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Lung function in micro- and in hypergravity

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ABSTRACT

The lung is extremely susceptible to gravity, even during short-term changes of the gravity vector, because it is a mixture of air and elastic tissue components. Yet, there is limited knowledge of the effects of gravity on the respiratory system. This is an important issue, for two reasons: 1) for understanding the physiology of space flight; and 2) because a better knowledge of these effects could help to understand the pulmonary changes that occur in a patient confined to bed, which is a partial simulation of a weightlessness (microgravity, 0 G) state.

The present thesis aims to understand the influence of moderately increased gravity (1.7-2 G), and of 0 G or simulated 0 G, on some pulmonary features, on a large (the whole lung) or small scale.

In a first study, six subjects were studied before, during, and after 120 days of bed rest. Forced expiratory flows and volumes, and diffusing capacity for carbon monoxide (DL_{CO}) were recorded. Peak flow did not change, whereas mid-maximal expiratory flow decreased in the supine posture by ~22%. DL_{CO} also decreased during bed rest, by 14%. These decreases had not recovered two weeks after bed rest. Such results speak against major muscle deconditioning caused by bed rest but are in favour of a decrease in lung elastic recoil and an alteration in gas exchange. These alterations are unlikely to influence daily life after bed rest but may limit maximal work capacity.

In two further experimental studies, an anti-G suit was used to manipulate stroke volume (SV) and central blood volume (CBV). Nine and twelve subjects were studied at 1 G and at 2 G in a human centrifuge. It was found that SV and CBV, which change with gravity, play major roles in cardiopulmonary interactions: they influence mechanically the emptying of lung alveoli. Moreover, when SV and CBV increase, the indices of perfusion heterogeneity decrease.

In a last study, twelve and six subjects were studied in different combinations of 1.7 G and 0 G during two series of parabolic flights. Indices of small and large-scale pulmonary perfusion heterogeneity were measured. All decreased but still existed at 0 G, compared to 1 G and to 1.7 G. This confirms previous reports of a large degree of gravity-independent heterogeneity of pulmonary perfusion.

In conclusion, gravity in the head-to-foot direction is useful for maintaining a normal lung capacity. In contrast, the heterogeneity of pulmonary perfusion distribution is only partially influenced by gravity. Cardiopulmonary interactions on a small scale are not mainly influenced by gravity but rather by changes in intra-thoracic blood content during the cardiac cycle.

Keywords: lung physiology, human, spirometry, rebreathing, cardiogenic oscillations, phase IV, anti-G suit, stroke volume, weightlessness, closing volume, DL_{CO}.

LIST OF PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals:

I. **Stéphanie Montmerle**, Jonas Spaak, and Dag Linnarsson.
Lung function during and after prolonged head-down bed rest
Journal of Applied Physiology 92: 75-83, 2002

II. **Stéphanie Montmerle**, Patrik Sundblad, and Dag Linnarsson.
Residual heterogeneity of intra- and interregional pulmonary perfusion in short-term microgravity
In Press, Journal of Applied Physiology.

III. **Stéphanie Montmerle** and Dag Linnarsson
Cardiovascular effects of anti-G suit inflation at 1 and 2 G
In Press, European Journal of Applied Physiology.

IV. **Stéphanie Montmerle** and Dag Linnarsson
Effects of short-term hypergravity and stroke volume on pulsatile thoracic gas flows and volumes
In Press, Journal of Applied Physiology.

CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
CBV	Central blood volume
$COS_{[x]}$	Cardiogenic oscillations of expired concentrations of a gas x measured on an expirogram
COS_{flow}	Cardiogenic oscillations of flow recorded during a breath holding with open glottis
CV	Closing volume
DL_{CO}	Lung diffusing capacity for carbon monoxide
FEF	Forced expiratory flow
$FEF_{25-75\%}$	Forced expiratory flow between 25 and 75% of expired volume
$FEV_{1,0}$	Forced expiratory volume during the first second of a FVC manoeuvre
FRC	Functional residual capacity
FVC	Forced vital capacity
HDT	long-term head-down tilt bed rest
HiG	Hypergravity (gravito-inertial levels higher than 1 G)
HR	Heart rate
MAP	Mean arterial pressure
MAPh	Mean arterial pressure at heart level
MEFV curves	Maximum expiratory flow-volume curves
IP	Inflation pressure
P_4	Amplitude of phase IV on an expirogram
PF	Peak expiratory flow
PV	Plasma volume
Q	Cardiac output
RV	Residual volume
SV	Stroke volume
SVR	Systemic vascular resistance
TLC	Total lung capacity
VC	Vital capacity
V_A	Alveolar volume
0 G	Weightlessness, microgravity
1 G	Normal gravity

NB: Cardiac output is stated as Q and not as $\dot{Q}$ for editorial reasons (this character changes the spacing).

