inherent to the lung structure as opposed to being a result of the influence of external factors.

Distribution of regional lung perfusion at normal gravity

The understanding of the distribution of regional lung blood flow has evolved from the classical model that West et al. developed in the 1960s after demonstrating an increase in regional lung blood flow from apex to base in humans sitting upright.[35, 36] The model consists of three zones with zone 1 being the most apical and zone 3 the most basal. Increasing blood flow in the direction of gravity is explained by the different relationships between alveolar and hydrostatic vascular pressure. In zone 1, alveolar pressure is higher than both arterial and venous pressure, hence no blood flow in this zone. In zone 2, alveolar pressure is lower than arterial but higher than venous pressure leading to increasing blood flow in the direction of gravity. In zone 3, alveolar pressure is lower than both arterial and venous pressure. Blood flow in zone 3 increases in the direction of gravity due to the increasing hydrostatic intravascular pressure and hence vascular diameter. The vertical gradient in blood flow is typically less in zone 3 than in zone 2. Later, a fourth zone was added to explain a decrease in blood flow in the most dependent part of the lung.[37]

Using different spatial resolution techniques, several studies have confirmed increasing lung blood flow in the direction of gravity[25, 37-44] in both upright and supine humans. Studies have moreover demonstrated a greater gravitational gradient in supine compared to prone posture,[22, 26, 30, 44-47] but also a preferential dorsal, non-dependent, distribution of perfusion in prone posture.[25] Petersson et al, using the same technique as in this thesis, showed that the redistribution of regional blood flow was small with a change from supine to prone posture if the effect of tissue distribution is excluded.[21]

In an animal study, Beck and Rehder[48] demonstrated that irrespective of body posture or lung volume, lung blood flow was predominantly distributed to the dorsal part of the lung, an observation confirmed in later studies.[20, 49, 50] Nitric Oxide, NO, is a potent vasodilator, and in studies on humans and pigs, Rimeika et al. demonstrated a higher NO synthase activity in dorsal than in ventral regions of the lung.[51, 52] In the study on humans, Rimeika et al., using SPECT, showed that inhibition of NO synthase resulted in a redistribution of blood flow from dorsal to ventral lung regions in the supine posture. In prone posture, on the other hand, no change in blood flow distribution was seen after NO synthase inhibition.[51] Later, in a study by Sánchez-Crespo et al.,[53] NO produced in the upper airways was also confirmed to have a significant influence on the distribution of lung blood flow.

As for regional ventilation, the development of techniques with higher spatial resolution revealed that lung blood flow distribution is heterogeneous also within isogravitational planes, and that the heterogeneity within an isogravitational plane is almost as large as in the vertical direction.[20, 49, 54, 55] Similar to regional ventilation, it has also been shown that regions with high blood flow are clustered together, as are regions with low blood flow.[56] This pattern has proved to be robust even under different gravitational conditions.[57] Several studies have shown that although gravity has an impact on the distribution, it only explains a minor part of the total heterogeneity in lung blood flow.[42, 49, 58-60] Instead, the structure of the pulmonary tree has demonstrated to be the major determinant of the distribution of regional lung blood flow.[33, 56, 61, 62]

The distribution of regional lung perfusion is now considered to be determined by:[63]

- The structure of the vascular tree affecting vascular conductance
- The hydrostatic gradient, which is induced by gravity and influenced by body posture
- The relationship between alveolar and vascular pressures
- The arteriolar smooth muscle tone

In the supine posture both the influence of the hydrostatic gradient and the structure of the vascular tree promotes lung blood flow to the dorsal, dependent, lung region. In the prone posture the influence of gravity and structure, respectively, counteract each other resulting in a more even distribution of lung blood flow. It has to be remembered that also structure is influenced by gravity through the redistribution of lung tissue with a change in e.g. body posture.

During normal conditions with spontaneous breathing, most of the lung probably functions in zone 3 conditions, with zone 2 in the most non-dependent region of the lung. Since the vertical distance in horizontal body postures (i.e. prone/supine) is much smaller than in the upright posture, the influence of gravity is also less. However, if pulmonary arterial pressure falls (decreased cardiac output), such as in hypovolemic shock, or alveolar pressure is raised, as during positive pressure ventilation, especially with positive end-expiratory pressure, zone 1 and 2 regions may increase.

Gas exchange and ventilation-to-perfusion match

Hypoxemia is a result of any, or a combination, of the following situations:

- A decrease in the inspired partial pressure of oxygen, for example at high altitude.
- Hypoventilation
- Diffusion limitation; for example in interstitial lung diseases, or too short transit time for blood exposed to alveolar gas in a situation of very high cardiac output.
- Ventilation-to-perfusion mismatch; uneven distribution of regional ventilation in relation to regional lung blood flow. Low ventilation-to-perfusion regions leads to hypoxemia.
- Shunt; an extreme form of ventilation-to-perfusion mismatch with blood flow to an unventilated region of the lung, hence a region where no gas exchange at all occur.

As described, both ventilation and perfusion are heterogeneously distributed in the lung. Despite this, regional ventilation and blood flow is intimately matched in normal subjects, which is crucial for optimal gas exchange. Both active and passive processes are involved in V/Q matching.[20, 64] Hypoxic pulmonary vasoconstriction (HPV), endogenously produced NO, as well as bronchoconstriction and –dilatation in response to changes in airway PCO_2 and PO_2 are active processes,[20, 51, 52, 65-68] while gravity-induced redistribution of ventilation and perfusion, matching of airway and vascular geometry and homogenizing effects (e.g. rebreathing gases from anatomical dead space) are passive processes.[35, 69-71] HPV is crucial for the maintenance of gas exchange in situations with regional alveolar hypoxia, but of little importance for gas exchange in the healthy lung.[72, 73]

Early studies demonstrated heterogeneous distribution of ventilation and perfusion from apex to base in the upright posture.[18, 22, 43, 74] Studies have also confirmed a greater gradient in perfusion than ventilation, leading to higher V/Q ratios in the apex than in the basal part of the lung.[35, 75, 76] Similar to the active mechanisms described above, the effect of passive mechanisms in a healthy lung, such as changes in body posture, has little effect on the overall gas exchange, but in patients with respiratory failure a change from supine to prone posture may have a large effect on gas exchange.[4, 12]

In a study on dogs, Treppo et al.[31] demonstrated a higher degree of spatial correlation between regional perfusion and alveolar ventilation in prone posture compared to supine, concluding that the higher heterogeneity in V/Q ratio in supine posture was primarily due to the gravitational gradient in perfusion not fully compensated by the gradient in regional ventilation. The authors further speculate that the gravitational forces affecting blood and lung tissue are largely counteracted by dorsal-to-ventral differences in lung structure in the prone posture. In the supine posture on the other hand, the effects of gravity and lung structure become additive. The increased correlation of regional ventilation and perfusion in the prone posture compared to supine was confirmed by Mure et al. in a study on mechanically ventilated pigs.[77]

Anesthesia and mechanical ventilation, and the impact on regional ventilation and lung perfusion

The first clinical use of respiratory support, in the form of negative pressure ventilation, was reported in 1929[78] and became widely used during the polio epidemics. The treatment of the large amount of patients with polio may be seen as the advent of mechanical ventilation as well as the development of intensive care units. From the 1950s and onward, mechanical ventilation is provided as positive pressure ventilation – although in the early days performed by manual bag ventilation.[79] Today, mechanical ventilation is used in the clinical every-day life, during anesthesia for surgical interventions as well as in the treatment of patients in the intensive care units for various reasons.

Induction of general anesthesia, with almost all anesthetic agents, causes a fall in the functional residual capacity (FRC). FRC is reduced both if spontaneous breathing is maintained and with the start of mechanical ventilation.[80-83] This is probably, at least partly, due to loss of muscle tone with a cranially displacement of the diaphragm leading to a decrease in lung volume.[84-86] Interestingly, anesthesia with ketamine without muscle paralysis, thereby keeping the muscle tone, does not reduce the FRC.[87] A reduction in FRC promotes airway closure leading to reduced distribution of ventilation to dependent lung regions. A further consequence might be atelectasis, secondary to absorption of gas in closed off lung regions.

Regional ventilation during anesthesia and mechanical ventilation

As opposed to the awake situation, studies have demonstrated increased ventilation towards non-dependent lung regions in anesthetized and mechanically ventilated humans in the supine and lateral posture.[23, 88-91] In prone posture, a preferential distribution of ventilation to the dependent region of the lung has been demonstrated in anesthetized and mechanically ventilated humans, no different from the awake state.[29] Using the same technique as in this thesis, Nyrén et al. demonstrated that when the effect of tissue distribution is taken into account, there is little difference in the vertical distribution of ventilation in mechanically ventilated normal subjects in supine and prone posture.[92]

Regional perfusion during anesthesia and mechanical ventilation

Similar to awake humans, a gravitational gradient with increasing regional lung blood flow from non-dependent to dependent parts of the lung has been demonstrated in supine anesthetized and mechanically ventilated humans.[29, 92] Tokics et al also reported reduced perfusion to the most dependent part, which was attributed to atelectasis.[91] In prone posture, Nyrén et al demonstrated a more uniform vertical distribution of lung blood flow compared to supine.[92]

Positive end-expiratory pressure and its impact on regional ventilation and lung perfusion

As described above, with a reduction in FRC atelectasis might occur when alveolar gas is absorbed distal to closed airways with reduced or no ventilation, leading to impaired gas exchange.[82] To avoid the formation of atelectasis, both in the intensive care patient and in the patient undergoing surgery, it is of importance to counteract the reduction of FRC and to keep the lung open. In 1965, Hill et al.,[93] studying patients undergoing cardiac surgery, was the first to describe an increase in FRC with the use of positive end-expiratory pressure (PEEP). A recruitment maneuver can reopen collapsed lung regions,[94] but to keep the lung open several studies have demonstrated the effect of applying PEEP, although the appropriate level of PEEP is debated.[95, 96] A combination of recruitment maneuvers and PEEP has been proposed,[97, 98] but a study by Östberg et al.[99] recently demonstrated that PEEP alone may be enough to avoid atelectasis and deteriorated gas exchange in anesthetized and mechanically ventilated lung-healthy subjects during non-abdominal surgery.

Mechanical ventilation with PEEP not only affects the airways, but also cardiac function by changing lung volume and hence intrathoracic pressure. Thus, PEEP may have deleterious effect on the hemodynamics with reduced cardiac output. Already in 1948, Cournand et al. concluded that positive-pressure ventilation reduces cardiac output due to the increased intrathoracic pressure leading to increased right ventricle filling pressure and impaired venous return.[100]

In clinical practise, PEEP is commonly used in connection with mechanical ventilation. A lower level of PEEP is normally chosen to lung-healthy individuals, while patients with respiratory insufficiency, with a higher tendency to atelectasis and consolidated lung regions, usually need a higher PEEP to optimize gas exchange.

Effects of PEEP on regional ventilation

In supine pigs and sheep, the application of PEEP redistributes regional ventilation towards dependent lung regions.[101, 102] In prone posture these two animal studies differed in that the addition of PEEP resulted in a redistribution towards non-dependent regions in sheep[101] in contrast to dependent regions in pigs.[102] Using electrical impedance tomography, studies on mechanically ventilated supine animals and humans with ARDS have demonstrated increased ventilation to the dependent lung regions with the addition of PEEP.[103, 104] In anesthetized humans in the lateral position, the application of PEEP increases ventilation to the dependent lung,[105] resembling the distribution of ventilation in the awake situation.

Effects of PEEP on regional perfusion

In animal studies, PEEP causes a redistribution of blood flow towards dependent parts of the lung in the supine posture.[102, 106-109] In prone posture, studies have reported conflicting results. Walther et al. demonstrated a more uniform distribution of blood flow in prone animals with no, or minimal, change in blood flow distribution with the addition of PEEP, in contrast to the findings in supine animals.[107, 108] On the other hand, Richard et al. reported an increase in blood flow towards dependent lung regions with the addition of PEEP in prone pigs.[106]

Taken together, the results from previous studies show that PEEP influences the distribution of ventilation and perfusion, and that the effect may differ with body posture.

Hypergravity and the human centrifuge

The standard acceleration of gravity, "g", is the acceleration due to the gravity of Earth, and is by definition 9.80665 m/s^2. Hypergravity, i.e. increased gravitational force, is the exposure to an additional force caused by angular, or linear, acceleration. Acceleration can be measured in "G", i.e. 3 G denotes three times normal gravity.

G = acceleration applied to the body / g

Hence, in order to expose a human to 3 G an acceleration of 3 x 9.80665 = 29 m/s^2 is needed. The force not only has a magnitude, but also a direction. G_z is acceleration parallel to the spine, in the head-to-foot direction, and. G_y is side-wise acceleration. The direction of acceleration in the present hypergravity studies is G_x, from front-to-back or the reverse, or "eyeballs in" or "eyeballs out".

Human centrifuges have been used for more than 200 years for various reasons, and can be used to study the effects of acceleration – or gravity. Erasmus Darwin, Charles Darwin´s grandfather, reported in 1794 about a stone wheel, also used to mill corn, which was rotated to induce sleep in a man.[110] In the 1800s, human centrifuges were used for both research and as a treatment for mental disorders. The first human centrifuge specifically intended for research was built in Germany in 1933, with a radius of 2.7 m and capacity of 15 G. The need for a deeper understanding of the impact of high acceleration on the human body was driven by the multiple aircraft accidents during World War I attributed to G-forces. During World War II several new types of G-protection devices, such as the anti-G suit, were developed, and at the end of the war six allied countries used human centrifuges for research. The largest and most powerful human centrifuge was the Johnsville Centrifuge at Johnsville Naval Air Development Center (NADC) in Pennsylvania, opened in 1949. The centrifuge had a 50 foot arm and could accelerate from a standstill to 178 miles per hour in less than 7 seconds, generating up to 40 G. Later on, the use of human centrifuges became of use for training of astronauts, including Neil Armstrong and Buzz Aldrin who received centrifuge training at Johnsville.

Distribution of regional ventilation at hypergravity

The effect of hypergravity on the human body has mostly been focused on the upright, seated posture (G_z) due to the problems encountered by pilots. The hypergravity-studies in this thesis are exploring the effect of gravity in the supine and prone posture (G_x). Glaister studied the distribution of ventilation and perfusion in supine humans at normal gravity and at exposure to 3 and 5 G, showing reduced ventilation in the dependent region of the lung at hypergravity.[111] Increasing levels of G-force was also associated with larger regions of hypo- or no ventilation in the most dependent part of the lung. The author suggested that the decreased ventilation was caused by a hypergravity-induced increase in transpulmonary pressure gradient causing airway closure in dependent lung regions. In supine, and to a lesser extent prone posture, hypergravity has been shown to reduce the FRC, which also promotes airway closure and consequently reduced ventilation in dependent regions.[74, 112-114] Atelectasis has been confirmed in dependent lung regions, but only when breathing oxygen during the hypergravity exposure.[115-117] Another possible cause of reduction of ventilation in dependent lung regions may be cranial displacement of the diaphragm during hypergravity, resulting in compression of the lung base.[113]

Distribution of regional lung perfusion at hypergravity

Several studies have focused on regional lung blood flow during hypergravity exposure, and reported somewhat contradictory results, possibly due to different techniques. In a study on supine humans exposed to hypergravity up to 8 G, Hoppin et al. did not demonstrate any significant change in the distribution of regional lung blood flow.[118] In that study, a radioactive agent was administered during hypergravity exposure, followed by scanning at 1 G. This is in contrast to a later study by Glaister on supine humans exposed to 3 and 5 G.[111] In this study both administration and scanning of the radioactive agent marking regional blood flow were performed during hypergravity. The study demonstrated an increase in regional blood flow in the direction of gravity, reaching a maximum in the midlung followed by a decrease in the dependent part of the lung. Furthermore, the results also indicated an unperfused region, zone 1, in the most non-dependent part of the lung. The author speculated that the airway closure might lead to changes in the local blood flow, such as an increase in capillary resistance in the most dependent lung regions. Another possible explanation, suggested by the author, is compression of lung tissue in dependent regions distorting the blood vessels.[111] Similarly, Chevalier et al. demonstrated a reduction in blood flow to the most dependent regions in dogs exposed to 2-6 G in the lateral posture.[119] Using a method with a higher spatial resolution, Hlastala et al.[120] demonstrated increased blood flow to dependent lung regions in awake prone pigs exposed to 2 and 3 G. The authors also concluded that less than 19% of the variance in blood flow was explained by the influence of gravity. In this study, the lungs were removed, re-inflated and dried before investigation, changing the in vivo distribution of lung tissue. Our group has previously reported results indicating increased heterogeneity in regional blood flow[113, 114, 121] and redistribution of blood flow from dependent towards non-dependent regions[122] in both supine and prone humans exposed to hypergravity.

Gas exchange and ventilation-to-perfusion match at hypergravity

Previous studies have demonstrated impaired gas exchange in both animals and humans exposed to hypergravity, and the degree of impairment has proved to be posture-dependent. In the upright, seated posture severe hypoxemia occurs already during moderate levels of hypergravity.[123-127] However, hypergravity exposure in the prone posture results in less severe arterial desaturation with better preservation of oxygenation compared to supine.[121, 128] As described above, exposure to hypergravity causes redistribution of both regional ventilation and blood flow. Presumably this results in V/Q mismatch due to an uneven redistribution of ventilation and perfusion, respectively, leading to arterial hypoxemia. This is supported by an early study on humans exposed to 5 G in the supine posture, demonstrating extremely high V/Q ratios in non-dependent lung regions and extremely low V/Q ratios in the most dependent regions.[111]

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) is a nuclear medicine imaging technique. It is based on gamma camera technique for detection of gamma rays generated by radionuclides, but in contrast to scintigraphy SPECT produces 3D images. While a normal X-ray sends gamma radiation *through* the body, SPECT is based on gamma radiation emitted *from* the patient. A gamma emitting radionuclide is administered to the patient, usually through an intravenous injection or by inhalation, and the radioactivity concentration in the region of interest is detected by the gamma camera. During SPECT data acquisition, the gamma camera rotates to acquire 2D images, or projections, from multiple angles. Through computerized reconstruction, such as filtered back-projection, these multiple projections are turned into a 3D image.

When photons emitted from the radiotracer interact with the surrounding tissues, scatter and attenuation occurs. Scattering means that the original direction and energy of the gamma ray is changed leading to a lower resolution. Attenuation means that not all photons from the radiotracer reach the gamma camera, which may lead to significant underestimation of regional radioactivity. Quantitative SPECT requires that the measured radioactivity is corrected for these factors. Correction for photon scattering can simply be performed using multiple energy acquisition windows.[129] Attenuation correction is generally performed by measuring photon transmission through the body by means of an integrated X-ray computed tomography (CT) or a transmission scan with a radioactive source.[130]

Spatial resolution refers to the ability of the imaging method to separate two objects close together and is commonly quantified with the full-width-at-half-maximum (FWHM) of the point spread response function. Additionally, the voxel size, or sampling distance, also influences spatial resolution. Voxel size should not be larger than FWHM/3 in order to acquire adequate resolution.[131] The spatial resolution for SPECT depends on the photon emission energy, the distance between the gamma camera and the emitting radiotracer, the camera´s physical characteristics and the reconstruction algorithm. FWHM is 10-20 mm for 140 keV photons (^{99m}Tc) for a typical SPECT system.[130] Note that the smaller the FWHM, the better the spatial resolution.