INTRODUCTION

The aim of this thesis is to understand the influence of gravitational force on aspects of lung mechanics and on cardio-pulmonary interactions. The lung is extremely susceptible to gravity, even during short-term changes of the gravity vector, because it is a mixture of air and elastic tissue components. Yet to date, there is limited knowledge of the effects of gravity on the respiratory system.

For example, declines in maximal inspiratory and expiratory flows and volumes have been observed during (112) and after (8, 112) long-term space flights (duration up to one year). Yet, it is not clear whether the cause of these alterations is a deconditioning of the respiratory muscles and/or structural changes of the lung tissue.

The distribution of pulmonary perfusion in humans is traditionally presented as a gravity-dependent four-zone model (Fig. 1). This model is now contested: experiments performed in short-term and sustained microgravity, using indirect methods, have suggested residual heterogeneity of perfusion (86, 98). However, these methods have not quantified the amount of gravity-independent heterogeneity.

These issues have implications for the understanding and monitoring of the pulmonary and cardio-vascular changes that occur in a patient confined to bed. Bed rest is a partial simulation of a 0 G state in the head-to-foot direction (21).

The present work focuses on the influence of a moderately increased gravito-inertial load (1.7-2 G) and of weightlessness (microgravity, 0 G) or simulated 0 G (bed rest) on selected pulmonary features, on a large (lung volumes) and small (yet larger than acinar size) scale.

First, some important concepts are defined, such as cardiogenic oscillations (COS) and phase IV phenomena. Then, a first review is made of the current knowledge about the effects of 0 G on the pulmonary and cardio-vascular systems. A second review about the effects of hypergravity (HiG) and/or anti-G suit inflation is presented. Four articles/experiments are subsequently discussed:

- I: Forced expiratory flows and lung volumes after long-term simulation of 0 G (bed rest)

- II: COS as indices of pulmonary perfusion distribution during short-term exposure to 0 G and 1.7 G (parabolic flight)

- III and IV: The mechanisms behind the generation of COS and how they are influenced by gravity changes. In addition, the roles of stroke volume (SV) and central blood volume (CBV) are studied by modulating them using an anti-G suit.

BACKGROUND

CLASSICAL MODEL OF DISTRIBUTION OF VENTILATION AND PERFUSION IN THE LUNG

In the upright human at normal gravity (1 G), there is a hydrostatic pressure gradient from the head down to the feet. The gravito-inertial force in that direction is commonly termed G_z, whereas the gravito-inertial force in the sagittal antero-posterior direction is termed G_x. Henceforth, for convenience, the term G will refer to G_z unless specified otherwise.

Several studies have shown that ventilation and perfusion are not homogeneously distributed in the lungs at 1 G. The classical explanation is that ventilation distribution is influenced by the pleural pressure gradient down the lung, which is caused by gravity. The most negative pleural pressures are located in the upper parts of the lung. Because of this gradient, alveolar size is larger at the apex and decreases down the lung. Dependent to non-dependent pleural pressure differences are only marginally influenced by changes in body position (56) . Regional lung expansion is also influenced by the position of the heart in the thoracic cage, at least in dogs (56).

Similarly, perfusion distribution has been described as gravity-dependent, as described by the four-zone model of Hughes et al. (Fig. 1)

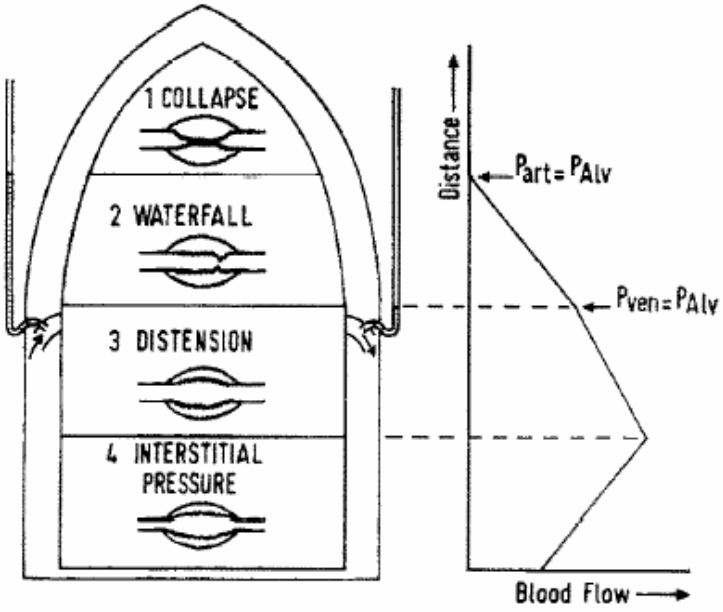

Fig. 1 (Hughes, J.M., Glazier, J.B., Maloney, J.E. & West, J.B. Effect of lung volume on the distribution of pulmonary blood flow in man. *Respir Physiol* 4, 58-72 (1968)(60): "Diagram to show the resistance vessels in different parts of the lung which are believed to determine the distribution of pulmonary blood flow. At the top of the lung the capillaries are collapsed if alveolar pressure exceeds arterial pressure, and no flow occurs (zone 1). In zone 2, arterial pressure exceeds alveolar pressure which in turn is greater than venous. Flow in this zone is under so-called waterfall conditions, and is governed by the arterio-alveolar pressure difference. Venous pressure exceeds alveolar pressure in zone 3 and flow now depends on the arterial-venous difference. Flow increases down this zone because of distension and possibly recruitment of vessels. The results in this paper show that at the bottom of the lung, blood flow decreases with distance towards the base (zone 4). We believe the added resistance in this zone

is due to interstitial pressure narrowing the calibre of the larger (extra-alveolar) pulmonary vessels."

However, this model is now contested: the role of the gravitational force in the distribution of pulmonary perfusion is debated. Moreover, the topographic repartition of lung blood flow at lung unit level is still unclear. Experiments in animals have given contradicting results: for example, the eggshell model described by Hakim *et al*, *i.e.* concentric oval territories with the innermost central area representing the highest flow, has not been reproduced by other teams and remains controversial (52, 53). For instance, the findings of Glenny *et al* on pigs suggested that, were there any central to peripheral gradient in blood flow, it would likely be low (44). In the dog, it seems that the geometry of the pulmonary vascular tree is an important determinant of regional blood flow (9). In baboons, measurements performed after prostacyclin infusion have shown that the regulation of pulmonary vascular tone is not responsible for inequalities of pulmonary perfusion during normoxia (45). Thus, lung perfusion distribution in animals is likely only partially determined by gravity.

Melsom *et al* observed a ~ 40% gravity-independent heterogeneity within horizontal slices in both inner and outer layers in the goat lung (82, 83). Comparable numbers have been estimated by electron-beam computerized tomography in dogs and in man (18, 67). Experiments in man have given contradicting results. Scintigrams performed on six sitting subjects during short-term microgravity showed that lung perfusion was more homogeneously distributed at 0 G than at normal gravity (119). On the other hand, recordings performed with the same technique on three subjects undergoing forward acceleration (injections at $1G_x$, $4G_x$ and $8G_x$) found that perfusion distribution was similar at all G loads (58).

CARDIOGENIC OSCILLATIONS

COS have been used as an indirect measurement of the degree of ventilation and perfusion heterogeneity in the human lung in different gravity conditions: normal gravity, parabolic flight, spaceflight, human centrifuge (23, 50, 86, 98, 104). A limitation of this method is that it does not give any information of a topographical nature.

Fig. 2. Schematic representation of the generation of COS, where the mechanical action of the heart beat influences the emptying of compliant lung alveoli.

There are two pre-requisites to the existence of COS (Fig. 2): first, gas concentrations must differ between pulmonary units; second, pulmonary units must not empty at the same time but sequentially within the same region of the lung. Otherwise, differences in gas concentrations will not appear in the expirate because of mixing of the gas to be expired. A typical expirogram (i.e. gas concentrations plotted as a function of expired volume), taking the gas O_2 as an example, is shown in Fig. 3.

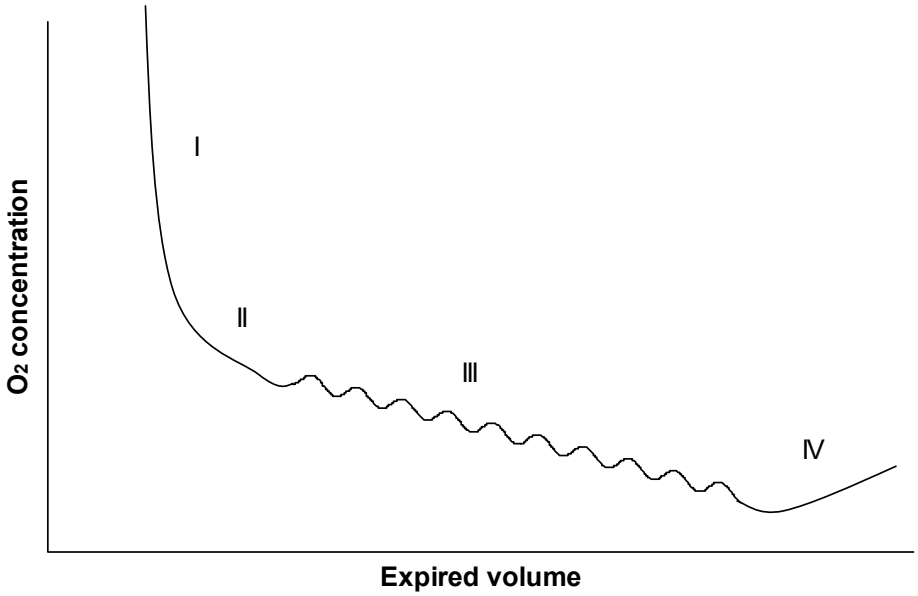

Fig. 3. Schematic representation of an expirogram for O_2 recorded during a slow expiration after a rebreathing – breath holding manoeuvre. Four phases are usually recognisable: I: dead space air; II: mix of dead space and alveolar air (bronchial phase); III: alveolar phase, where cardiogenic oscillations (or heart-synchronous variations of gas concentrations) can be observed; IV: signs of airway closure.