Image related spatial resolution effects are commonly referred to as partial volume effects.[132] The partial volume effect means that the measured concentration of a radiotracer at the center of a volume element (voxel) with uniform concentration is influenced by the surrounding concentration if the volume is smaller than two to three times the FWHM in any direction. Hence, the measured concentration of a radiotracer in a voxel below the spatial resolution represents the average for a cluster of juxtapositioned voxels but weighted for the voxel of interest. Furthermore, the partial volume effect may lead to a gradual attenuation at the border, edge, of the volume of radiotracer distribution – the edge effect.[130] A lower resolution results in a greater impact of partial volume effect.

SPECT imaging usually uses a radionuclide attached to a ligand, forming a radiotracer. The ligand is chosen for its potential to bind to specific tissues or organs or to map a physiological or pathophysiological process. Thus, SPECT is functional imaging in contrast to anatomical X-ray imaging.

Technegas is one option for gamma camera imaging of the distribution of inhaled air. Technegas is an aerosol of ultra-fine carbon particles (size 0.005 to 0.2 µm[133]) labeled with radioactive technetium (^{99m}Tc, photon energy 140 keV, half-life 6 h). The basis of our use of the Technegas – SPECT method, is that the radiotracer is distributed in the lung in proportion to regional alveolar ventilation.[129, 130, 134, 135] As Figure 2 depicts, the Technegas particles remain in a fixed position after administration. Due to the size of the Technegas particles, Technegas is considered to behave in a Brownian motion fashion (particles <1 µm) with no influence of gravity, resulting in a predominant alveolar deposition.[136, 137] Our research group has previously shown that gas exchange calculated using Technegas measurement of regional ventilation correlates to gas exchange assessed with the multiple inert gas elimination technique.[134] Johansson et al.[101] demonstrated a good correlation between regional ventilation measured using Technegas and fluorescent

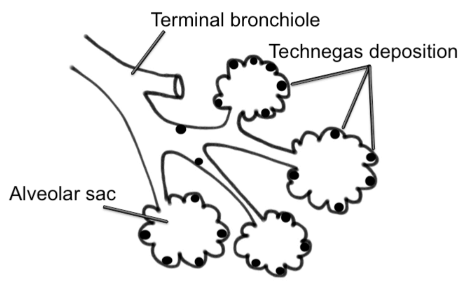


Figure 2. Simplified representation of peripheral lung structure with Technegas deposition.

microspheres. Taken together these results provide strong support for the use of Technegas to measure regional ventilation.

For the study of lung blood flow, macroaggregates of human albumin can be labeled with technetium-99m (^{99m}Tc-MAA) or indium-113m (^{113m}In-MAA, ^{113m}In: photon energy 392 keV, half-life 1.7 hours), as well as other radionuclides. After an intravenous injection, the particles (size 15 to 100 μm) deposit in the pulmonary capillaries and in the precapillary arterioles in proportion to regional perfusion. Importantly, only a very small fraction of the pulmonary vessels are occluded by the radiotracer.[138]

A unique characteristic of the SPECT technique is that it allows simultaneous imaging of several radiotracers with different energies, e.g. technetium (^{99m}Tc) and indium (^{113m}In).

AIMS

The overall aim of this thesis was to gain further knowledge about the influence of gravity and body posture on the distribution of lung perfusion and ventilation in healthy subjects.

Specific aims were to:

- Investigate the interaction between posture and the effect of positive end-expiratory pressure on regional lung perfusion and ventilation in anesthetized healthy subjects (**Study I**).
- Evaluate the influence of gravity on lung perfusion in upright and head-down postures (**Study II**).
- Develop a technique to map regional ventilation during exposure to hypergravity (**Study III**).
- Test the hypothesis that hypergravity, in the supine posture, is associated with reduced ventilation in dependent lung regions (**Study III**).
- Test the hypothesis that regional ventilation during exposure to hypergravity is redistributed in a similar manner in the prone and supine postures and that the effect of a shift between supine and prone is greater at hypergravity than at normal gravity (**Study IV**).

MATERIALS AND METHODS

Subjects and Ethics

In total, 36 volunteers participated in the four studies. Details are presented in Table 1. No subject participated in more than one study. All were healthy non-smokers. None of the subjects was pregnant at the time of the investigation. All studies were approved by the local ethical and radiation protection committees (**Study I**: references 2005/184-31/4, 2005/671-39, 04/05, 11/06; **Study II**: references 2008/200-31/3, 10/2008; **Study III**: references 2008/1351-31/3, Ö 29-2008, 04/2009, 40/2009; **Study IV**: references 2008/1351-31/3, Ö 29-2008, 04/2009, 40/2009), and performed in agreement with the latest revision of the Declaration of Helsinki at the time of the study. Written information was given and informed consent was obtained from all subjects. The total radiation exposure, including CT-scanning, for each subject was estimated as 2.5-8 mSv. For comparison, the yearly background radiation in Sweden is estimated to be approximately 3 mSv. A chest CT used for diagnostic purpose exposes the patient to approximately 5 mSv.

Table 1. Subject data, **Study I-IV**

	Study I	Study II	Study III	Study IV
n	12	8	10	6
Men	3	5	5	3
Women	9	3	5	3
Age	20-52	21-37	20-35	21-27
Height	155-183	160-185	163-183	163-180
Weight	54-80	51-77	65-78	49-85

Number of subjects (n), gender distribution, age (years), height (cm) and weight (kg) presented for the different studies. Age, height and weight are presented as range.

Study protocols

The protocol for each study is outlined in the figures and figure legends below.

Study I

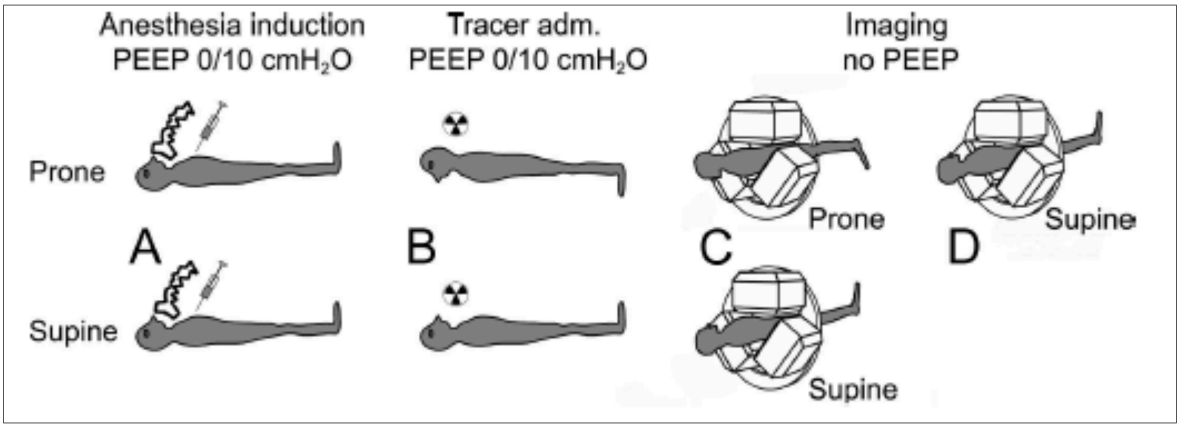


Figure 3. Study I. Half of the subjects were studied in the supine and the other half in the prone posture. Each subject was studied twice, once ventilated with the addition of 10 cmH_2O PEEP during radiotracer administration, and once during ventilation without PEEP. (**A**) Induction of anesthesia in supine posture followed by (**B**) administration of inhaled Technegas (^{99m}Tc) via the ventilator and intravenous injection of ^{113m}In-labeled macroaggregates in the prone or supine posture. (**C**) SPECT imaging in the same posture as during radiotracer administration, and (**D**) repeated SPECT imaging in supine posture for subjects where radiotracers were administered prone. All images were obtained during ventilation without PEEP. PEEP, positive end-expiratory pressure.

Study II

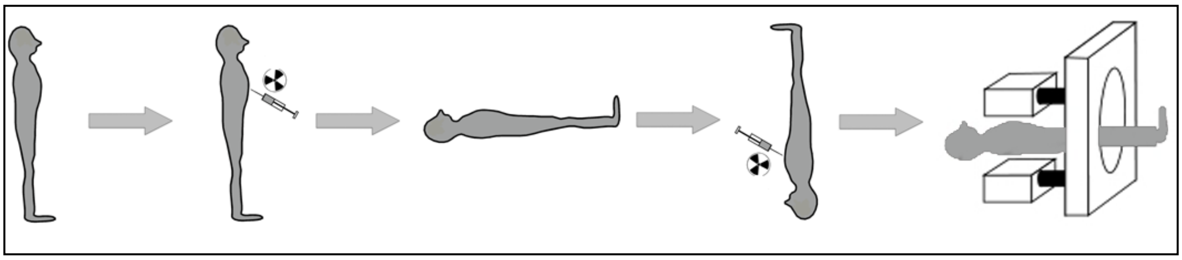


Figure 4. Study II. All subjects were studied, each on one occasion, in both the upright and head-down posture. Macroaggregates labelled with either ^{99m}Tc or ^{113m}In was first administered intravenously in the upright posture followed by a short rest in the supine posture. A second administration of macroaggregates labelled with the other radionuclide was performed in the head-down posture. The protocol was completed by SPECT imaging that simultaneously imaged the distribution of both radiotracers.

Study III

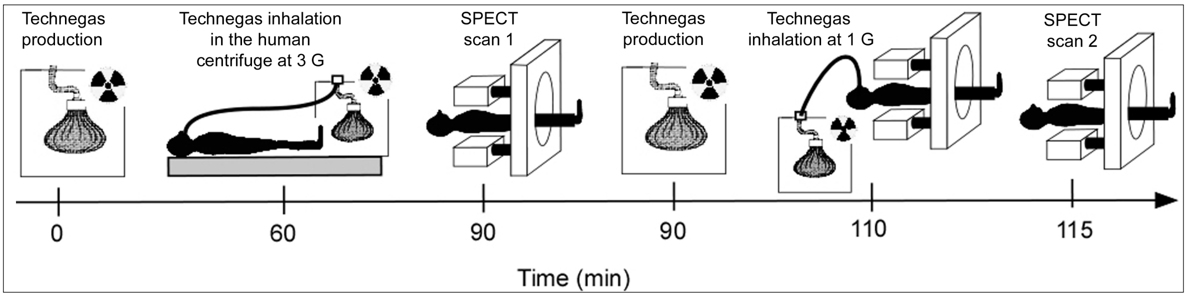


Figure 5. Study III. All subjects were studied supine. First, inhalation of Technegas (^{99m}Tc) was used to mark regional ventilation during exposure to three times normal gravity (3 G) in a human centrifuge. The subjects were then transported to the SPECT laboratory for the first image acquisition. Thereafter the subjects again inhaled Technegas, now at normal gravity (1 G) followed by a second SPECT image acquisition. Subtraction of the first images from the second yielded the radiotracer distribution at the second administration of Technegas. SPECT, single photon emission computed tomography.

Study IV

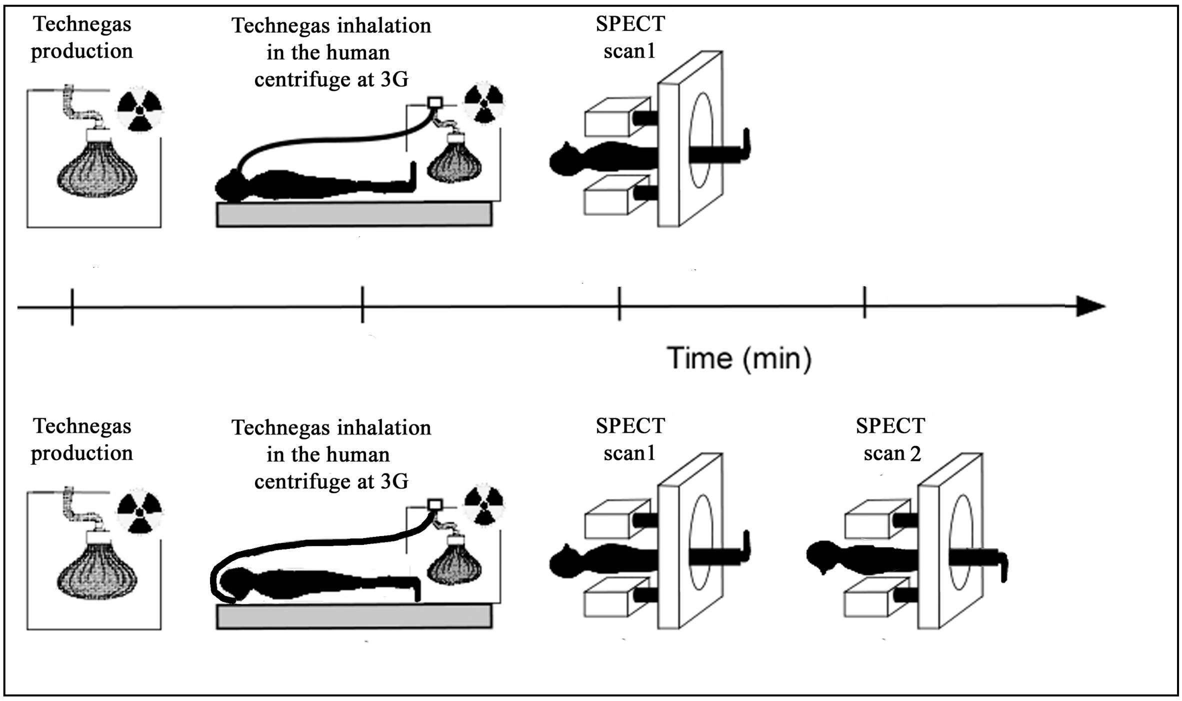


Figure 6. Study IV. All subjects were studied at two occasions, once in supine and once in prone posture, in a randomized order. Regional ventilation was marked with Technegas (^{99m}Tc) during exposure to three times normal gravity (3 G) in a human centrifuge. The subjects were thereafter transported to the SPECT laboratory for image acquisition in the supine posture at normal gravity. A second set of SPECT images were obtained in the prone posture after radiotracer administration prone. SPECT, single photon emission computed tomography.

Anesthesia (Study I)

The subjects were monitored with electrocardiogram, blood pressure, pulse oximetry, arterial blood gases, respiratory rate, airway pressures, tidal volumes, and oxygen and carbon dioxide (CO_2) concentration in inhaled and exhaled gases. Induction of anesthesia was performed with alfentanil and propofol, and maintained with propofol infusion and boluses of alfentanil as needed. Muscle paralysis was achieved with rocuronium and maintained until imaging was completed. The subjects were orally intubated and mechanically ventilated using volume control with a tidal volume of 8 ml/kg; respiratory rate was adjusted to a normal end tidal CO_2 concentration. The inspired fraction of oxygen was 30% and increased if pulse oximeter readings decreased below 95%. A recruitment maneuver using a continuous airway pressure of 40 cmH_2O during 20 seconds was performed 15 minutes before radiotracer administration and after each change of posture.

Tilt table (Study II)

We used a manually operated tilt table to study the distribution of blood flow in the inverse upright, head down, posture. The tilt table had a footplate, and the subjects were secured with a padded harness over the ankles, (Fig. 7). During the experiment the subjects were monitored with pulse oximetry, electrocardiogram and blood pressure. The head-down posture was maintained 60 seconds before radiotracer administration and 60 seconds after the administration was completed.

Figure 7. Tilt table, picture used with permission from the subject.

The human centrifuge (Study III-IV)

The hypergravity experiments were performed in the human centrifuge at Karolinska Institutet (Fig. 8). The centrifuge has a gondola that rotates with a radius of 7.25 m and has its floor perpendicular to the resultant gravitational vector. In both studies, the floor of the gondola was covered with a mattress and, during hypergravity exposure in the supine posture, a head support to accommodate the subject. The subjects were secured to the gondola floor with a 5-point safety belt and monitored at all time with a two-way audio communication system and a color video system. Physiological monitoring was obtained with electrocardiogram from chest electrodes and pulse oximetry from an earlobe using a clinical monitoring system. Expiratory flow was acquired from measurement through a mouthpiece and stored using a digital acquisition system.

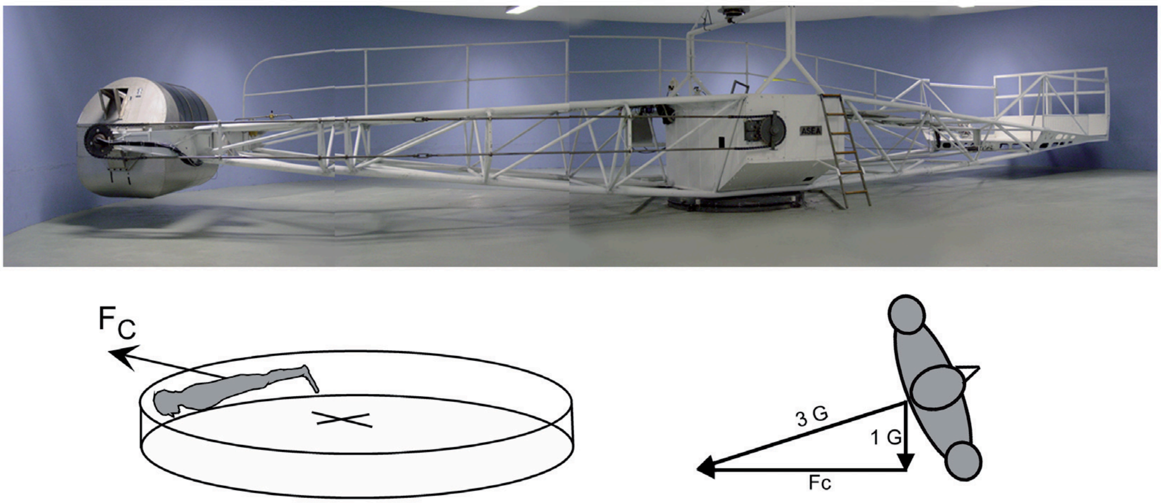


Figure 8. The human centrifuge at Karolinska Institutet. Upper figure: the gondola to the left was used in the hypergravity studies in this thesis. Lower figure: During hypergravity exposure the gondola adjust itself automatically so that the floor of the gondola is perpendicular to the resultant of gravity and the centrifugal G (Fc) vectors. The angular velocity of the centrifuge is chosen so that the resultant equals 3 G.

SPECT (Study I-IV)

Regional ventilation was mapped using inhaled Technegas (**Study I**, **III-IV**). The duration of Technegas administration depends on the intended dose, whether the gas generated is diluted by air as in **Study III-IV**, and on the subjects breathing pattern. We used an external scintillation counter to measure the administered radioactivity.

Regional lung perfusion was marked with macroaggregates of human albumin labeled with radioactive indium (^{113m}In) (**Study I-II**) and radioactive technetium (^{99m}Tc) (**Study II**).

SPECT images were obtained with a two-headed gamma camera (Millennium VG; General Electric Medical Systems, Milwaukee, WI), equipped with low energy high-resolution parallel-hole collimators and recorded in 72 projections, 25 seconds per projection. The images, one set for each principal photon energy, were corrected for radioactive decay before image reconstruction using filtered back projection. In addition to the SPECT scan a sequential CT scan was performed for anatomical lung delimitation as well as for correction of attenuation and scatter.