It has been shown that COS of expired gases are representative mostly of intra-regional differences in the concentrations of these gases (6, 71). The definition of the term intra-regional is generally vague in the literature (30, 71, 79). Here, we envision a lung unit of the order 10-100 ml, that is one or two orders of magnitude larger than an acinus (acinus = functional unit). This volume corresponds roughly to the resolution of current methods to study regional blood flow. The possible participation of inter-regional (basal-to-apical) differences to COS has been studied by Laviolette and Cormier (71) and by Arieli *et al* (6). These authors showed that COS are not generated from gas concentration differences between apical and basal parts of the lung. This result speaks strongly for a small – if not totally absent – effect of inter-regional gas differences on COS amplitude.

PHASE IV PHENOMENA

At the final stage of expiration, a deviation in the phase III slope, referred to as phase IV, can be observed in the expirogram (Fig. 3). This is due to airflow limitation in certain parts of the lung (91). Airflow limitation leads to closure of airways in pulmonary units where the pleural pressure becomes greater than the airway pressure (17, 30). Phase IV phenomena are an index of inter-regional differences in pulmonary gas concentrations (71) such that the greater the basal-to-apical differences, the greater the amplitude of phase IV (P_4) (30). The volume at which signs of airway closure can be detected is called closing volume.

In the presence of the pleural pressure gradients induced by gravity, basal regions of the lung are relatively more deflated at the end of expiration, due to the overlying weight of the rest of the lung (87). As a consequence, airway closure is not homogeneous in the lung; the highest (least negative) pleural pressures being in the dependent parts, a basal-to-apical sequential emptying occurs. This basal-to-apical sequential emptying, together with differences in gas concentrations between lung regions, is a pre-requisite for the existence of phase IV phenomena.

CARDIOGENIC OSCILLATIONS OF FLOW

COS_{flow} (Fig. 4) are heart-synchronous gas movements, which can be measured at the mouth during a breath holding performed with open glottis. In these movements, inflow is in phase with systole (77). Although the first clinical observation of COS_{flow} was made already in 1875 (36, 39), this phenomenon has hardly been studied since then. COS_{flow} have been related to the intra-thoracic blood movements which occur during the cardiac cycle. In particular, it has been suggested that they are correlated with stroke volume, although this has only been studied in dogs (131).

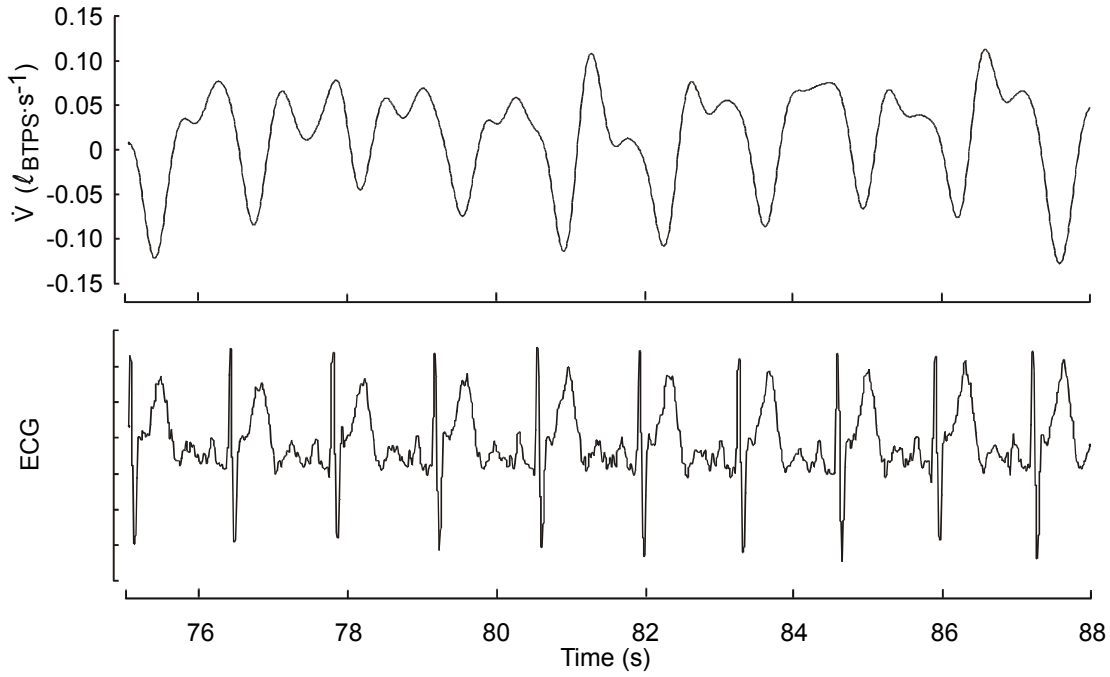

Fig. 4 (reproduced from article IV). Typical recording of heart-synchronous air movements (COS_{flow}) measured at the mouth during a breath holding performed with open glottis. Airflow is shown on the upper tracing. The flow meter was set so that outflow was positive and inflow negative. The lower tracing shows a simultaneous recording of the ECG.

CURRENT KNOWLEDGE OF THE EFFECTS OF MICROGRAVITY ON THE CARDIOVASCULAR AND PULMONARY SYSTEMS

At 0 G, the rib cage expands and takes a rounder shape, and the unopposed abdominal recoil displaces the abdominal contents and the diaphragm cranially. Furthermore, the anterior abdominal wall is relaxed and does not generate any net recoil pressure (25). Thoracic compliance is relatively high and constant in the volume range >20% of vital capacity during short-term exposures to 0 G (11).

Table 1 shows a review of previous findings by other groups of the effects of 0 G or simulated 0 G on the cardiovascular and pulmonary systems of humans. Because the difference between the upright and sitting postures in their findings is small, the term “upright” refers to either of these postures taken as reference.

Variables	Upright → supine	Upright → long-term bedrest	Upright → short-term 0 G	Upright → sustained 0 G
FRC	↓ (113)	= (10, 113)	↓ (93)	↓ (29, 130)
ERV	↓ (85, 89)			
TLC	↓	↑ compared to supine (10)		
VC	↓	↑ compared to supine (10), = (111)		↓ (112) or = (28)
FVC	↓ (4, 51)	↑ compared to supine, (10)	↓ (51)	↑ (112), = (28) or ↓ (8)
$FEV_{1.0}$	↓ (51)	↑ compared to supine, (10), = (111)	↓ (51)	= (28, 112)
PF	↓ (51)		↓ (51)	↓ (8)
$FEF_{25-75\%}$				↑ first day (112) or = (28)
DL_{CO}	↑ (97) or = (113)	↓ (111, 113)		↑ (97, 130), also when compared to supine
Lung tissue volume	= (113)	= (113)		↓ (130)
Thoracic compliance	↑ (90)		↑ (11)	
Lung compliance	↓ (85, 90)			
Heterogeneity of ventilation distribution (COS)			More homogeneous (86)	More homogeneous (50)
Heterogeneity of perfusion distribution (COS)			More homogeneous (86)	More homogeneous (98)
Leg volume			↓ (11)	↓ (121)
PV		↓ (10, 24, 34, 35, 63, 111)		
Red blood cell volume		↓ (35, 111)		
Hb	= (116)	= (116)		

Variables	Upright → supine	Upright → long-term bedrest	Upright → short-term 0 G	Upright → sustained 0 G
Central blood volume	↑ (129)		↑ (7, 99)	
Cardiac output (Q)	↑ (97, 113) or ↓ after 60 days but not later (116)	↓ after 60 days but not later (111, 113, 116, 120) cardiac atrophy (73, 111)	↑ (65)	↑ (97), also when compared to supine but only during the 2 first days cardiac atrophy (15, 40)
SV	↓ (116)	↓ (111, 116, 120)	↑ (65, 70)	↑ (97, 130)
HR	↑ (116)	↑ (20, 116)	↓ (65, 70)	= (97, 130)
MAP	= (116)	= (20, 116)	↓ (99)	↓ (37)

Table 1. Effects of exposure to 0 G and its simulations on some cardiovascular and pulmonary parameters. In bold are the parameters that were also measured in the present thesis. These are addressed in the *Discussion* section.

CURRENT KNOWLEDGE OF THE EFFECTS OF HYPERGRAVITY (HIG) ON THE CARDIOVASCULAR AND PULMONARY SYSTEMS, WITH AND WITHOUT INFLATION OF AN ANTI-G SUIT

The hydrostatic pressure gradient from the head down to the feet increases in situations of increased gravitoinertial force. The sudden increase in weight of the blood caused by HiG initiates a two-step reaction: an initial period of circulatory failure (7-10 s) followed by a period of compensation (135). The G-induced loss of consciousness (G-LOC), which appears when the cerebral perfusion pressure is less than 20 mmHg, usually does not occur during exposures to less than 4 G.