Specific for **Study III**, where two different conditions are imaged with ^{99m}Tc, the activity recorded (projections at SPECT) after the first Technegas administration (3 G) was subtracted from the projections in the second SPECT (1 G) prior to image reconstruction. To avoid image noise amplification at subtraction, the dosage of Technegas was doubled at the second administration (approximately 50 and 100 MBq at 3 G and 1 G, respectively).

SPECT data analysis (Study I-IV)

The original two-dimensional SPECT images are reconstructed into three-dimensional images, consisting of a number of voxels (size 4.42x4.42x4.42 mm^3) with spatial coordinates. Each voxel has a value (counts per voxel) for each imaged radionuclide, which represents the perfusion or ventilation to that part of the lung at the time of radiotracer administration. For each set of images, voxel values are normalized to the mean for all voxels in that image. The normalized values therefore represent ventilation or perfusion to that voxel relative to the mean for all voxels in that subject in each situation.

The SPECT results were analyzed in different ways:

1. **Study I-IV**: The lungs were divided into 10 isogravitational segments, each representing 10% of the total distance from the most dependent to the most non-dependent region of the lung. Distributions of normalized ventilation, perfusion or

ventilation-to-perfusion ratio per voxel were illustrated with plots of mean values for all voxels within each segment versus vertical height.

2. **Study II**: Redistribution of blood flow was visualized using plots of the mean difference in blood flow per voxel between the upright and head-down posture for each isogravitational segment.

3. **Study I-II and IV**: Vertical gradients were estimated as the regression coefficients from linear regressions of regional ventilation, perfusion, and ventilation-to-perfusion ratios per voxel. Gradients were quantified as the change in normalized ventilation, blood flow, and ventilation-to-perfusion ratio per cm.

4. **Study I**: The PEEP-induced redistribution of ventilation and blood flow, respectively, were estimated by subtracting the gradient during ventilation with PEEP from the gradient without PEEP, for each posture.

5. In **Study II** we analysed our data similar to Glenny et al.[60] to assess the effect of gravity on the distribution of regional blood flow. The effect of gravity can be thought of as increased or decreased flow to each voxel, in a situation with no effect of gravity. As we measured blood flow per voxel in two postures with the opposite effect of gravity, the mean flow per voxel across the two situations could hence be taken as the blood flow per voxel with the effect of gravity excluded. The heterogeneity in blood flow per voxel when voxel values were averaged across both postures then represents the heterogeneity caused by lung structure. These data and multiple-stepwise linear regressions were used to calculate the relative contribution of structure and height up the lung (i.e. gravity) to the blood flow heterogeneity in each posture. Blood flow to a voxel (i) in posture (j) was modeled as

   $$Q_{ij} = \alpha \bullet Q_{meani} + \beta \bullet \text{height}_i + \varepsilon_i$$

   where Q_{meani} was the mean flow to that voxel (i) across the two postures, height was the distance up the lung in each posture (j), and ε_i was the residual component for each voxel. The difference in r^2 value between including both structure and height up the lung and only structure in the regression model was taken as the contribution of height up the lung to the overall blood flow heterogeneity.

6. **Study II**: The partial volume effect is shared between the two postures, which induce a correlation in flow per voxel across the two postures. This enhances the correlation ascribed to lung structure. To quantify this correlation, the CT images for each subject and posture were used to create a data set with voxel values randomly sampled from a Poisson distribution with a mean equal to the original SPECT image for each subject. The two sets of images were convolved with the corresponding point spread function of the SPECT system with the tracer used in each posture. The voxel-wise linear correlation was used to estimate the influence of the partial volume effect on the blood flow heterogeneity ascribed to lung structure.

7. **Study III**: The heterogeneity of regional ventilation was estimated using variance analysis. Global heterogeneity (SStotal) was obtained as the sum of squares of the voxel-wise differences from the mean for all voxels. The variation of ventilation within isogravitational planes (SSiso) was estimated by calculation of the sum of squares for voxel-wise differences between each voxel value and the corresponding mean voxel value for each isogravitational plane. The heterogeneity explained by the vertical direction was calculated by subtracting SSiso from SStotal. All calculations were done separately for each subject and gravitational condition.

8. **Study III-IV**: The redistribution of ventilation (per unit volume of the lung) caused by hypergravity was estimated by comparing the ratio between the mean ventilation per voxel for the non-dependent and dependent half of the lung.

9. **Study IV**: For comparison with the distribution of ventilation in supine and prone humans at normal gravity, results from a prior study from the research team was included in the study. These data are from other subjects.[21]

Statistics

All continuous data are presented as mean ± SD. Paired and un-paired two-tailed Student´s *t*-tests were used for statistical analysis of physiological parameters and differences between conditions as appropriate. Results were considered statistically significant if $p<0.05$.

RESULTS

Study I

The SPECT image, Figure 9, depicts the distribution of ventilation and perfusion, respectively, with and without PEEP in the supine and prone postures in one of the subjects.

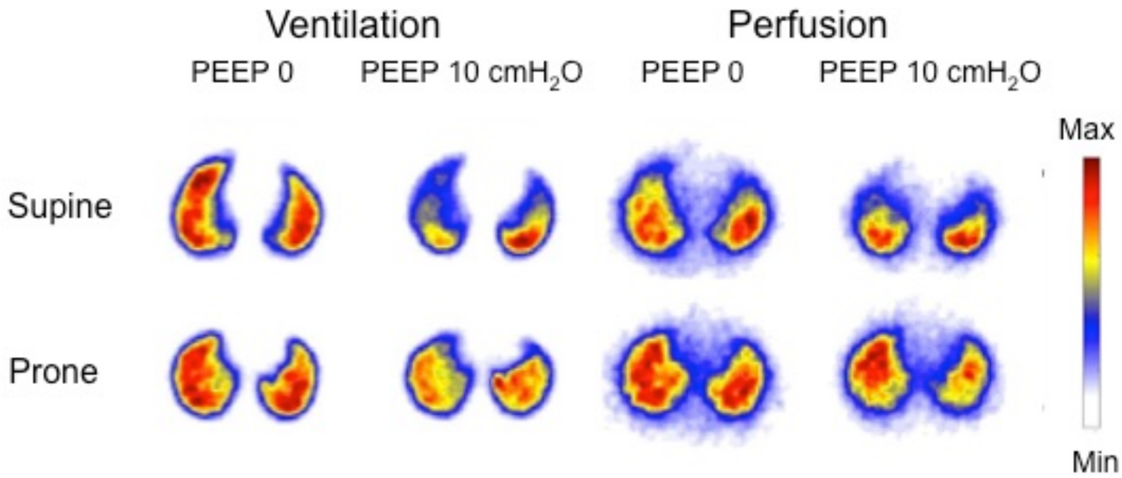


Figure 9. Single photon computed tomography images of regional ventilation and blood flow, respectively, with and without PEEP 10 cmH_2O, in the supine and prone posture. Images are from the same subject and represent a transversal section of both lungs at midlung level. Image acquisition was obtained supine without PEEP. Coloring is according to a relative scale individual for all images. PEEP, positive end-expiratory pressure.

PEEP and regional ventilation

Figure 10 A-D shows the vertical distributions of ventilation, with and without PEEP. In supine subjects ventilated without PEEP, ventilation is rather uniform but shifted to dependent regions with the addition of PEEP (Fig. 10 A). In prone posture, a predominant, and similar, distribution of ventilation to the non-dependent region is demonstrated both with and without PEEP (Fig. 10 B). A shift from supine to prone posture without PEEP result in a redistribution of ventilation to dorsal, now non-dependent lung regions (Fig 10 C). In contrast, a shift from supine to prone with PEEP lead to a slight increase in ventilation to ventral, now dependent, parts of the lung in the prone posture (Fig. 10 D). Table 2 presents the gradients from dependent to non-dependent lung regions in regional ventilation with and without PEEP. The effect of PEEP on the dependent-to-non-dependent distribution of ventilation and perfusion can also be estimated as the difference in gradient (gradient with PEEP minus gradient without PEEP) from least squares regression. The difference in ventilation gradients was -0.062 ± 0.057 in supine and -0.017 ± 0.011 in prone (Table 3). A difference in gradient >0 means a PEEP-induced redistribution from dependent to non-dependent regions, a difference <0 the opposite. Hence, these results confirm the redistribution towards dependents regions in supine compared to the relatively unchanged regional ventilation in prone with the addition of PEEP, as indicated in Figure 10.

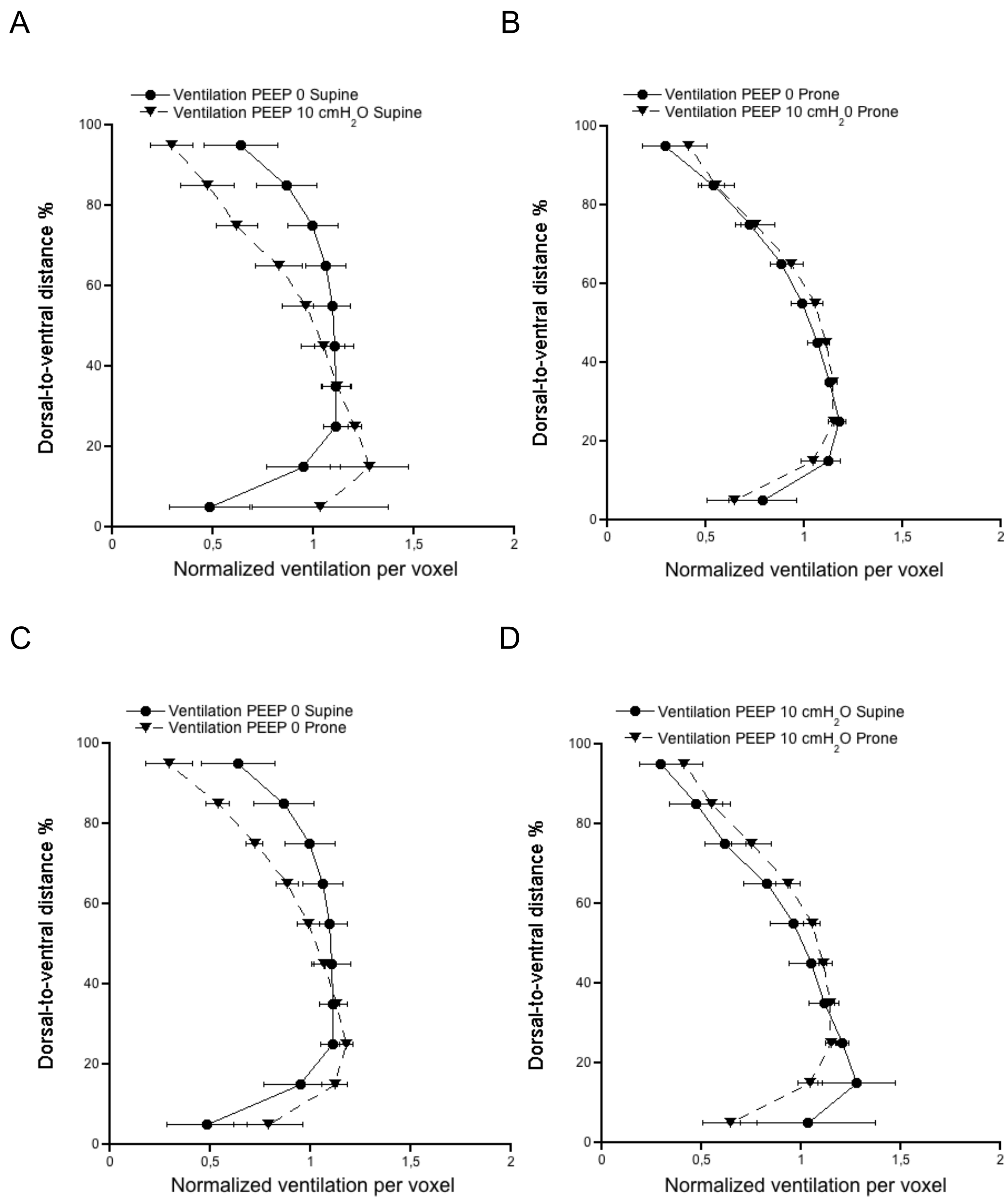


Figure 10. Plots A-B illustrates the change in regional ventilation with the addition of PEEP in supine and prone posture, respectively. **Plots C-D** show the same data but now combined with the intention to illustrate the redistribution of ventilation within the lung at a change in posture during ventilation with and without PEEP. For these plots, the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Normalized regional ventilation per voxel was averaged within each section. Plotted values are the mean values across all individuals for each section; error bars illustrate SD for individual mean values for each section. All data are from SPECT image acquisition supine. PEEP, Positive end-expiratory pressure.

PEEP and regional perfusion

Figure 11 illustrates the vertical distribution of perfusion, with and without PEEP. In supine subjects, there is a predominant blood flow to the dependent region, which is accentuated with the addition of PEEP (Fig. 11 A). In prone posture, the more uniform distribution of blood flow without PEEP is shifted to greater perfusion in dependent lung regions with the addition of PEEP (Fig. 11 B). In contrast to ventilation, without PEEP a shift from supine to prone posture lead to a redistribution of blood flow towards ventral, now dependent parts of the lung (Fig. 11 C). Thus, a shift from supine to prone shifts blood flow to dependent regions both during ventilation without and with PEEP, and the redistribution is accentuated with the addition of PEEP (Fig. 11 D). As indicated in both the plots in Figure 11, as well as from the gradients in Table 2, PEEP causes a redistribution of regional blood flow from non-dependent to dependent regions in both supine and prone posture. The differences between perfusion gradients with and without PEEP were -0.050 ± 0.029 in supine and -0.054 ± 0.015 in prone, implying a quantitatively similar redistribution in the two postures (Table 3).

Table 2. Gradients from dependent to non-dependent lung regions

	Ventilation		**Perfusion**	
	PEEP 0	**PEEP 10 cmH_2O**	**PEEP 0**	**PEEP 10 cmH_2O**
Supine	0.012 ± 0.031	-0.050 ± 0.028	-0.047 ± 0.017	-0.097 ± 0.026
Prone	0.040 ± 0.012	0.023 ± 0.006	0.000 ± 0.016	-0.054 ± 0.014

Estimates of dependent-to-non-dependent gradients obtained from linear least squares regression. Values are mean ± SD. Units are normalized ventilation and perfusion per cm. All data are from SPECT image acquisition supine. PEEP, positive end-expiratory pressure.

Table 3. Effect of PEEP on gradients from dependent to non-dependent lung regions

	Ventilation	**Perfusion**	**Ventilation-to-perfusion ratio**
Supine	-0.062 ± 0.057†	-0.050 ± 0.029*	-0.003 ± 0.049
Prone	-0.017 ± 0.011*	-0.054 ± 0.015*	0.045 ± 0.024*

Effect of PEEP on the vertical distribution of perfusion, ventilation and ventilation-to-perfusion ratios, estimated as differences in gradients (gradient with PEEP minus gradient without PEEP) from linear least squares regressions. Values are mean ± SD. Units are normalized perfusion, ventilation or ventilation-to-perfusion ratios per cm. All data are from SPECT image acquisition supine. A difference in gradient >0 signifies a PEEP-induced redistribution from dependent to non-dependent regions, a difference <0 a shift in the opposite direction. Hence, a difference of 0 implies that the addition of PEEP did not change the gradient at all. † $p<0.05$; *$p<0.01$ for being different from zero (single sample t-test). PEEP, positive end-expiratory pressure.

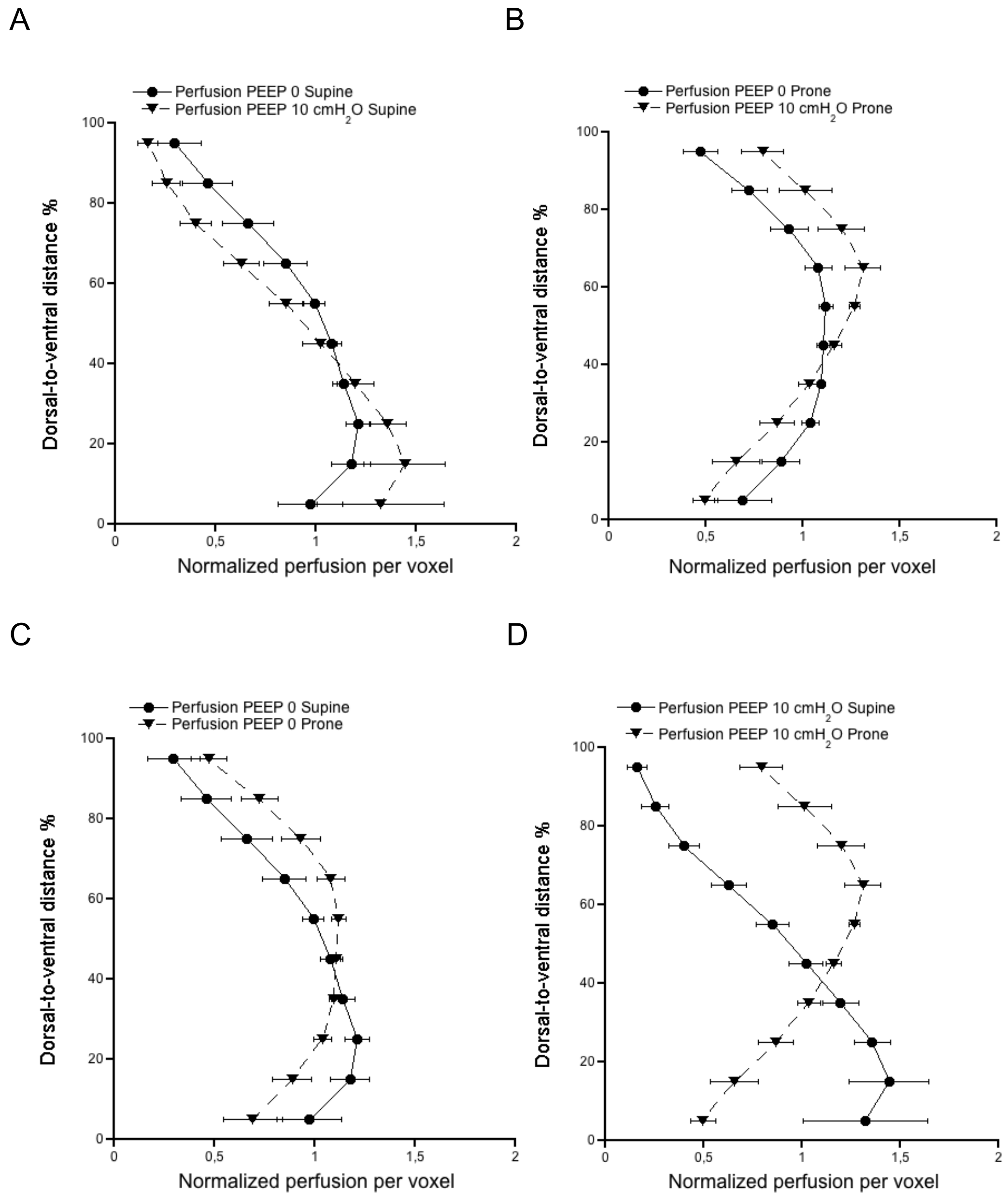


Figure 10. Plots A-B illustrates the change in regional lung blood flow with the addition of PEEP in supine and prone posture, respectively. **Plots C-D** show the same data but now combined with the intention to illustrate the redistribution of ventilation within the lung at a change in posture during ventilation with and without PEEP. For these plots, the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Normalized regional ventilation per voxel was averaged within each section. Plotted values are the mean values across all individuals for each section; error bars illustrate SD for individual mean values for each section. All data are from SPECT image acquisition supine. PEEP, Positive end-expiratory pressure.