Anti-G suits were originally designed during the Second World Ward to increase pilots' tolerance to the HiG created by fighter aircraft. At that time, aircraft accelerations were such that only 1-1.5 G_z of protection was needed. However, modern aircraft like the JAS-Gripen currently used by the Swedish Air Force can reach 9 G_z and more effective anti-G suits had to be designed. In this thesis the full-coverage anti-G suit has been used. This model increases G-tolerance by ~ 3 G (26).

Most of the experiments studying the cardiovascular and respiratory effects of anti-G suit inflation were performed between the forties and the sixties, and thus with anti-G suits providing 1-1.5 G_z of protection. The cardiovascular and pulmonary effects of full-coverage anti-G suits have not been extensively studied. However, it is likely that most of the effects observed with older models of anti-G suits also occur with a full-coverage anti-G suit, although they are probably enhanced.

Table 2 presents a general review of previous studies on the effects of HiG and/or anti-G suit inflation in humans. Note the scarcity of data on anti-G suit inflation.

Variables	1 G rest → inflated anti-G suit	1 G rest → HiG	1 G rest → HiG + inflated anti-G suit	HiG → HiG + inflated anti-G suit
FRC	↓ (42, 43, 59)	= up to 3 G (103)		
VC	↓ (49)	= (11), ↓ (49, 68)	↓ (49)	= (49)
FVC		= (51)		
Pleural pressure gradient		↑ (59, 136)		
Chest wall compliance	Probably ↓ (43)	↓ (11, 25, 43)		↓ (27)
Lung compliance	↓ (2), (12)	↓ (43)	= (43)	
Intra-abdominal pressure	↑, upward movement of the diaphragm (42, 43, 59).		↑ (43)	
Heterogeneity of ventilation distribution (COS)		↑ (86)		
Heterogeneity of perfusion distribution (COS)		↑ (86)		
Blood pressure at eye level	↑ (134)	↓ (135)	↑ (134)	
Preload	↑ (59, 133)	↓ (75)		
Central blood volume	↑ (59, 133) + counteract the downward movement of the heart (108)	↓ (7, 105)		
Afterload	↑ (46-48, 59, 133)	↑ (38, 107)		
MAPh	↑ (75)	= until 5 G (135) or ↑ (75)	↑ (75)	↑ (75)

Variables	1 G rest → inflated anti-G suit	1 G rest → HiG	1 G rest → HiG + inflated anti-G suit	HiG → HiG + inflated anti-G suit
Pulmonary capillary wedge and pulmonary artery pressures	↑ (102)			
SVR	↑ (75)	↑ (75)	↑ (75)	↑ (75)
Cardiac output	↓ (75)	↓ (75, 103, 105)	= at 2 G, ↓ at 3 and 4 G (75)	Less ↓ than without anti-G suit (75)
HR	= (75)	↑ (75, 135)	= (75)	Less ↑ than without anti-G suit (16, 59, 75)
SV	↓ (75)	↓ (75, 103, 105)	↓ (75)	= (75) or less ↓ than without anti-G suit (16, 59, 75)
Venous pooling in the legs	No (59, 133)	Yes	No	No

Table 2. Review of the effects of hypergravity, with and without inflation of an anti-G suit, on some cardiovascular and pulmonary parameters. Measurements were performed on seated subjects. In bold are the parameters that were also measured in the present thesis. These are addressed in the *Discussion* section.

AIMS

1) To determine whether the reductions in dynamic lung function (lung volumes and forced expiratory flows) previously observed after long-term space flight would occur also after long-term head-down tilt bed rest **(article I)**

2) To determine the influences of stroke volume and central blood volume on indirect indices of perfusion distribution in the lungs **(articles III and IV)**.

3) To determine the extent of large-scale and small-scale gravity-independent heterogeneity of pulmonary perfusion with improved methods taking the results under 2) above into account **(article II)**.

EQUIPMENT

GAS ANALYSIS

Three generations of devices were used for gas analysis during the bed rest and parabolic flight experiments. All had been designed by the Damec/Innovision company, Odense, Denmark. The two newest models were prototypes ordered by the European Space Agency (ESA) for use in space. These devices had not been tested at different G-levels before our experiments. Thus, an additional goal of the parabolic flights was to test them using the protocols described in the present thesis and those of another group. The latter protocols were to be used in future space flight experiments.

The first-generation device was the mass spectrometer AMIS 2000 (articles III and IV) or an equivalent device, especially developed for ESA (article I).