PEEP and regional ventilation-to-perfusion ratios

The addition of PEEP caused different effects on ventilation-to-perfusion ratio depending on posture. In supine posture, PEEP caused a similar redistribution of both perfusion and ventilation towards dependent lung regions. Hence, little change in the ventilation-to-perfusion ratios occurred as demonstrated by the difference in gradients with and without PEEP; -0.003 ± 0.049 (Table 3). In the prone posture, the addition of PEEP lead to a redistribution of both perfusion and ventilation to dependent regions, although much smaller for ventilation. Thus, PEEP resulted in a dependent increase and non-dependent decrease in ventilation-to-perfusion ratios, with a difference between gradients with and without PEEP of 0.045 ± 0.024 (Table 3).

Study II

Redistribution of perfusion in the head-down posture

A change from upright to head-down posture redistributed blood flow from basal towards apical regions of the lung, hence in the direction of gravity, as illustrated by SPECT images from one subject in Figure 12.

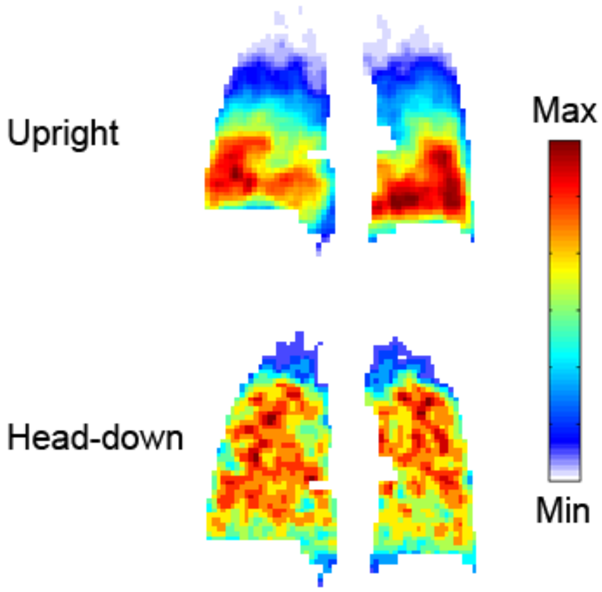


Figure 12. Single photon computed tomography images of regional blood flow in the upright and head-down posture, respectively, from one subject. Images represent a sagittal section of both lungs. Image acquisition was obtained supine. Coloring is according to a relative scale individual for all images.

The blood flow redistribution illustrated by Figure 12 is confirmed in Figure 13, showing plots of the vertical blood flow distribution across all individuals. As Figure 13 A demonstrates, in upright posture blood flow is predominantly distributed to the dependent, basal, part of the lung. A shift to the head-down posture redistributes blood flow towards the apical, now dependent lung region; hence in the direction of gravity. Figure 13 B shows blood flow redistribution with a shift in posture from upright to head-down. The negative values in the basal part imply less blood flow in head-down posture while the positive values in the apical part means increased blood flow with a shift in posture.

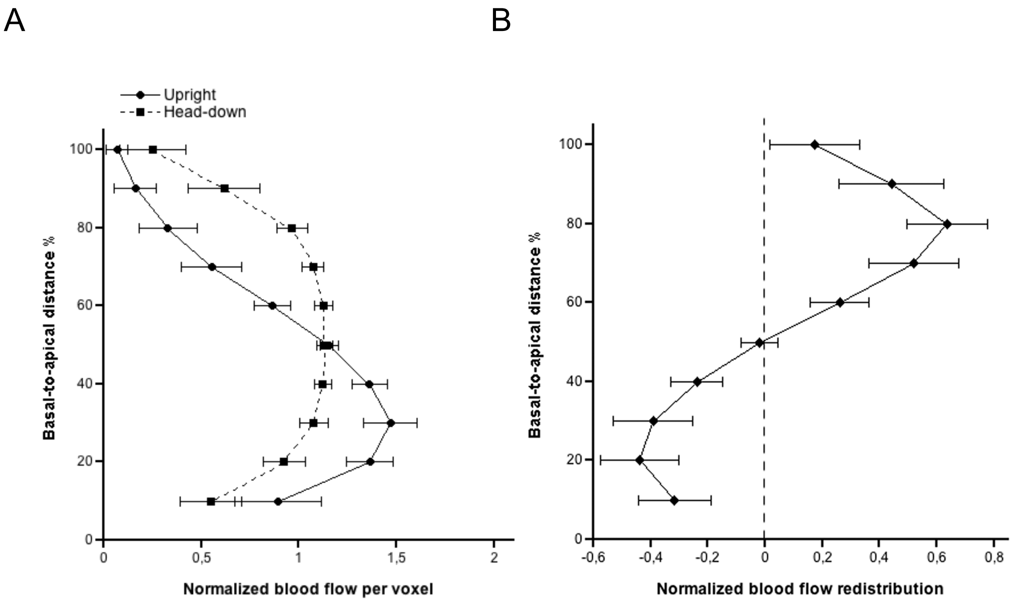


Figure 13. Regional blood flow distribution in upright and head-down posture **(A),** and redistribution of regional blood flow with a change from upright to head-down posture **(B)**, derived from SPECT data. For these plots the lungs were divided into 10 sections of equal height along the basal-to-apical distance of the lung. Mean blood flow per voxel was calculated for each section, each subject and each posture. **Plot A.** Normalized blood flow, blood flow per voxel normalized to the mean for all voxels in each situation and individual. Plotted values are the mean values across all individuals for each section; error bars illustrate SD for individual mean values for each section. **Plot B.** For each section and each individual, the difference in blood flow per voxel between the head-down and upright posture was calculated. A negative value implies less blood flow in the head-down posture compared to upright, positive values the opposite. Plotted values are the mean difference for each section across all individuals; error bars illustrate SD for these differences. All data are from SPECT image acquisition supine.

The redistribution of blood flow was quantified by comparing the percentage of total perfusion distributed to the apical and basal halves of the lung, respectively, and by the vertical gradients from linear regression as presented in Table 4. It has to be remembered that these percentages are influenced by the shape of the lung, i.e. the basal part of the lung is larger than the apical half. Both the changes in blood flow to the two halves of the lung and the gradients were statistically different between the two postures. In both postures, the linear regressions demonstrated increasing blood flow in the direction of gravity, although much less in head-down than upright (Table 4).

Table 4. Distribution of regional perfusion, apical and basal lung halves, as well as apical-to-basal gradients

	Upright	Head-down	*P* value
Apical half (%)	21 ± 6	37 ± 7	< 0.05
Basal half (%)	79 ± 6	63 ± 7	< 0.05
Apical-to-basal gradient	0.073 ± 0.019	-0.006 ± 0.006	< 0.05

Distribution of perfusion to the apical and basal half of the lung. Estimates of apical-to-basal gradients obtained from linear least squares regression. Values are mean ± SD. Units are normalized blood flow per cm.

Influence of gravity on regional perfusion

The relative contribution of gravity (height up the lung) and structure to blood flow heterogeneity in upright and head-down posture was calculated as described in the methods section, and presented in Table 5. The results show that gravity on the average explains only 6% (r^2) of the variability (in blood flow per voxel) in the upright posture and 15% in the head-down posture. The variability ascribed to the influence of structure, independent of gravity, is 86% in upright respectively 71% in head-down posture. The r^2 values for structure include the influence of the partial volume effect that is inherent to the SPECT method (addressed further in the discussion). Our estimation of the effect of the SPECT method on the calculated correlation suggests that the SPECT method substantially contributes to the r^2 values. Calculated r^2 ascribed to the method was on the average 34% ± 10%.

Table 5. Relative contribution of structure and height up the lung to perfusion heterogeneity in the upright and head-down posture

	r^2 Structure*	r^2 Structure* + Height	r^2 Added by Height
Upright Mean	0.86	0.93	0.06
Head-down Mean	0.71	0.86	0.15

*The r^2 values ascribed to structure include the effect of the method; see Methods section, SPECT data analysis.

Mapping of regional ventilation at hypergravity

The use of Technegas administration during exposure to 3 G to explore the distribution of ventilation at hypergravity proved feasible.

Redistribution of regional ventilation at hypergravity

SPECT images from one subject illustrating the redistribution of regional ventilation from dependent towards non-dependent lung regions with a change from normal to three times normal gravity are shown in Figure 14. These images suggest that exposure to hypergravity redistributes ventilation in the opposite direction of gravity in supine posture, which was confirmed by the overall analysis of the SPECT data (Fig. 15).

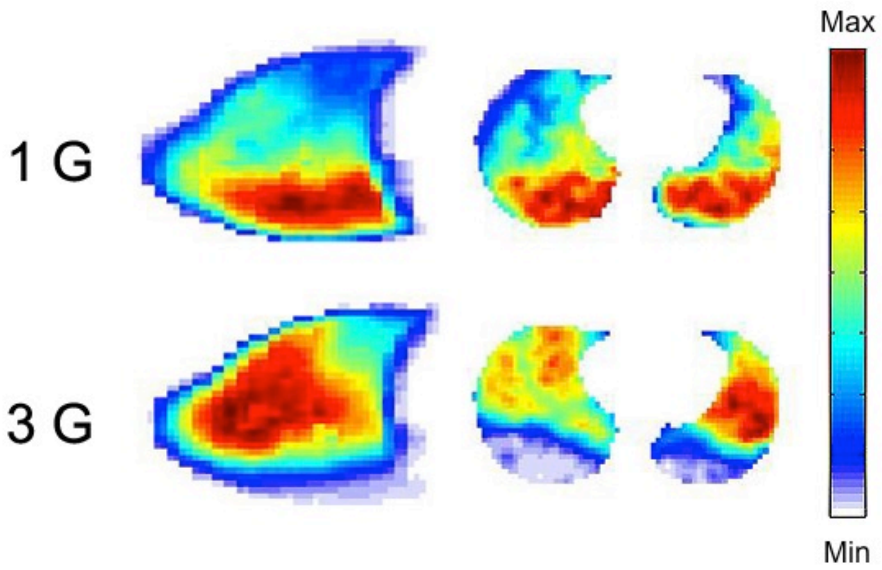
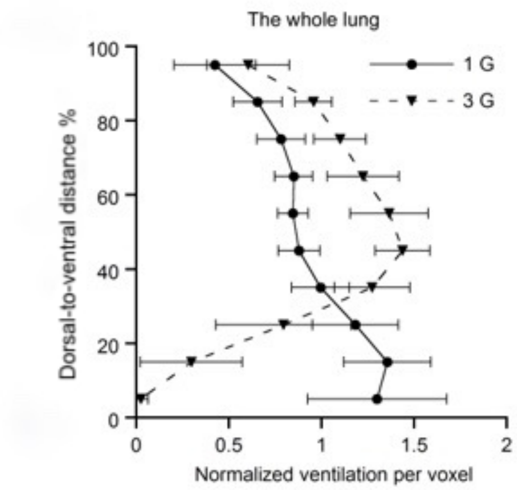


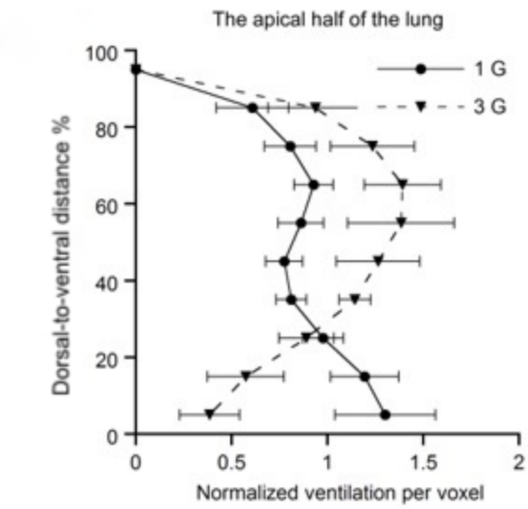
Figure 14. Single photon emission computed tomography images of regional ventilation during normal (1 G) and three times normal gravity (3 G). Images are from the same subject and represent a sagittal section of the right lung and a transverse section of both lungs at midheart level, respectively. Image acquisition was obtained supine at normal gravity. Coloring is according to a relative scale individual for all images.

To address whether the hypergravity-induced vertical shift in ventilation occurred along the whole apical-to-basal distance, the changes in distribution of ventilation between 1 and 3 G in the whole lung as well as separately for the apical and basal half of the lung are illustrated in plots in Figure 15. The results clearly demonstrate the same pattern of redistribution of ventilation towards the non-dependent part of the lung in both the apical and basal half.

A



B



C

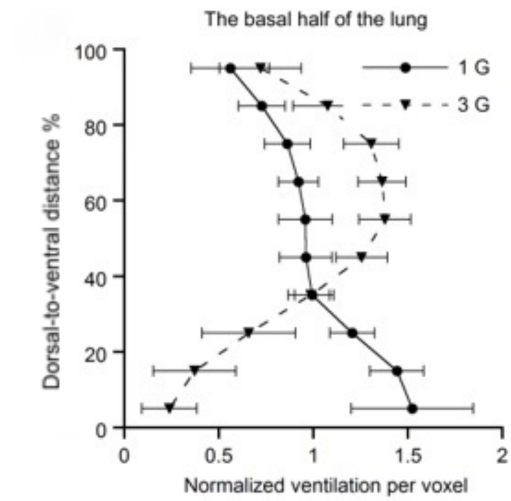


Figure 15. Distribution of regional ventilation in the supine and prone posture at normal (1 G) and three times normal gravity (3 G). The plots show data from the whole lung, the apical, and the basal half of the lung. For these plots the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Mean ventilation per voxel was calculated for each section, each subject and each gravitational condition. Normalized ventilation, ventilation per voxel normalized to the mean for all voxels in each situation and individual. Plotted values are the mean value across all individuals for each section; error bars illustrate SD for individual mean values for each section. All data are from SPECT image acquisition supine at normal gravity.

Similarly, the mean ventilation per voxel in the non-dependent and dependent part of the lung as well as the non-dependent to dependent ratio demonstrate greater ventilation per unit lung volume in the non-dependent half of the lung during 3 G, as opposed to 1 G (Table 6). The percentage of ventilation distributed to the non-dependent respectively dependent half of the lung is reported in Table 7.

In addition to the non-dependent-to-dependent changes in regional ventilation, the change in distribution of ventilation to the apical and basal half was also quantified. As reported in Table 6 and 7, both the percentage of ventilation distributed to the apical half of the lung and mean ventilation per voxel in the same region increase at exposure to hypergravity. Hence, a hypergravity-induced increase in the fraction of ventilation distributed to apical regions was also demonstrated.

Table 6. Non-dependent to dependent and apical to basal distributions of regional ventilation

	1 G	3 G	*P* value
Mean ventilation per voxel			
Non-dependent half	0.87 ± 0.09	1.31 ± 1.15	<0.0001
Dependent half	1.08 ± 0.05	0.82 ± 0.10	<0.0001
Apical half	0.91 ± 0.08	1.00 ± 0.09	<0.01
Basal half	1.02 ± 0.05	0.93 ± 0.03	<0.01
Ratios			
Non-dependent-to-dependent	0.81 ± 0.12	1.63 ± 0.35	<0.0001
Apical-to-basal	0.90 ± 0.11	1.09 ± 0.12	<0.01

Ratios between mean ventilation per voxel for the non-dependent, dependent, apical, and basal half of the lung. Values are mean ± SD across all subjects. 1 G, normal gravity; 3 G, three times normal gravity.

Table 7. Distribution of regional ventilation; non-dependent and dependent, apical and basal lung halves

	1 G	3 G
Non-dependent half (%)	34 ± 6	52 ± 5
Dependent half (%)	66 ± 6	48 ± 5
Apical half (%)	39	47
Basal half (%)	61	53

Percentage of total ventilation distributed to the non-dependent and dependent, as well as the apical and basal half of the lung respectively. These percentages are however confounded by the shape of the lung, i.e. the dependent halves being larger than the non-dependent as well as the basal regions also being more dependent. Values are mean ± SD across all subjects. 1 G, normal gravity; 3 G, three times normal gravity.

Isogravitational variance of ventilation

The results from variance analysis show that the variation within isogravitational planes constitute 83% of the total variation at 1 G and 66% at 3 G. The variation in the vertical direction increased significantly between 1 and 3 G, $p < 0.01$. In contrast, the variation within isogravitational planes did not increase significantly, $p = 0.55$.

Study IV

Regional ventilation supine

In the supine posture, the SPECT image shown in Figure 16 (A) indicates greater regional ventilation in the non-dependent, ventral, part of the lung at 3 G. Similarly, Figure 17 (A) demonstrates greater regional ventilation in the non-dependent than dependent lung region in all subjects at 3 G in the supine posture. Compared to regional ventilation at normal gravity, these results indicate a redistribution of ventilation from dependent towards non-dependent lung regions at exposure to hypergravity (Fig. 17 B). Mean ventilation per voxel in the non-dependent and dependent part of the lung, respectively, as well as the ratio between the values consistently demonstrate a greater ventilation per unit volume of the non-dependent lung at 3 G as opposed to 1 G (Table 8). Table 8 also presents the vertical gradient in the dependent-to-non-dependent direction. These results are in agreement with the results from Study III.

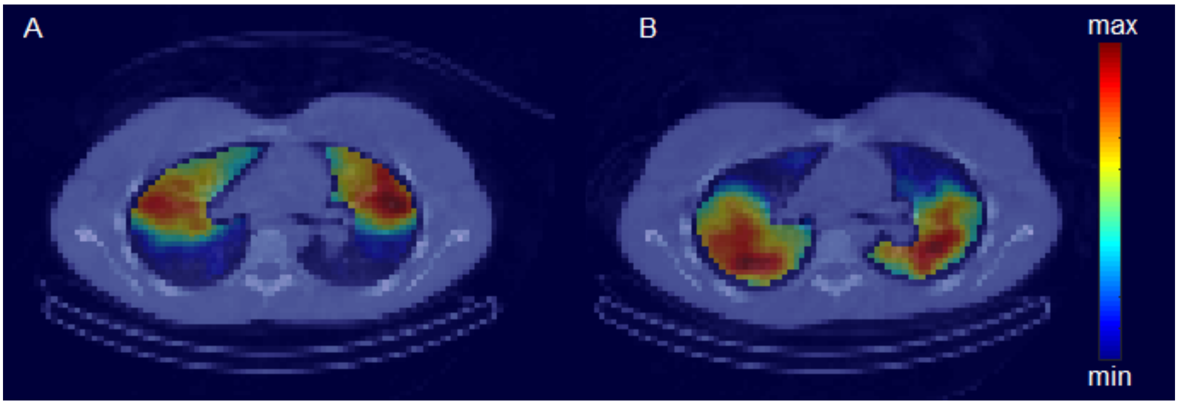


Figure 16. Combined single photon emission computed tomography and computed tomography images of the distribution of ventilation during exposure to three times normal gravity (3 G) in the (**A**) supine and (**B**) prone posture. Images are from the same subject and represent a transversal section of both lungs at midlung level. Image acquisition was obtained supine at normal gravity. Coloring is according to a relative scale individual for all images.

Regional ventilation prone

Similar to supine, the SPECT image (Fig.16 B) as well as plots (Fig. 17 C-D) demonstrate a predominant distribution of ventilation to the non-dependent, now dorsal, part of the lung in the prone posture at 3 G. Again, the pattern is consistent for all subjects (Fig. 17 C). In the prone posture, ventilation is predominately distributed to dorsal regions both at 1 and 3 G but the ventral-to-dorsal increase in regional ventilation was greater at hypergravity (Fig. 17 D). This is confirmed by the comparison of the mean ventilation per voxel for the non-dependent and dependent lung regions and the vertical gradients (Table 8).

Table 8. Non-dependent to dependent distributions of regional ventilation

	Supine 3 G n=6	Supine 1 G n=7	Prone 3 G n=6	Prone 1 G n=7
Non-dependent	1.23 ± 0.12	0.80 ± 0.07	1.25 ± 0.09	1.07 ± 0.02
Dependent	0.88 ± 0.07	1.08 ± 0.03	0.46 ± 0.20	0.84 ± 0.07
ND:D ratio	1.42 ± 0.25	0.74 ± 0.08	3.33 ± 1.87	1.28 ± 0.12
Vertical D-ND gradient	0.083 ± 0.038	-0.052 ± 0.23	0.123 ± 0.036	0.041 ± 0.016

Mean ventilation per voxel in the non-dependent (ND) and dependent (D) part of the lung and the ratio between these mean values (ND:D ratio. Vertical gradient D-ND, estimates of the gradients in ventilation per voxel in the dependent-to-non-dependent direction, from least squares linear regression. All data are from SPECT image acquisition supine. Values are mean ± SD across all subjects, units mean normalized ventilation per voxel and normalized ventilation per voxel per cm. 3 G, three times normal gravity. For comparison we also included data in the same posture but at normal gravity (1 G), these data are from a prior study using other subjects.[21]

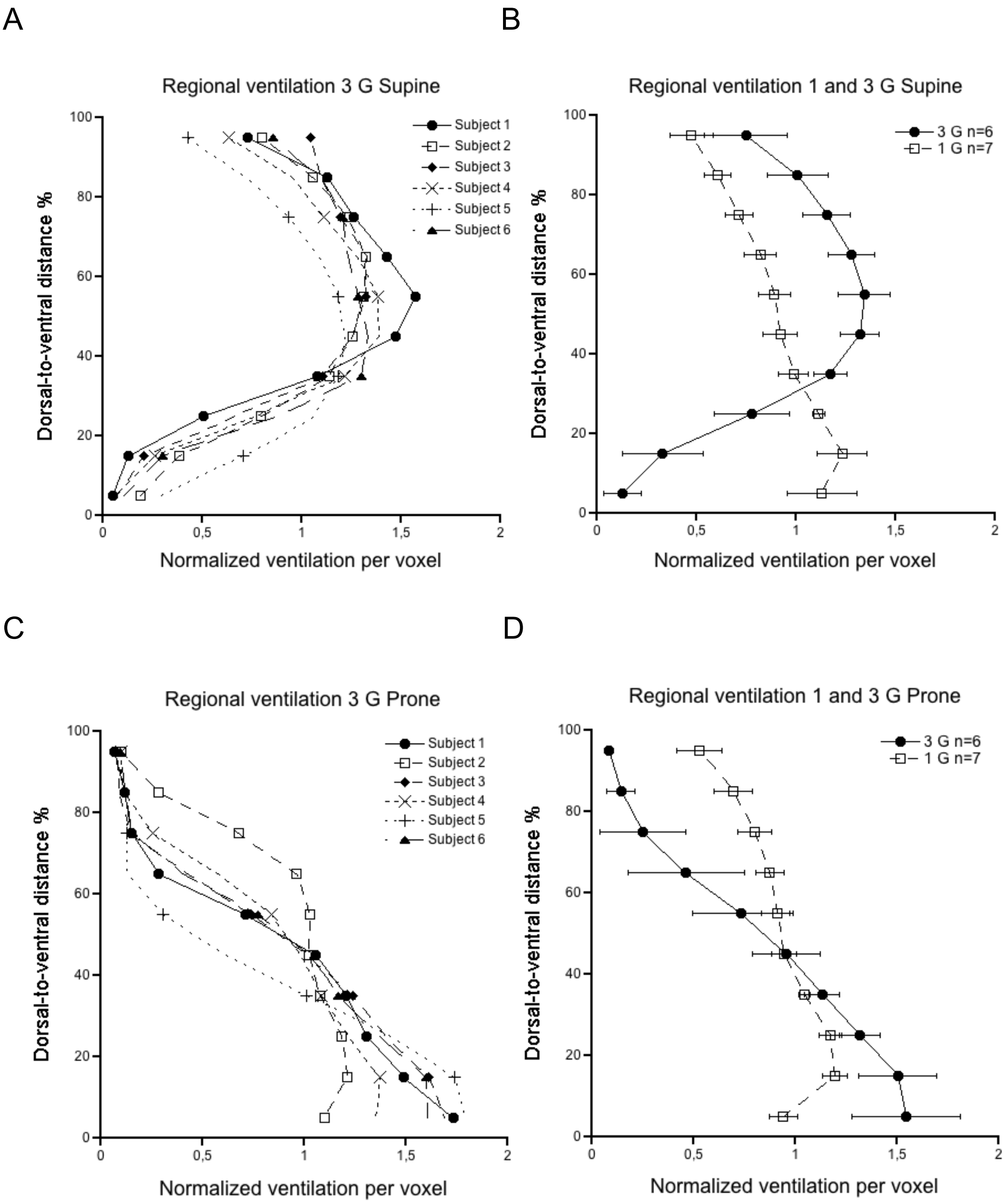


Figure 17. Distribution of regional ventilation in the supine and prone posture at normal (1 G) and three times normal gravity (3 G). For these plots the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Mean ventilation per voxel was calculated for each segment, each subject and each posture. **Plots A and C** show the data for each subject and situation at 3 G. **Plots B and D** show mean ventilation for each section across all subjects. For comparison data were included for the distribution of ventilation in the same body posture but at 1 G. These data are from a prior study using other subjects.[21] Normalized ventilation per voxel, normalized to the mean for all voxels in each posture and individual. Error bars illustrate SD for individual mean values for each section. All data are from SPECT image acquisition supine.

Figure 18 summarizes the results of **Study IV**. At normal gravity, ventilation is predominantly distributed to the dorsal part of the lung in both supine and prone posture with very similar vertical gradients in both postures. Exposure to 3 G redistributes ventilation towards non-dependent, ventral, lung regions in supine posture, while a corresponding shift in regional ventilation to dorsal, non-dependent regions occur in prone posture. Importantly, all these results refer to images obtained in the supine posture. This means the comparisons relates to the distribution of ventilation within the airways. For the prone posture, the actual distribution per unit lung volume while prone is different.

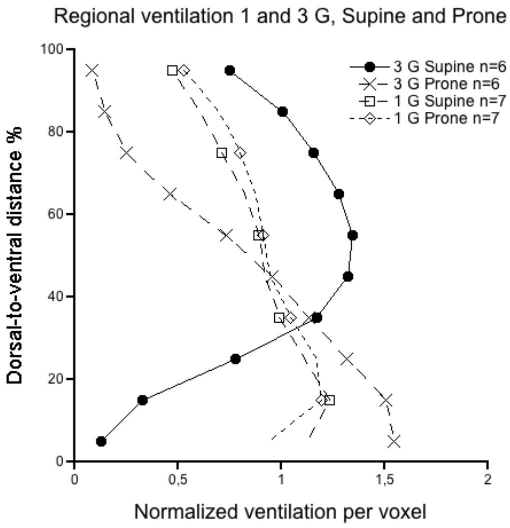


Figure 18. Distribution of regional ventilation in the supine and prone posture at normal (1 G) and three times normal gravity (3 G). For these plots the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Mean ventilation per voxel was calculated for each segment, each subject and each posture. Plotted values are the mean ventilation for each section across all individuals for each situation. Data are identical to those in Figure 17 but in this plot combined to further illustrate the effect of gravity on the distribution of regional ventilation along the vertical distance of the lung. For comparison data were included for the distribution of ventilation in the same body posture but at 1 G. These data are from a prior study using other subjects.[21] Differences between the different situations therefor reflect the effect of the direction and magnitude of the gravitational force on the distribution of ventilation within the lung parenchyma. Error bars marking SD are omitted to enhance clarity. All data are from SPECT image acquisition supine.

DISCUSSION

Determinants of lung perfusion and ventilation

As the title implies, the overall aim of this thesis has been to investigate the role of body posture and gravity as determinants of regional lung perfusion and ventilation. The results show that neither body posture nor gravity is the sole determinant of these distributions, although they both play important roles. If posture was the only, or predominant, determinant of the distribution of ventilation and lung blood flow, and all other factors identical, the comparisons upright – head-down, respectively supine – prone would be mirror images and this is clearly not the case. Figure 19 combines SPECT images from **Study II** and an earlier supine – prone study from the research group,[21] and depicts the changes in distribution of perfusion if the body is seen as a spinning wheel. The images serve to give a schematic illustration of the influence of gravity on regional lung blood flow in these postures. Just looking at the images gives the impression that gravity is a major determinant of lung blood flow distribution. However, the results from **Study II** suggest otherwise. In **Study II**, exploring the maximal influence of posture under normal gravitational conditions, we conclude that lung structure is the main determinant of regional lung blood flow, which is in agreement with earlier studies using the same approach.[60]

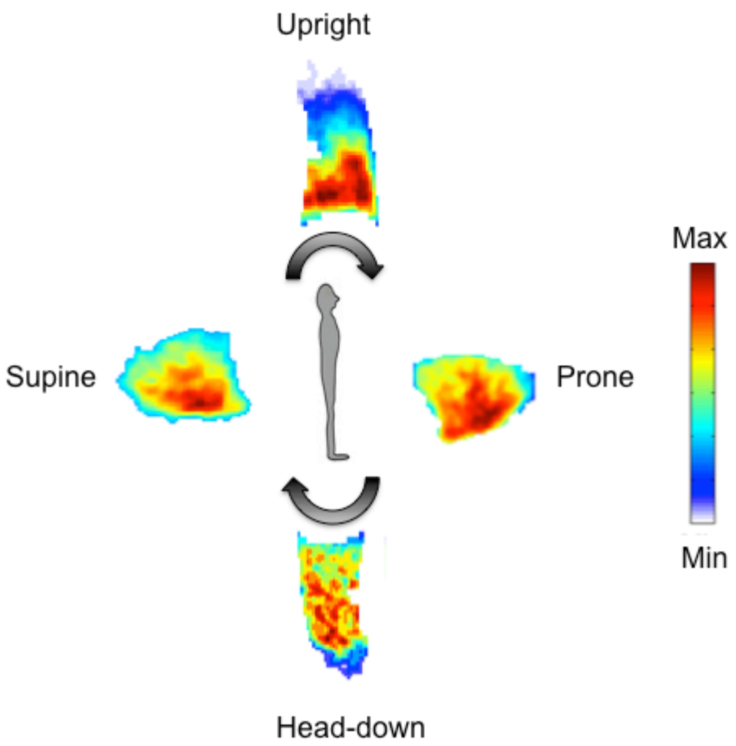


Figure 19. Single photon emission computed tomography images of the distribution of regional blood flow in different postures at normal gravity. For comparison, images for the supine and prone postures are included from a prior study using a different subject.[21] Images for upright and head-down are from the same subject (**Study II**). Images represent a sagittal section of the lung. Image acquisition was obtained supine. Coloring is according to a relative scale individual for all images.

Distribution of ventilation

The studies included in this thesis have examined the distribution of regional ventilation under various conditions, all in healthy humans:

- Anesthetized and mechanically ventilated with and without PEEP 10 cmH_2O, supine and prone (**Study I**)
- Awake supine at normal gravity and hypergravity (**Study III**)
- Awake supine and prone at hypergravity (**Study IV**)

Although not the same subjects, the following discussion compares the results from these and earlier studies from the research team, aiming at further clarifying the influence of posture and gravity. These prior studies used SPECT methods that were identical, or very similar, to the method used in this thesis. The plots in Figure 20 illustrate the distribution of ventilation in the supine and prone human in the different situations.

Ventilation supine

The results from **Study III** demonstrate that regional ventilation in the awake supine human is most pronounced in the dependent, dorsal, part of the lung. This is consistent with earlier studies.[18, 21-28] As Figure 20 A depicts, our results suggest that general anesthesia and mechanical ventilation without PEEP causes a shift of regional ventilation from dependent to non-dependent lung regions (**Study I**). This is in agreement with the study by Tokics et al.[91], but in contrast with the findings by Nyrén et al.[92] demonstrating an increasing gradient in the opposite direction. Both studies used SPECT, as the studies in this thesis. Nyrén et al. argued that an explanation to these diverging results might be that Tokics et al. noted atelectasis in the most dependent lung. Nyrén et al. performed recruitment maneuvers, and the subjects were mechanically ventilated with a PEEP of 4-5 cmH_2O, which may have prevented formation of atelectasis and thereby a decreased dependent ventilation. However, as a recruitment maneuver was performed also in **Study I**, and no atelectasis was seen on the CT scan, the presence of significant atelectasis cannot explain the different findings in this study. With the addition of PEEP 10 cmH_2O in **Study I**, ventilation was redistributed towards the dependent (dorsal) part of the lung – mimicking the pattern in the awake situation (Fig. 20 A). In earlier studies, the addition of PEEP has proved to increase ventilation to the dependent lung in anesthetized and mechanically ventilated humans in lateral position.[105] In supine anesthetized and mechanically ventilated humans, Hulands et al. demonstrated a distribution of ventilation slightly in favor of the dependent lung region during inflation of the lung to 1 liter above FRC, although not significantly different from the awake situation.[89]

Returning to awake supine subjects, **Study III-IV** demonstrates the redistribution of ventilation from dependent towards non-dependent lung regions with a change from normal to three times normal gravity (Fig. 20 A).

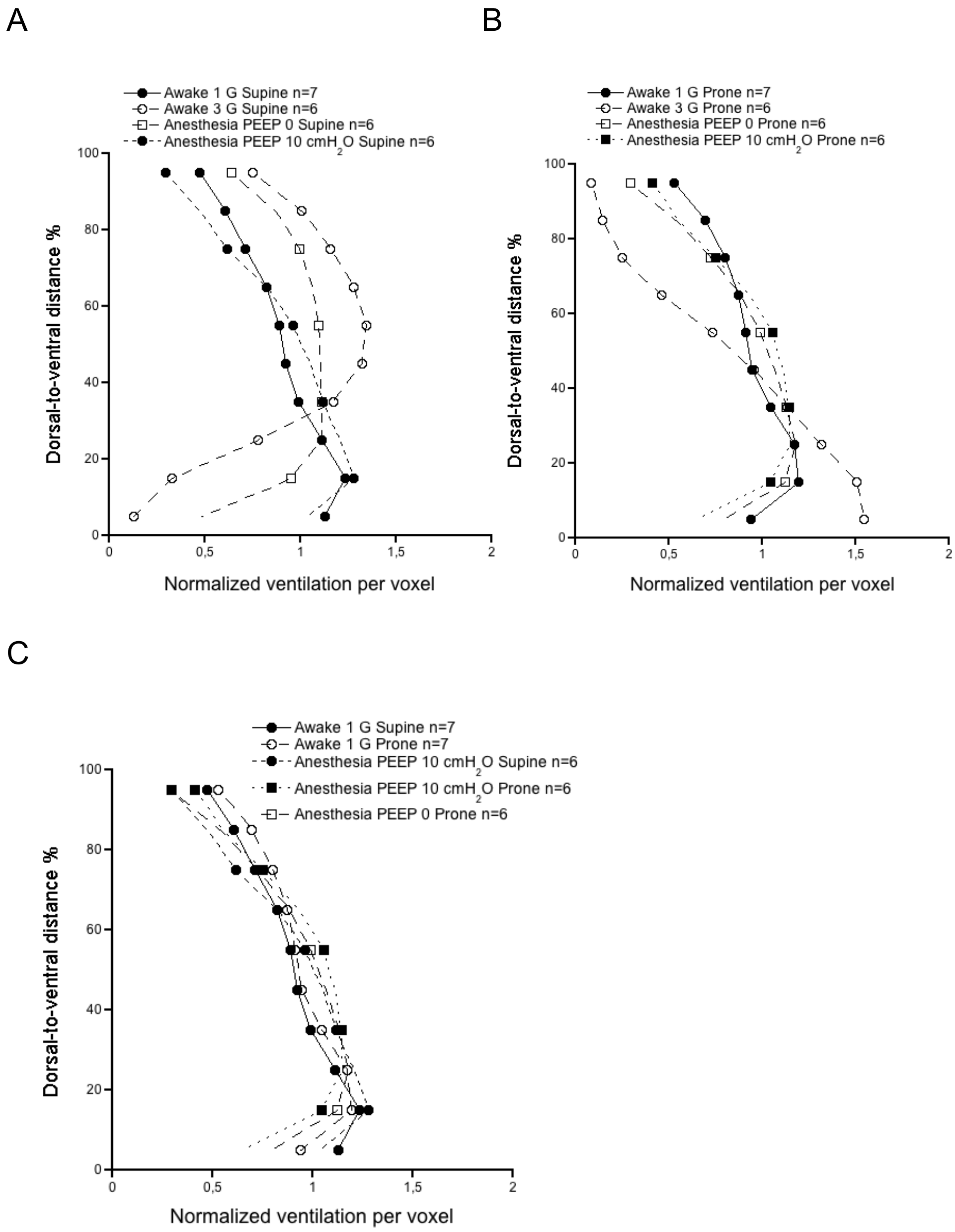


Figure 20. Plots A-B summarizes the distribution of ventilation in supine and prone posture, respectively. **Plot C** show the same data for normal gravity but now combined with the intention to illustrate the remarkably similar pattern of distribution of ventilation in different situations. For these plots, the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Normalized regional ventilation per voxel was averaged within each section. Plotted values are the mean values across all individuals for each section, error bars marking SD are omitted to enhance clarity. For comparison, data for the awake situation in both postures are included. These data are from a prior study using different subjects.[21] All data are from SPECT image acquisition supine. PEEP, Positive end-expiratory pressure; 1 G, normal gravity; 3 G, three times normal gravity.

Ventilation prone

Comparing the results from awake prone humans in an earlier study[21] with the results from **Study I** on anesthetized and mechanically ventilated humans, a similar pattern of ventilation, regardless of level of PEEP is indicated. In all three situations, regional ventilation is most pronounced in the dorsal, non-dependent, region of the lung as illustrated in Figure 20 B. Exposure to hypergravity (**Study IV**) results in a redistribution of ventilation from dependent towards non-dependent lung regions compared to 1 G conditions (Fig. 20 B). Interesting to note is the similar, predominantly dorsal, distribution of ventilation in the different situation shown in Figure 20 C.