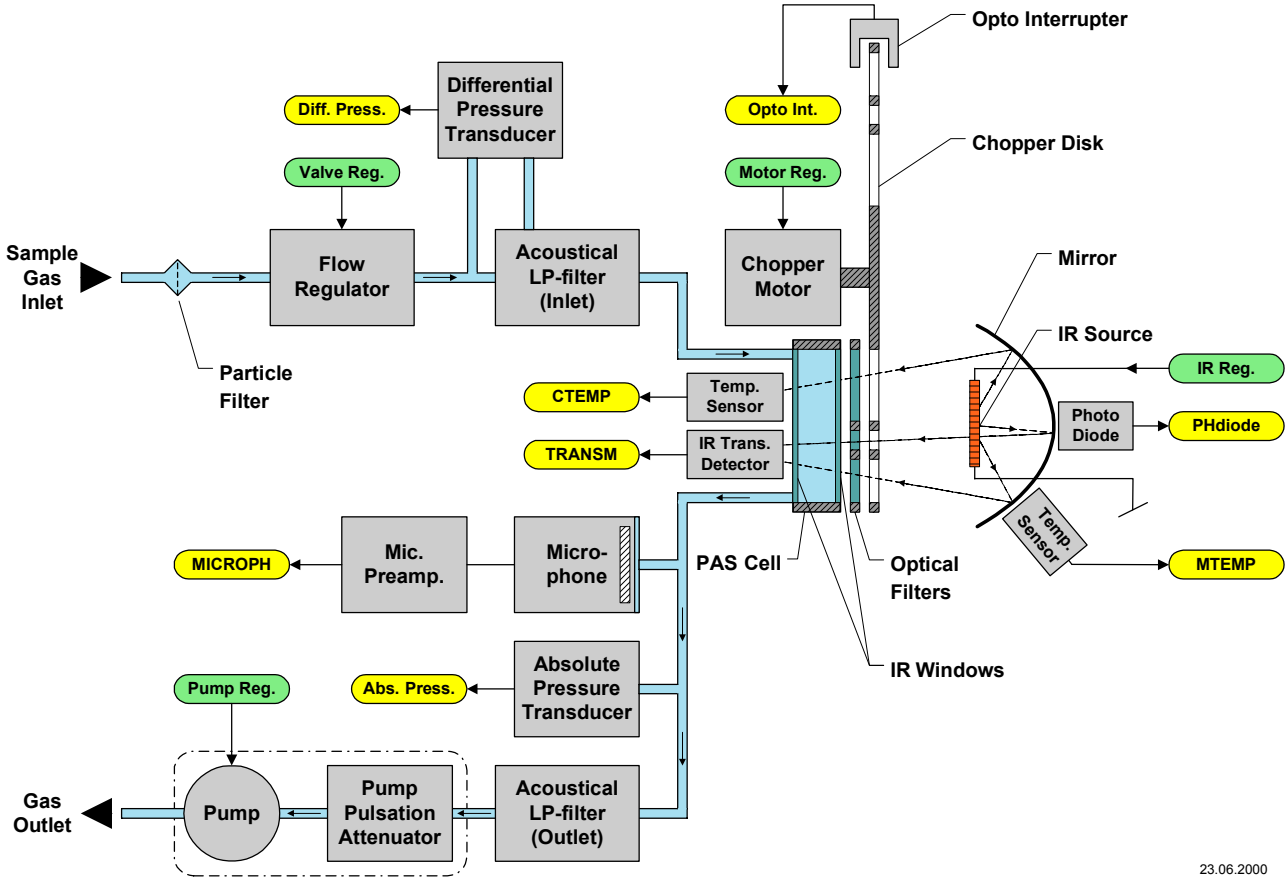

Fig. 5. Schematic representation of a photo-acoustic gas analyser (reproduced with permission from Damec/Innovision, Odense, Denmark). Two such units operated in parallel. The downstream O_2 sensor is not shown.

The next generation was the Advanced Respiratory Monitoring System (ARMS), a photo-acoustic gas analyser designed for the NASA Space Shuttle flight STS-107. This device is described in article II. The principle of photo-acoustic spectroscopy is the following (Fig. 5): the gas sample is irradiated by three components of pulsed, narrow-band infrared light, each with a specific pulsation frequency and wavelength; gas molecules absorb light energy in proportion to their concentration and convert it to heat. Temperature variations generate pressure oscillations

(= sound waves), which are detected by a microphone. The microphone signal is filtered to determine the three frequency components. The amplitude of the sound wave, at a given frequency, is directly proportional to the concentration of the corresponding gas. The major problem with this device is the low signal-to-noise ratio for gases present in low concentrations. Another limitation is that it cannot analyse gases such as O_2 and N_2 which do not absorb infrared light. Therefore, a paramagnetic O_2 sensor was included in series with the infrared sensing unit.

The most recently used device was the Pulmonary Function System (PFS, Fig. 6) (article II), a further development of the ARMS, designed for use on the International Space Station. A sensor based on absorption of ultraviolet light had replaced the paramagnetic O_2 sensor. Although this device should have been better than the ARMS, the signals of the soluble gases were not analysable during the G-transitions of the parabolas. The manufacturer suggests that the PFS is designed for use at a constant gravity level and was not designed for adapting quickly to gravity and pressure changes.