To summarize; ventilation is predominantly distributed to the dorsal (dependent in supine and non-dependent in prone) part of the lung in both supine and prone awake subjects, as well as in anesthetized subjects mechanically ventilated with PEEP 10 cmH_2O in supine, and regardless of PEEP 0 or 10 cmH_2O in the prone posture (Fig. 20 C). Hypergravity increases ventilation to the non-dependent part of the lung, i.e. ventral in supine and dorsal in prone posture. Compared to awake subjects, the same shift is seen in the anesthetized subjects mechanically ventilated without PEEP in the supine posture.

We suggest that airway closure may be a possible shared explanation to the decrease in ventilation in the dependent lung regions in supine humans with the induction of general anesthesia and mechanical ventilation without PEEP, as well as at exposure to hypergravity in both supine and prone posture. In both situations, a reduction of FRC occurs with increased airway closure resulting in reduced regional ventilation in the dependent region of the lung.

Distribution of perfusion

The distribution of regional lung perfusion in healthy subjects has been addressed in the following situations:

- During general anesthesia and mechanical ventilation with and without PEEP 10 cmH_2O, supine and prone (**Study I**)
- Awake in the upright and inverse upright posture (**Study II**)

Perfusion supine

As for regional ventilation, the following discussion compares the results from these and earlier studies from our group, aiming at further clarifying the influence of posture and gravity. Studying healthy subjects with the same SPECT technique, Petersson et al.,[21] in accordance with several other studies,[22, 26, 30, 44-47] demonstrated a predominant distribution of perfusion in the dependent, dorsal, part of the lung in awake supine subjects. When compared to awake supine subjects, the results from **Study I** demonstrates that general anesthesia and mechanical ventilation are associated with a redistribution of blood flow from non-dependent towards dependent lung regions and that this is accentuated during mechanical ventilation with PEEP (Figure 21 A).

Perfusion prone

In the prone awake human, the same study by Petersson et al.[122] showed a predominant distribution of perfusion in the non-dependent, dorsal, region of the lung in the awake human. With induction of general anesthesia and mechanical ventilation, the results from **Study I** demonstrates a redistribution of regional blood flow towards dependent, ventral, lung regions, again even more pronounced with the addition of PEEP (Figure 21 B).

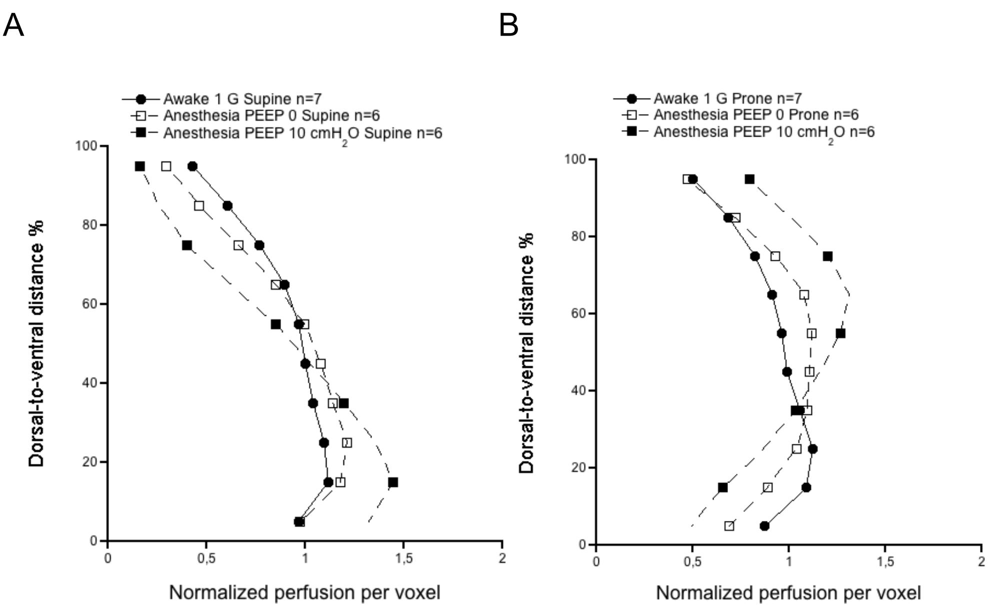


Figure 21. The plots summarize the distribution of blood flow in supine and prone posture, respectively. For these plots, the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung Normalized regional perfusion per voxel was averaged within each section. Plotted values are the mean value across all individuals for each section, error bars marking SD are omitted to enhance clarity. For comparison, data for the awake situation in both postures are included. These data are from a prior study using different subjects.[21] All data are from SPECT image acquisition supine. PEEP, Positive end-expiratory pressure; 1 G, normal gravity.

Possible mechanisms causing the redistribution of blood flow with the addition of PEEP are increasing vascular resistance due to hyperinflation of non-dependent lung regions, decreased cardiac output and pulmonary artery pressure (PAP), and increased airway pressure. As discussed, these factors might induce, and/or increase, zone 1 and 2 conditions in a greater region of the lung. Another explanation might be reduced hypoxic vasoconstriction in previously atelectatic or poorly ventilated dependent lung regions.

Ventilation-to-perfusion match

The ventilation-to-perfusion match was directly addressed in **Study I**. However, the results from **Study IV**, distribution of regional ventilation in supine and prone posture at 3 G, together with the results from a prior study on regional perfusion with the same technique and conditions,[122] also enables a discussion of the ventilation-to-perfusion match at 3 G.

Anesthesia, mechanical ventilation and PEEP

Figure 22 presents the distribution of ventilation and perfusion, respectively, in supine and prone posture, with and without PEEP. In supine posture, the addition of PEEP caused a similar redistribution of both perfusion and ventilation towards dependent lung regions with little changes in V/Q ratios (Fig. 22 A-B). In prone subjects on the other hand, the redistribution of perfusion towards dependent lung regions was much greater compared to the redistribution of ventilation, leading to an increased V/Q mismatch (Fig. 22 C-D). With PEEP, the vertical ventilation-to-perfusion gradient was similar in both supine and prone posture. However, without PEEP the gradient was less in prone than in supine posture. From the results, derived from normal subjects, it is clear that the influence of posture (supine vs. prone) is greater in anesthetised and mechanically ventilated normal subjects than under awake, spontaneously breathing conditions. Hence, both posture and PEEP affects the ventilation-to-perfusion match.

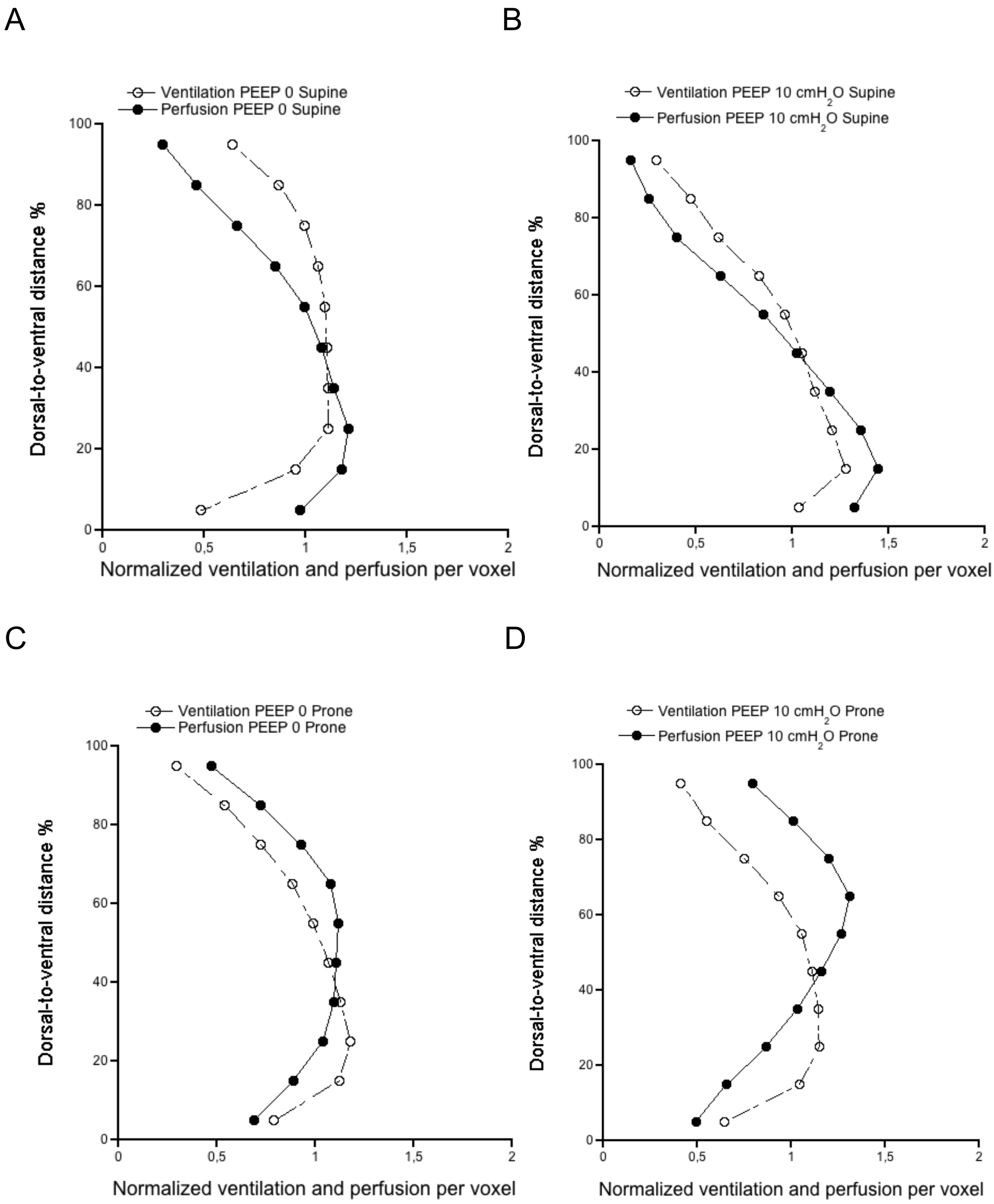


Figure 22. These plots combine regional ventilation (V) and perfusion (Q) and illustrate the redistribution of V and Q with the addition of PEEP in (**A-B**) supine and (**C-D**) prone posture. For these plots, the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Normalized regional ventilation and perfusion, respectively, per voxel was averaged within each section. Plotted values are the mean value across all individuals for each section, error bars marking SD are omitted to enhance clarity. All data are from SPECT image acquisition supine. PEEP, Positive end-expiratory pressure.

Hypergravity

As discussed in the introduction, impaired arterial oxygenation can be caused by hypoventilation, diffusion limitation, shunt, or ventilation-to-perfusion mismatch. In this thesis, the subjects exposed to hypergravity in **Study III and IV** demonstrated a clinically significant impairment in gas exchange with arterial desaturation, but why? The respiratory measurements exclude hypoventilation to be the cause of the impaired gas exchange. Diffusion limitation is a rare cause of impaired gas exchange and, although possible, we consider parenchymal oedema formation unlikely during this short exposure to 3 G. Thus, the probable cause of the hypergravity-induced desaturation is ventilation-to-perfusion mismatch, or shunt.

Adding the results from **Study IV** to the corresponding results for perfusion in the earlier study from the research group[122] enables a comparison of the regional ventilation and blood flow, respectively, in supine and prone humans exposed to hypergravity. As showed in Figure 23, these results demonstrate a predominant distribution of ventilation and perfusion to the non-dependent lung region during hypergravity in both supine and prone posture. Since arterial saturation is better preserved in prone, it is reasonable to argue that the degree of ventilation-to-perfusion mismatch is less in this posture. With the SPECT technique, shunt cannot be excluded.

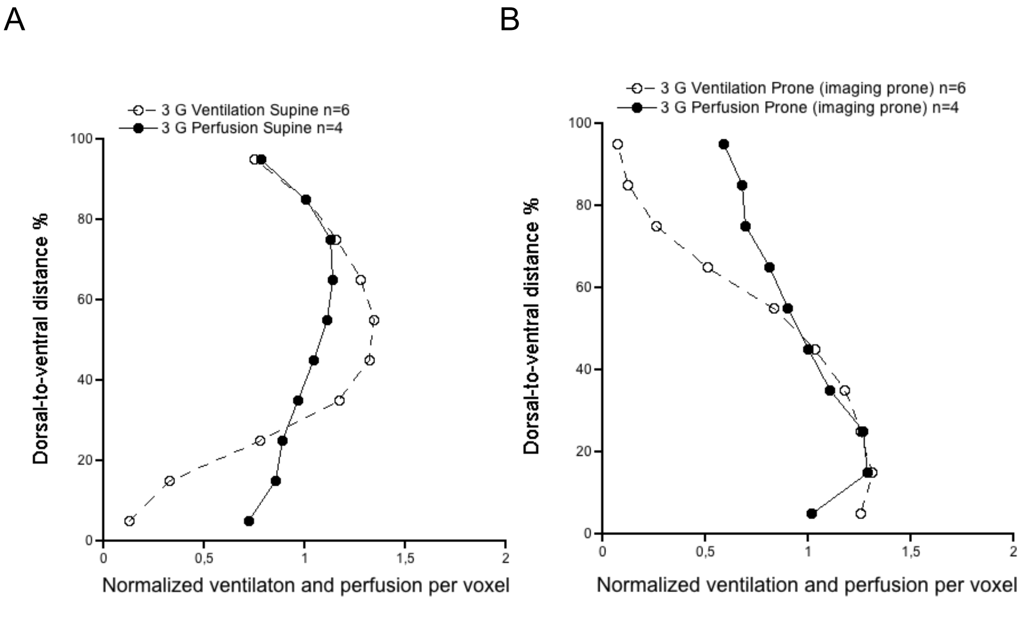


Figure 23. These plots illustrate the distribution of ventilation and perfusion in supine and prone posture, respectively. For these plots, the lungs were divided into 10 sections of equal height along the dorsal-to-ventral distance of the lung. Normalized regional ventilation and perfusion per voxel, respectively, were averaged within each section. Plotted values are the mean value across all individuals for each section, error bars marking SD are omitted to enhance clarity. For comparison, data for distribution of perfusion in both postures at 3 G are included. These data are from a prior study using different subjects.[122] Ventilation data are from the whole lung; perfusion data are from a transverse section of the lung. Supine data are from SPECT image acquisition supine, while prone data are from SPECT image acquisition prone. 1 G, normal gravity; 3 G, three times normal gravity.

Important to keep in mind is that the distribution of tissue is different during exposure to hypergravity compared to during normal gravity. With increased gravitational force, lung parenchyma is shifted towards a more dependent position within the thorax. A lung region that is in the upper half (non-dependent) of the vertical height of the lung at 1 G might be shifted to the lower half (dependent) at hypergravity. With the return to normal gravity, the displaced lung tissue moves back to the normal non-dependent position. This is probably more pronounced in supine posture, due to the greater influence of the heart and abdominal contents on the lung in supine compared to prone posture. This phenomenon has to be taken into account when discussing the results from the hypergravity studies. The mapped vertical gradient in regional ventilation would have looked different if imaged during hypergravity, i.e. ventilation to the dependent half of the lung would have been greater. Equally important, our method, with all images obtained at normal gravity and in the same posture, captures the different distribution of ventilation within the lung during different conditions.

Other factors influencing regional lung blood flow

As discussed in the introduction, several factors influence regional ventilation and perfusion. Among them, cardiac output and hypoxic pulmonary vasoconstriction will be discussed further in relation to the studies in this thesis.

Cardiac output

An increase or decrease in cardiac output secondary to a change in body posture or gravitational force may influence the distribution of lung blood flow and hence ventilation-to-perfusion match. An increase in cardiac output results in only a small increase in PAP, approximately 1 mmHg per liter of cardiac output in healthy young humans.[139] However, as cardiac output rises, the increased pressure in the pulmonary vessels exceeds the pressure in the alveoli resulting in recruitment of more capillaries as well as an increase in vessel caliber (distension). Studies have demonstrated a more homogenous ventilation-to-perfusion match in humans during exercise-induced increase in cardiac output, due to increased blood flow to the non-dependent part of the lung.[40, 140, 141] In contrast, a reduction in cardiac output might cause a reduction of blood flow to non-dependent regions, i.e. increasing zone 1. A second mechanism that might cause worsened arterial oxygenation at a decrease in cardiac output, in the presence of V/Q mismatch, is a decrease in the mixed venous oxygen saturation.

With a change between supine and prone posture, Savaser et al.[142] found no statistically significant difference in cardiac output. There are few studies on the hemodynamic effects on steep (>45°) head-down tilt in humans, and the results are inconsistent. Of three human studies on 90° head down tilt, two found no significant changes in cardiac output[143, 144] while one demonstrated an increase in cardiac output.[145] Considering the overall stable physiological parameters (presented in Table 9) in **Study II**, we do not believe that the redistribution of regional blood flow demonstrated with a change from upright to head-down posture was caused by hemodynamic changes.

Table 9. Physiological data, **Study II**

	Upright	Head-down	*P* value
Pulse Oximetry, %	97 ± 1	98 ± 2	0.41
Heart rate, beats/min	78 ± 18	76 ± 10	0.83
Systolic blood pressure, mmHg	129 ± 12	129 ±14	0.97
Diastolic blood pressure, mmHg	83 ±7	75 ± 11	0.02

Physiological measurements during injection of radiotracer. Values are mean ± SD.

In a study on humans exposed to 5 G in the supine and prone posture, Rodin et al.[114] demonstrated a decrease in cardiac output during hypergravity compared to 1 G. However, studies in humans exposed to up to 5 G in the launch position (i.e. with elevated legs and hips and knee joints in 90-100° angle),[146, 147] as well as supine humans exposed to 2 G,[148] did not demonstrate a systematic/significant change in cardiac output. An earlier study from our research group (unpublished data) exposing volunteers to 3 G in the strict horizontal posture demonstrated only a small decrease (mean 8%) in cardiac output. Since the subjects in **Study III and IV** did not significantly increase their heart rate (presented in Table 10), and considering their position in the centrifuge to be closer to the launch position together with the relatively low level of hypergravity, we do not believe decreased cardiac output was a major contributor to our results.

Table 10. Physiological response to hypergravity exposure, summary of results from **Study III-IV**

	Supine				Prone	
	1 G (III)	**3 G (III)**	**1 G (IV)**	**3 G (IV)**	**1 G (IV)**	**3 G (IV)**
Pulse Oximetry, %	97.8 ± 0.5	89.7 ± 3.5	98 ± 0.6	90 ± 2.0	98 ± 0.4	94 ± 1.7
Respiratory rate, breaths/min	13 ± 3	15 ± 5	14 ± 4	16 ± 5	14 ± 3	15 ± 3
Tidal volume, L	0.06 ± 0.14	0.50 ± 0.10	0.77 ± 0.35	0.63 ± 0.29	0.67 ± 0.26	0.57 ± 0.28
Minute ventilation, L/min	7.3 ± 1.1	7.2 ± 1.5	9.6 ± 3.9	9.2 ± 2.7	9.3 ± 3.3	8.1 ± 3.3
Heart rate, beats/min	67 ± 9	77 ± 13	80 ± 16	84 ± 11	81 ± 15	84 ± 13

Physiological measurements for the last 2 minutes at normal gravity before acceleration (1 G) and for the last 2 minutes during the exposure to three times normal gravity (3 G). Study III, n=10; Study IV, n=6. Values are mean ± SD. Statistical comparisons are reported in the individual paper III-IV.

Hypoxic pulmonary vasoconstriction

Global alveolar hypoxia causes pulmonary hypertension through hypoxic pulmonary vasoconstriction (HPV) and, if long-standing, vascular remodeling occurs.[149] Similarly, regional alveolar hypoxia results in regional vasoconstriction. If the region with alveolar hypoxia is only a small part of the lung, the result is a reduction in regional lung blood flow but with little effect on the pulmonary arterial pressure. If the extent of the hypoxic region is large the redistribution of blood flow is less and the increase in pulmonary arterial pressure greater. In a previous study we exposed healthy humans to 5 G with and without prior administration of drugs suppressing HPV.[150] No difference in arterial desaturation was seen between the groups. The results suggest that HPV do not have a major influence on the V/Q mismatch caused by this exposure to hypergravity.

Limitations

Limitations specific for each study have been discussed in the separate papers. The SPECT technique used in all studies in this thesis have some characteristics important to acknowledge for the understanding of the results.

Different imaging techniques provide estimates of regional lung blood flow and ventilation expressed in units with different denominators, for instance unit lung volume, unit lung tissue or unit alveolar gas volume. This hampers direct comparisons between different methods since the amount of lung tissue or alveolar gas volume per unit lung volume differ between lung regions as well being influenced by posture, total lung volume, breathing pattern etc.

SPECT results are commonly expressed per unit lung volume making a comparison between images difficult if a redistribution of tissue can be assumed to have occurred. In all studies in this thesis, the comparisons between different conditions have always been with SPECT image acquisition supine. Thereby, the differences noted are differences in the distribution of perfusion or ventilation within the vasculature or airways because the distribution of lung tissue does not differ between images. Another advantage with imaging in the same posture is that attenuation and scatter do not contribute to differences between images.

The radionuclides used in this thesis result in SPECT images with slightly different spatial resolution, which in turn results in different partial volume effects. With the SPECT system used in the thesis FWHM is around 10-20 mm for ^{99m}Tc. For ^{113m}In the spatial resolution is slightly lower (FWHM 20-30 mm[151]). To determine whether the differences in spatial resolution lead to differences in the mapped distributions, we performed a pilot experiment as part of **Study II**. When the two radiotracers were injected simultaneously in an upright subject, and the SPECT data was analyzed in the same way as the experiments included in the study, no differences in the distribution of regional blood flow between the radiotracers were demonstrated as shown in Figure 24. We therefore conclude that the comparisons made using the two different radiotracers are not influenced by the different spatial resolutions. As reported in the results section, the SPECT method (i.e. the partial volume effect) contributes substantially to the r^2 values of the variability in blood flow per voxel ascribed to structure. Hence, the SPECT method results in an overestimation of the influence of structure in both body postures. However, taking the results from our analysis of the influence of the partial volume effect into account, the results in **Study II** still suggests that structure is the major determinant of regional blood flow, because the correlation induced by the method is a minor part of the total correlation ascribed to structure.

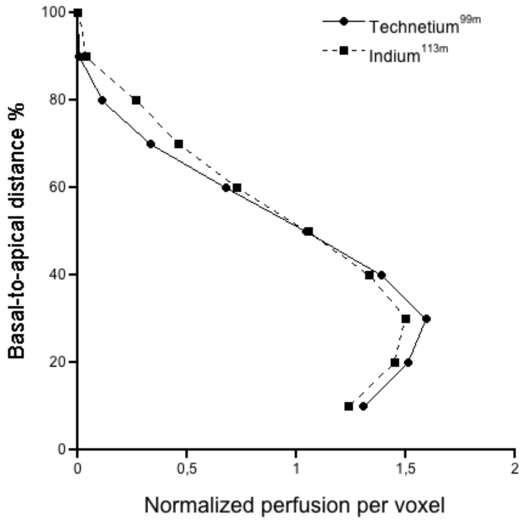


Figure 24. Distribution of normalized perfusion per voxel, mapped with technetium^{99m} and indium^{113m}, respectively.

As all subjects included in this thesis were healthy, the effect of PEEP, posture and gravity on regional lung ventilation and blood flow might be different in patients with respiratory failure. Due to ethical reasons, i.e. the administration of radioactivity, the subjects are different in each study, hampering the comparison between the different series of experiments. Despite this evident limitation, comparisons have been made in order to visualize the changes in ventilation and perfusion during the same body postures but under different conditions as well as comparing different postures. For the same ethical reasons the number of subjects in each study is small. Therefore, a number was chosen which has allowed identification of physiologic meaningful differences in previous studies.

Clinical implications - optimizing gas exchange

In the normal lung, during normal gravitational conditions, the ventilation-to-perfusion match is almost perfect. In patients with respiratory failure, the impairment of gas exchange is due to some degree of mismatch between regional ventilation and perfusion. The goal for both the intensivist working with a patient with lung failure and the anesthetist handling the anesthetized patient during surgery is to optimize gas exchange. To do so, it is important to understand the impact of body posture and gravity on the distribution of ventilation and lung blood flow as well as being able to use the ventilator in an optimal way.

The results of **Study I** tell us that adding PEEP to mechanically ventilated healthy humans in the supine posture adds little to the overall ventilation-to-perfusion match, redistributing both ventilation and blood flow towards the dependent parts of the lung. In the prone posture, the addition of PEEP leads to a much greater shift in blood flow than ventilation, increasing the ventilation-to-perfusion mismatch. In the clinical practice, this leads to the suggestion that optimal PEEP might be lower in the prone posture compared to supine, and that addition of PEEP may have a negative effect on gas exchange. The understanding that the impact of posture, supine vs. prone, on regional lung blood flow and ventilation in normal subjects is much greater in the anesthetized mechanically ventilated human than in the awake is also important to bear in mind.

CONCLUSIONS

The general conclusion based on the results of this thesis is that body posture and gravity both affect the distribution of ventilation and perfusion in the lung.

Specific conclusions are:

- In anesthetized and mechanically ventilated healthy humans, the addition of PEEP 10 cmH_2O results in a similar redistribution of both ventilation and blood flow towards dependent regions of the lung in the supine posture. This results in little change in the ventilation-to-perfusion match. In prone posture, in contrast, PEEP causes a much greater redistribution of blood flow than ventilation, leading to increased mismatch. The vertical ventilation-to-perfusion gradient is less in prone than supine posture without PEEP, but similar with the addition of PEEP (**Study I**).

- With a shift in body posture from upright to head-down posture, lung blood flow is redistributed from basal to apical lung regions. Our results also suggests that lung structure is a greater determinant of regional blood flow than gravity in all body postures (**Study II**).

- The use of Technegas to map regional ventilation in humans exposed to hypergravity is feasible (**Study III**).

- Exposure to 3 G results in a redistribution of ventilation from dependent to non-dependent lung regions in spontaneously breathing supine humans (**Study III and IV**).

- In spontaneously breathing healthy humans subjected to hypergravity (3 G) ventilation shifts from dependent to non-dependent lung regions in both supine and prone postures. The difference in vertical distribution between the supine and prone postures is much larger at 3 G compared to normal gravity. Compared to supine, the prone posture has a protective effect against hypergravity-induced arterial desaturation (**Study IV**).

I shall pass through this world but once.
Any good, therefore,
that I can do
or any kindness that I
can show to any fellow human being,
let me do it now.
Let me not defer nor
neglect it, for I shall not pass
this way again.

Anonymous

Retold by Dr. David in Magburaka, Sierra Leone, during the Ebola epidemic.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to everyone who has supported me and contributed to this thesis, especially the volunteers. Without their participation, no studies would have been possible.

Associate Professor Johan Petersson, main supervisor. Thank your for sharing your vast knowledge in a wide variety of fields, from respiratory physiology to beer and music. You have continuously encouraged me to find out what´s in “the black box”, and your curiosity is impressive. You are indeed one of a kind!

Associate Professor Margareta Mure, co-supervisor. You have been a role model from my years as a resident and PhD student, but also as a woman. Thank you for being just all that.

Associate Professor Alejandro Sánchez-Crespo, co-supervisor. Warm as the Spanish sun. Thank you for always keeping your door open for me, and for guiding me through the radiating field of nuclear medicine.

Professor Sten Lindahl, co-supervisor, and the godfather of our research group. Thank you for sharing your deep knowledge and experience, and for your positive spirit!

Professor Lars I Eriksson, thank you for most valuable support in the realization of this book, and for your reassuring smile.

Professor Dag Linnarsson, the maestro of physiology. Thank you for outstanding and invaluable input in the studies. Lars Karlsson, co-writer, former co-PhD student, and future colleague – welcome to the other side of Solnavägen! Björn Johannesson and Bertil Lindborg at the human centrifuge, and Anette Ebberyd, laboratory manager, thank you for excellent support during the experiments.

Elisabeth Anjou, wonderful mentor and former colleague at Cardiothoracic anesthesia and intensive care. Your enthusiasm, as well as thoughtfulness, has been very important to me during these years. I always leave our meetings feeling light at heart. Thank you. I hope to share many more dinners with you, even though I´m not a PhD student any longer!

Anders Franco-Cereceda, Professor of Cardiothoracic Surgery. For invaluable support and, equally important, encouragement when needed the most. Thank you.

Professor Rob Glenny. Thank you for most valuable feedback over the years, but also for warming thoughts. Although “over there”, you are a very present member of the research team. At the ATS congress in San Diego 2014, you said about research “It´s like beer – longer time makes it stronger”. I cherished that possible truth for five more years, but now, enough is enough!

Former head at former ANOPIVA, Lars Irestedt (or, as Jessica and I call you: Konungen) who, together with late Per Gannerdahl, opened the door for me to the world of anesthesia and intensive care with the decision to hire me in the first place. Kristina Hambraeus-Jonzon, former head of residents at former ANOPIVA, for guiding me through my residency with both competence and style. Åke Hellström, former head of Cardiothoracic anesthesia and intensive care, who welcomed me to the heart of our speciality, and Björn Persson, current head of PMI FO Thoraxoperation och thoraxintensivvård, thank you for encouragement.

Fredrik Bredin and Lena Nilsson, my boss and our scheduler, respectively, at PMI Thorax. Thank you for your never-ending support and warm friendship when life takes its toll, and all other days as well. I could never wish for more.

Jessica Kåhlin, from med-school through vik UL, internship and residency to PhD – but above all an exceptional friend. I would literally have been lost without you. Anna Olsson, you make any grey Monday feel like a cozy Friday. I truly appreciate the magnitude of our discussions. Especially in the cottage in Skåne! Emma Larsson, you wonderful human. Thank you for being a fixare larger than life and for very important tips.
Together, you made all the difference.

Laura Saiepour, my dear friend. Thank you for always providing comfort for both belly and mind, and an x-ray vision when needed. Your kitchen… probably the homiest place in town.

Thomas Fux, colleague and friend extraordinaire. Thank you for sharing tears and laughter, and occasional outbursts, always.

Dearest Karin Eriksson, Claire Rimes-Stigare, Francesca Campoccia-Jalde, Jesper, Emelie, Anders, Mark, Susanne, and all you wonderful colleagues, all categories. Thank you for being there, both on and off duty. Imagine hanging out with friends all day, doing fun and interesting things together. That's my workplace – that´s how lucky I am!

My best friends from the best coast, from the time when it was actually called "bästisar" – I wouldn't be me if it weren't for you. For numerous picnics to come! And my dear friends from and on other coasts, you are invaluable in so many ways.

My beloved Mamma and Pappa, thank you for always, always, believing in me and for all encouragement and support throughout life, and for being such apparent sources of inspiration. I love you more than all the houses in the world. And you too Farmor, Moster, Peter and Maria!

Conny. "And when it rains you´re shining down for me, and I just can´t get enough…"
You are simply amazing.

REFERENCES

1. Hutchinson J. Thorax. In: RB T, ed. *Encyclopaedia of anatomy and physiology 4*. London: Logmans; 1849-1852:1059.

2. Orth J. *Atiologisches und anatomisches uber Lungenschwindsucht*. Berlin: August Hirschwald; 1887.

3. Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. *Am Rev Respir Dis.* 1974;110:143-144.

4. Langer M, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients. A clinical study. *Chest.* 1988;94:103-107.

5. Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. *Am Rev Respir Dis.* 1977;115:559-566.

6. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *The New England journal of medicine.* 2001;345:568-573.

7. Mancebo J. A Multicenter Trial of Prolonged Prone Ventilation in Severe Acute Respiratory Distress Syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2006;173:1233-1239.

8. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Medicine.* 2008;34:1487-1491.

9. Guerin C. Effects of Systematic Prone Positioning in Hypoxemic Acute Respiratory Failure: A Randomized Controlled Trial. *JAMA: The Journal of the American Medical Association.* 2004;292:2379-2387.

10. Pelosi P, Caironi P, Taccone P, Brazzi L. Pathophysiology of prone positioning in the healthy lung and in ALI/ARDS. *Minerva Anestesiol.* 2001;67:238-247.

11. Albert RK, Leasa D, Sanderson M, Robertson HT, Hlastala MP. The prone position improves arterial oxygenation and reduces shunt in oleic-acid-induced acute lung injury. *Am Rev Respir Dis.* 1987;135:628-633.

12. Mure M, Martling CR, Lindahl SG. Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. *Crit Care Med.* 1997;25:1539-1544.

13. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *The New England journal of medicine.* 2013;368:2159-2168.

14. Fowler WS. Lung function studies; uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J Appl Physiol.* 1949;2:283-299.

15. Martin CJ, Cline F, Jr., Marshall H. Lobar alveolar gas concentrations; effect of body position. *J Clin Invest.* 1953;32:617-621.

16. Rahn H, Sadoul P, Farhi LE, Shapiro J. Distribution of ventalation and perfusion in the lobes of the dog's lung in the supine and erect position. *J Appl Physiol.* 1956;8:417-426.

17. Ball WC, Jr., Stewart PB, Newsham LG, Bates DV. Regional pulmonary function studied with xenon 133. *J Clin Invest.* 1962;41:519-531.

18. Milic-Emili J, Henderson JA, Dolovich MB, Trop D, Kaneko K. Regional distribution of inspired gas in the lung. *J Appl Physiol.* 1966;21:749-759.

19. Glazier JB, Hughes JM, Maloney JE, Pain MC, West JB. Decreasing alveolar size from apex to base in the upright lung. *Lancet.* 1966;2:203-204.

20. Glenny RW, Robertson HT. Spatial distribution of ventilation and perfusion: mechanisms and regulation. *Compr Physiol.* 2011;1:375-395.

21. Petersson J, Rohdin M, Sánchez-Crespo A, et al. Posture primarily affects lung tissue distribution with minor effect on blood flow and ventilation. *Respiratory Physiology & Neurobiology.* 2007;156:293-303.

22. Kaneko K, Milic-Emili J, Dolovich MB, Dawson A, Bates DV. Regional distribution of ventilation and perfusion as a function of body position. *J Appl Physiol.* 1966;21:767-777.

23. Rehder K, Sessler AD, Rodarte JR. Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed man. *J Appl Physiol.* 1977;42:391-402.

24. Amis TC, Jones HA, Hughes JM. Effect of posture on inter-regional distribution of pulmonary ventilation in man. *Respir Physiol.* 1984;56:145-167.

25. Mure M, Nyren S, Jacobsson H, Larsson SA, Lindahl SG. High continuous positive airway pressure level induces ventilation/perfusion mismatch in the prone position. *Crit Care Med.* 2001;29:959-964.

26. Musch G, Layfield JD, Harris RS, et al. Topographical distribution of pulmonary perfusion and ventilation, assessed by PET in supine and prone humans. *J Appl Physiol.* 2002;93:1841-1851.

27. Sa RC, Cronin MV, Henderson AC, et al. Vertical distribution of specific ventilation in normal supine humans measured by oxygen-enhanced proton MRI. *J Appl Physiol.* 2010;109:1950-1959.

28. Wilson JE, 3rd, Bynum LJ, Ramanathan M. Dynamic measurement of regional ventilation and perfusion of the lung with Xe-133. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 1977;18:660-668.

29. Rehder K, Knopp TJ, Sessler AD. Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed prone man. *J Appl Physiol.* 1978;45:528-535.

30. Henderson AC, Sa RC, Theilmann RJ, Buxton RB, Prisk GK, Hopkins SR. The gravitational distribution of ventilation-perfusion ratio is more uniform in prone than supine posture in the normal human lung. *Journal of applied physiology.* 2013;115:313-324.

31. Treppo S, Mijailovich SM, Venegas JG. Contributions of pulmonary perfusion and ventilation to heterogeneity in V(A)/Q measured by PET. *J Appl Physiol (1985).* 1997;82:1163-1176.

32. Marcucci C, Nyhan D, Simon BA. Distribution of pulmonary ventilation using Xe-enhanced computed tomography in prone and supine dogs. *J Appl Physiol (1985).* 2001;90:421-430.

33. Altemeier WA, McKinney S, Krueger M, Glenny RW. Effect of posture on regional gas exchange in pigs. *Journal of applied physiology.* 2004;97:2104-2111.

34. Altemeier WA, McKinney S, Glenny RW. Fractal nature of regional ventilation distribution. *Journal of applied physiology.* 2000;88:1551-1557.

35. West JB. Regional differences in gas exchange in the lung of erect man. *J Appl Physiol.* 1962;17:893-898.

36. West JB, Dollery CT, Naimark A. Distribution of Blood Flow in Isolated Lung; Relation to Vascular and Alveolar Pressures. *J Appl Physiol.* 1964;19:713-724.

37. Hughes JM, Glazier JB, Maloney JE, West JB. Effect of lung volume on the distribution of pulmonary blood flow in man. *Respiration physiology.* 1968;4:58-72.

38. Anthonisen NR, Milic-Emili J. Distribution of pulmonary perfusion in erect man. *Journal of applied physiology.* 1966;21:760-766.

39. Arborelius M, Lilja B. Haemodynamic changes at different lung volumes. *Scandinavian journal of clinical and laboratory investigation.* 1972;29:359-369.

40. Bryan AC, Bentivoglio LG, Beerel F, Macleish H, Zidulka A, Bates DV. Factors Affecting Regional Distribution of Ventilation and Perfusion in the Lung. *Journal of applied physiology.* 1964;19:395-402.

41. Landmark SJ, Knopp TJ, Rehder K, Sessler AD. Regional pulmonary perfusion and V/Q in awake and anesthetized-paralyzed man. *J Appl Physiol.* 1977;43:993-1000.

42. Petersson J, Rohdin M, Sánchez-Crespo A, et al. Regional lung blood flow and ventilation in upright humans studied with quantitative SPECT. *Respiratory Physiology & Neurobiology.* 2009;166:54-60.

43. West JB, Dollery CT. Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive carbon dioxide. *Journal of applied physiology.* 1960;15:405-410.

44. Nyren S, Mure M, Jacobsson H, Larsson SA, Lindahl SG. Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. *Journal of Applied Physiology.* 1999;86:1135-1141.

45. Jones AT, Hansell DM, Evans TW. Pulmonary perfusion in supine and prone positions: an electron-beam computed tomography study. *J Appl Physiol.* 2001;90:1342-1348.

46. Prisk GK, Yamada K, Henderson AC, et al. Pulmonary perfusion in the prone and supine postures in the normal human lung. *J Appl Physiol.* 2007;103:883-894.

47. Cao JJ, Wang Y, Schapiro W, et al. Effects of respiratory cycle and body position on quantitative pulmonary perfusion by MRI. *J Magn Reson Imaging.* 2011;34:225-230.

48. Beck KC, Rehder K. Differences in regional vascular conductances in isolated dog lungs. *J Appl Physiol (1985).* 1986;61:530-538.

49. Glenny RW, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. *Journal of applied physiology.* 1991;71:620-629.

50. Glenny RW, Robertson HT. A computer simulation of pulmonary perfusion in three dimensions. *Journal of applied physiology.* 1995;79:357-369.

51. Rimeika D, Nyren S, Wiklund NP, et al. Regulation of regional lung perfusion by nitric oxide. *Am J Respir Crit Care Med.* 2004;170:450-455.

52. Rimeika D, Wiklund NP, Lindahl SG, Wiklund CU. Regional differences in nitric oxide-mediated vasorelaxation in porcine pulmonary arteries. *Acta Anaesthesiol Scand.* 2006;50:947-953.

53. Sanchez Crespo A, Hallberg J, Lundberg JO, et al. Nasal nitric oxide and regulation of human pulmonary blood flow in the upright position. *J Appl Physiol.* 2010;108:181-188.

54. Melsom MN, Flatebo T, Kramer-Johansen J, et al. Both gravity and non-gravity dependent factors determine regional blood flow within the goat lung. *Acta physiologica Scandinavica.* 1995;153:343-353.

55. Glenny RW, Polissar L, Robertson HT. Relative contribution of gravity to pulmonary perfusion heterogeneity. *Journal of applied physiology.* 1991;71:2449-2452.

56. Glenny RW. Spatial correlation of regional pulmonary perfusion. *Journal of applied physiology.* 1992;72:2378-2386.

57. Glenny RW, Lamm WJ, Bernard SL, et al. Selected contribution: redistribution of pulmonary perfusion during weightlessness and increased gravity. *J Appl Physiol.* 2000;89:1239-1248.

58. Walther SM, Domino KB, Glenny RW, Polissar NL, Hlastala MP. Pulmonary blood flow distribution has a hilar-to-peripheral gradient in awake, prone sheep. *Journal of applied physiology.* 1997;82:678-685.

59. Hlastala MP, Bernard SL, Erickson HH, et al. Pulmonary blood flow distribution in standing horses is not dominated by gravity. *Journal of applied physiology.* 1996;81:1051-1061.

60. Glenny RW, Bernard S, Robertson HT, Hlastala MP. Gravity is an important but secondary determinant of regional pulmonary blood flow in upright primates. *J Appl Physiol.* 1999;86:623-632.

61. Glenny RW, Robertson HT. Fractal properties of pulmonary blood flow: characterization of spatial heterogeneity. *Journal of applied physiology.* 1990;69:532-545.

62. Glenny RW, Robertson HT. Determinants of pulmonary blood flow distribution. *Compr Physiol.* 2011;1:39-59.

63. Johnson NJ, Luks AM, Glenny RW. Gas Exchange in the Prone Posture. *Respir Care.* 2017;62:1097-1110.

64. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *Eur Respir J.* 2014;44:1023-1041.

65. Lundberg JO, Lundberg JM, Settergren G, Alving K, Weitzberg E. Nitric oxide, produced in the upper airways, may act in an 'aerocrine' fashion to enhance pulmonary oxygen uptake in humans. *Acta Physiol Scand.* 1995;155:467-468.

66. Emery MJ, Eveland RL, Kim SS, Hildebrandt J, Swenson ER. CO2 relaxes parenchyma in the liquid-filled rat lung. *J Appl Physiol (1985).* 2007;103:710-716.

67. D'Angelo E, Calderini IS, Tavola M. The effects of CO_2 on respiratory mechanics in anesthetized paralyzed humans. *Anesthesiology.* 2001;94:604-610.

68. Barer GR, Shaw JW. Pulmonary vasodilator and vasoconstrictor actions of carbon dioxide. *J Physiol.* 1971;213:633-645.

69. Weibel ER, Sapoval B, Filoche M. Design of peripheral airways for efficient gas exchange. *Respir Physiol Neurobiol.* 2005;148:3-21.

70. Ross BB, Farhi LE. Dead-space ventilation as a determinant in the ventilation-perfusion concept. *J Appl Physiol.* 1960;15:363-371.

71. Tsukimoto K, Arcos JP, Schaffartzik W, Wagner PD, West JB. Effect of common dead space on VA/Q distribution in the dog. *J Appl Physiol (1985).* 1990;68:2488-2493.

72. Sylvester JT, Shimoda LA, Aaronson PI, Ward JP. Hypoxic pulmonary vasoconstriction. *Physiol Rev.* 2012;92:367-520.

73. Naeije R, Brimioulle S. Physiology in medicine: importance of hypoxic pulmonary vasoconstriction in maintaining arterial oxygenation during acute respiratory failure. *Crit Care.* 2001;5:67-71.

74. Bryan AC, Milic-Emili J, Pengelly D. Effect of gravity on the distribution of pulmonary ventilation. *J Appl Physiol.* 1966;21:778-784.

75. West JB. Distribution of gas and blood in the normal lungs. *Br Med Bull.* 1963;19:53-58.

76. West JB. Pulmonary gas exchange. *Int Rev Physiol.* 1977;14:83-106.

77. Mure M, Domino KB, Lindahl SG, Hlastala MP, Altemeier WA, Glenny RW. Regional ventilation-perfusion distribution is more uniform in the prone position. *Journal of applied physiology.* 2000;88:1076-1083.

78. Drinker P, Shaw LA. An apparatus for the prolonged administration of artificial respiration: I. A Design for Adults and Children. *J Clin Invest.* 1929;7:229-247.

79. Lassen HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet.* 1953;1:37-41.

80. Wahba RW. Perioperative functional residual capacity. *Can J Anaesth.* 1991;38:384-400.

81. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. *J Appl Physiol.* 1973;34:81-86.

82. Hedenstierna G, Edmark L. Effects of anesthesia on the respiratory system. *Best Pract Res Clin Anaesthesiol.* 2015;29:273-284.

83. Strandberg B. The incidence of atelectasis after heart operations with and without breathing exercises. *Ann Phys Med.* 1956;3:18-20.

84. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *Anesthesiology.* 1974;41:242-255.

85. Krayer S, Rehder K, Vettermann J, Didier EP, Ritman EL. Position and motion of the human diaphragm during anesthesia-paralysis. *Anesthesiology.* 1989;70:891-898.

86. Krayer S, Rehder K, Beck KC, Cameron PD, Didier EP, Hoffman EA. Quantification of thoracic volumes by three-dimensional imaging. *Journal of applied physiology.* 1987;62:591-598.

87. Tokics L, Strandberg A, Brismar B, Lundquist H, Hedenstierna G. Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. *Acta Anaesthesiol Scand.* 1987;31:684-692.

88. Bindslev L, Santesson J, Hedenstierna G. Distribution of inspired gas to each lung in anesthetized human subjects. *Acta anaesthesiologica Scandinavica.* 1981;25:297-302.

89. Hulands GH, Greene R, Iliff LD, Nunn JF. Influence of anaesthesia on the regional distribution of perfusion and ventilation in the lung. *Clinical science.* 1970;38:451-460.

90. Rehder K, Hatch DJ, Sessler AD, Fowler WS. The function of each lung of anesthetized and paralyzed man during mechanical ventilation. *Anesthesiology.* 1972;37:16-26.

91. Tokics L, Hedenstierna G, Svensson L, et al. V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. *J Appl Physiol (1985).* 1996;81:1822-1833.

92. Nyren S, Radell P, Lindahl SG, et al. Lung ventilation and perfusion in prone and supine postures with reference to anesthetized and mechanically ventilated healthy volunteers. *Anesthesiology.* 2010;112:682-687.

93. Hill JD, Main FB, Osborn JJ, Gerbode F. Correct use of respirator on cardiac patient after operation. *Arch Surg.* 1965;91:775-778.

94. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Re-expansion of atelectasis during general anaesthesia: a computed tomography study. *Br J Anaesth.* 1993;71:788-795.

95. Anaesthesiology PNIftCTNotESo, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet.* 2014;384:495-503.

96. Ferrando C, Suarez-Sipmann F, Tusman G, et al. Open lung approach versus standard protective strategies: Effects on driving pressure and ventilatory efficiency during anesthesia - A pilot, randomized controlled trial. *PLoS One.* 2017;12:e0177399.

97. Bluth T, Teichmann R, Kiss T, et al. Protective intraoperative ventilation with higher versus lower levels of positive end-expiratory pressure in obese patients (PROBESE): study protocol for a randomized controlled trial. *Trials.* 2017;18:202.

98. Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med.* 2013;369:428-437.

99. Ostberg E, Thorisson A, Enlund M, Zetterstrom H, Hedenstierna G, Edmark L. Positive End-expiratory Pressure Alone Minimizes Atelectasis Formation in Nonabdominal Surgery: A Randomized Controlled Trial. *Anesthesiology.* 2018;128:1117-1124.

100. Cournand A, Motley HL, et al. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am J Physiol.* 1948;152:162-174.

101. Johansson MJ, Wiklund A, Flatebø T, Nicolaysen A, Nicolaysen G, Walther SM. Positive end-expiratory pressure affects regional redistribution of ventilation differently in prone and supine sheep*. *Critical Care Medicine.* 2004;32:2039-2044.

102. Richard JC, Bregeon F, Costes N, et al. Effects of prone position and positive end-expiratory pressure on lung perfusion and ventilation. *Critical Care Medicine.* 2008;36:2373-2380.

103. Mauri T, Bellani G, Confalonieri A, et al. Topographic distribution of tidal ventilation in acute respiratory distress syndrome: effects of positive end-expiratory pressure and pressure support. *Crit Care Med.* 2013;41:1664-1673.

104. Zick G, Elke G, Becher T, et al. Effect of PEEP and tidal volume on ventilation distribution and end-expiratory lung volume: a prospective experimental animal and pilot clinical study. *PLoS One.* 2013;8:e72675.

105. Hedenstierna G, Baehrendtz S, Klingstedt C, et al. Ventilation and perfusion of each lung during differential ventilation with selective PEEP. *Anesthesiology.* 1984;61:369-376.

106. Richard JC. Effects of Positive End-Expiratory Pressure and Body Position on Pulmonary Blood Flow Redistribution in Mechanically Ventilated Normal Pigs*. *Chest.* 2002;122:998-1005.

107. Walther SM, Domino KB, Glenny RW, Hlastala MP. Positive end-expiratory pressure redistributes perfusion to dependent lung regions in supine but not in prone lambs. *Critical care medicine.* 1999;27:37-45.

108. Walther SM, Johansson MJ, Flatebo T, Nicolaysen A, Nicolaysen G. Marked differences between prone and supine sheep in effect of PEEP on perfusion distribution in zone II lung. *Journal of Applied Physiology.* 2005;99:909-914.

109. Hedenstierna G, White FC, Mazzone R, Wagner PD. Redistribution of pulmonary blood flow in the dog with PEEP ventilation. *J Appl Physiol Respir Environ Exerc Physiol.* 1979;46:278-287.

110. Darwin E. *Zoonomia; or, The Laws of Organic Life.* . London: Johnson, E.; 1794.

111. Glaister DH. Distribution of pulmonary blood flow and ventilation during forward (plus Gx) acceleration. *J Appl Physiol.* 1970;29:432-439.

112. Jones JG, Clarke SW, Glaister DH. Effect of acceleration on regional lung emptying. *J Appl Physiol.* 1969;26:827-832.

113. Rohdin M, Petersson J, Mure M, Glenny RW, Lindahl SG, Linnarsson D. Distributions of lung ventilation and perfusion in prone and supine humans exposed to hypergravity. *J Appl Physiol.* 2004;97:675-682.

114. Rohdin M, Petersson J, Sundblad P, et al. Effects of gravity on lung diffusing capacity and cardiac output in prone and supine humans. *J Appl Physiol.* 2003;95:3-10.

115. Glaister DH. Regional ventilation and perfusion in the lung during positive acceleration measured with xenon 133. *J Physiol* 1964;177:73-74.

116. Tacker WA, Jr., Balldin UI, Burton RR, Glaister DH, Gillingham KK, Mercer JR. Induction and prevention of acceleration atelectasis. *Aviat Space Environ Med.* 1987;58:69-75.

117. Dussault C, Gontier E, Verret C, et al. Hyperoxia and hypergravity are independent risk factors of atelectasis in healthy sitting humans: a pulmonary ultrasound and SPECT/CT study. *J Appl Physiol (1985).* 2016;121:66-77.

118. Hoppin FG, Jr., York E, Kuhl DE, Hyde RW. Distribution of pulmonary blood flow as affected by transverse (+Gx) acceleration. *J Appl Physiol.* 1967;22:469-474.

119. Chevalier PA, Reed JH, Jr., Vandenberg RA, Wood EH. Effect of gravitational and inertial forces on vertical distribution of pulmonary blood flow. *Aviat Space Environ Med.* 1978;49:768-778.

120. Hlastala MP, Chornuk MA, Self DA, et al. Pulmonary blood flow redistribution by increased gravitational force. *J Appl Physiol.* 1998;84:1278-1288.

121. Rohdin M, Petersson J, Mure M, Glenny RW, Lindahl SG, Linnarsson D. Protective effect of prone posture against hypergravity-induced arterial hypoxaemia in humans. *J Physiol.* 2003;548:585-591.

122. Petersson J, Rohdin M, Sanchez-Crespo A, et al. Paradoxical redistribution of pulmonary blood flow in prone and supine humans exposed to hypergravity. *J Appl Physiol.* 2006;100:240-248.

123. Glaister DH. The effect of positive centrifugal acceleration upon the distribution of ventilation and perfusion within the human lung, and its relation to pulmonary arterial and intraoesophageal pressures. *Proc R Soc Lond B Biol Sci.* 1967;168:311-334.

124. Glaister DH. Effects of acceleration on the lung. In: Prisk GK, Paiva M, West JB, eds. *Gravity and the lung*. New York: Marcel Dekker; 2001:p. 30-74.

125. Rohdin M, Linnarsson D. Differential changes of lung diffusing capacity and tissue volume in hypergravity. *J Appl Physiol.* 2002;93:931-935.

126. Barr PO. Hypoxemia in man induced by prolonged acceleration. *Acta Physiol Scand.* 1962;54:128-137.

127. Rosenhamer G. Influence of increased gravitational stress on the adaptation of cardiovascular and pulmonary function to exercise. *Acta Physiol Scand Suppl.* 1967;276:1-61.

128. Smedal HA, Rogers TA, Duane TD, Holden GR, Smith JR, Jr. The physiological limitations of performance during acceleration. *Aerospace medicine.* 1963;34:48-55.

129. Sanchez-Crespo A, Petersson J, Nyren S, et al. A novel quantitative dual-isotope method for simultaneous ventilation and perfusion lung SPET. *Eur J Nucl Med Mol Imaging.* 2002;29:863-875.

130. Petersson J, Sanchez-Crespo A, Larsson SA, Mure M. Physiological imaging of the lung: single-photon-emission computed tomography (SPECT). *J Appl Physiol.* 2007;102:468-476.

131. Rosenthal MS, Cullom J, Hawkins W, Moore SC, Tsui BM, Yester M. Quantitative SPECT imaging: a review and recommendations by the Focus Committee of the Society of Nuclear Medicine Computer and Instrumentation Council. *J Nucl Med.* 1995;36:1489-1513.

132. Erlandsson K, Buvat I, Pretorius PH, Thomas BA, Hutton BF. A review of partial volume correction techniques for emission tomography and their applications in neurology, cardiology and oncology. *Phys Med Biol.* 2012;57:R119-159.

133. Lemb M, Oei TH, Eifert H, Gunther B. Technegas: a study of particle structure, size and distribution. *Eur J Nucl Med.* 1993;20:576-579.

134. Petersson J, Sanchez-Crespo A, Rohdin M, et al. Physiological evaluation of a new quantitative SPECT method measuring regional ventilation and perfusion. *J Appl Physiol.* 2004;96:1127-1136.

135. Petersson J, Glenny RW. Imaging regional PAO2 and gas exchange. *J Appl Physiol.* 2012;113:340-352.

136. Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. *Am Rev Respir Dis.* 1979;120:1325-1373.

137. Stuart BO. Deposition of inhaled aerosols. *Arch Intern Med.* 1973;131:60-73.

138. Bajc M, Neilly B, Miniati M, Mortensen J, Jonson B. Methodology for ventilation/perfusion SPECT. *Semin Nucl Med.* 2010;40:415-425.

139. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J.* 2009;34:888-894.

140. Bake B, Bjure J, Widimsky J. The effect of sitting and graded exercise on the distribution of pulmonary blood flow in healthy subjects studied with the 133Xenon technique. *Scandinavian journal of clinical and laboratory investigation.* 1968;22:99-106.

141. Harf A, Pratt T, Hughes JM. Regional distribution of VA/Q in man at rest and with exercise measured with krypton-81m. *J Appl Physiol Respir Environ Exerc Physiol.* 1978;44:115-123.

142. Savaser DJ, Campbell C, Castillo EM, et al. The effect of the prone maximal restraint position with and without weight force on cardiac output and other hemodynamic measures. *J Forensic Leg Med.* 2013;20:991-995.

143. Bundgaard-Nielsen M, Sorensen H, Dalsgaard M, Rasmussen P, Secher NH. Relationship between stroke volume, cardiac output and filling of the heart during tilt. *Acta anaesthesiologica Scandinavica.* 2009;53:1324-1328.

144. Jennings T, Seaworth J, Howell L, Tripp L, Goodyear C. Effect of body inversion on hemodynamics determined by two-dimensional echocardiography. *Critical care medicine.* 1985;13:760-762.

145. Haennel RG, Teo KK, Snydmiller GD, Quinney HA, Kappagoda CT. Short-term cardiovascular adaptations to vertical head-down suspension. *Arch Phys Med Rehabil.* 1988;69:352-357.

146. Lindberg EF, Marshall HW, Sutterer WF, Mc GT, Wood EH. Studies of cardiac output and circulatory pressures in human beings during forward acceleration. *Aerospace medicine.* 1962;33:81-91.

147. Wood EH, Sutterer WF, Marshall HW, Lindberg EF, Headley RN. Effect of headward and forward accelerations on the cardiovascular system. *WADC Tech Rep United States Air Force Wright Air Dev Cent Day Ohio.* 1961;60-634:1-48.

148. Arvedsen SK, Eiken O, Kolegard R, Petersen LG, Norsk P, Damgaard M. Body height and arterial pressure in seated and supine young males during +2 G centrifugation. *Am J Physiol Regul Integr Comp Physiol.* 2015;309:R1172-1177.

149. Barbera JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J.* 2003;21:892-905.

150. Karlsson LL, Rohdin M, Nekludov M, Ax M, Petersson J. No protective role for hypoxic pulmonary vasoconstriction in severe hypergravity-induced arterial hypoxemia. *Eur J Appl Physiol.* 2011;111:2099-2104.

151. Sanchez Crespo A. *Novel computational methods for image analysis and quantification using position sensitive radiation detectors* Stockholm, Sweden: Department of medical radiation physics Stockholm University and Karolinska Institutet; 2005.