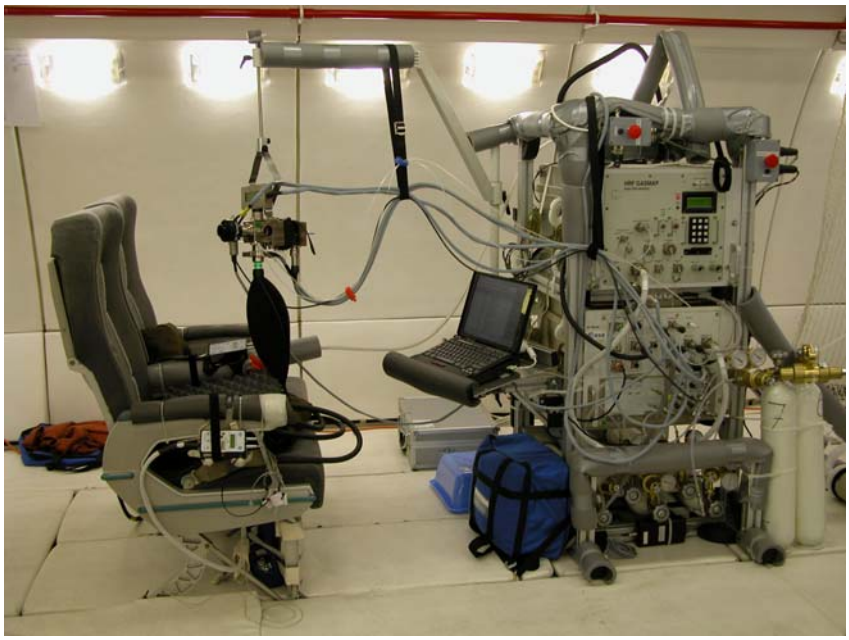

Fig. 6. The Pulmonary Function System installed in the Airbus A-300 Zero-G.

ANTI-G SUIT

The anti-G suits were of the full coverage model utilized by Swedish military pilots in the aircraft JAS 39 Gripen (Anti-G ensemble 39; AGE-39, Swedish Defence Material Administration, Stockholm). Maximum pressurization of this model is 525 mmHg.

The upper edge of the trousers was placed at iliac crest level and the lower edge at ankle level. The suit was inflated with air from a compressed gas cylinder fixed in the centre of the centrifuge.

METHODS

BED REST

In the present experiments, the subjects were supine, reclining from the horizontal plane with a 6° angle (head-down tilt, Fig. 7). This posture is commonly used in bed rest studies and aims at abolishing the hydrostatic pressure gradients in the head-to-foot direction. Subjects were not allowed to sit up or stand at any time but lateral and prone postures were permitted.

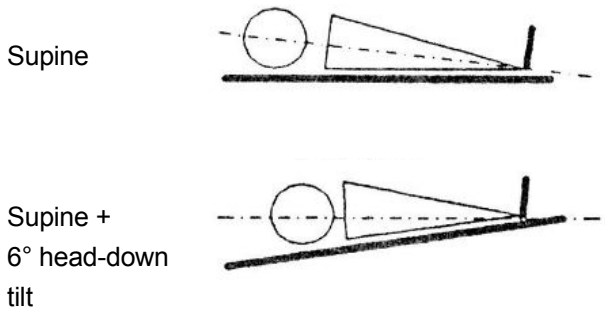

Fig. 7. Schematic representation of the posture of a subject undergoing 6° head-down tilt.

Head-down tilt bed rest (HDT) has been frequently used as a simulation of space flight because it enables good follow-up, longer studies, and the possibility to perform invasive tests if necessary. However, there are differences between bed rest and space flight: gravity in the head-to-foot direction is abolished during bed rest (loss of hydrostatic gradients in that direction) but there is still a gravitational force in the antero-posterior direction. Moreover, going from the upright to the supine posture causes a larger cephalad displacement of the diaphragm than when going from the upright posture to microgravity (31, 93). Thus, the diaphragm needs to overcome the weight of the abdominal organs.

PARABOLIC FLIGHT

Parabolic flights were first introduced for astronaut training. Today, they are mainly used for testing space technology and for short duration scientific experiments. This is because research opportunities in sustained and long-term 0 G are scarce due to the small number of space flights and low crew availability.

The sequence of a typical parabola is the following (Fig. 8): starting from a steady normal horizontal flight, the aircraft takes a 1.8 G load factor, nosing up to 45° and climbing to 7600 m (23 000 ft) over an interval of about 20 s (pull-up period). The engine thrust is then reduced to the point where it just overcomes the aerodynamic drag (injection period) separating the 1.8 G pull-up period from the 0 G period. The 0 G period lasts between 20 and 25 s and is followed by a 1.7 G pull-out period where the aircraft noses down and is brought back to horizontal.

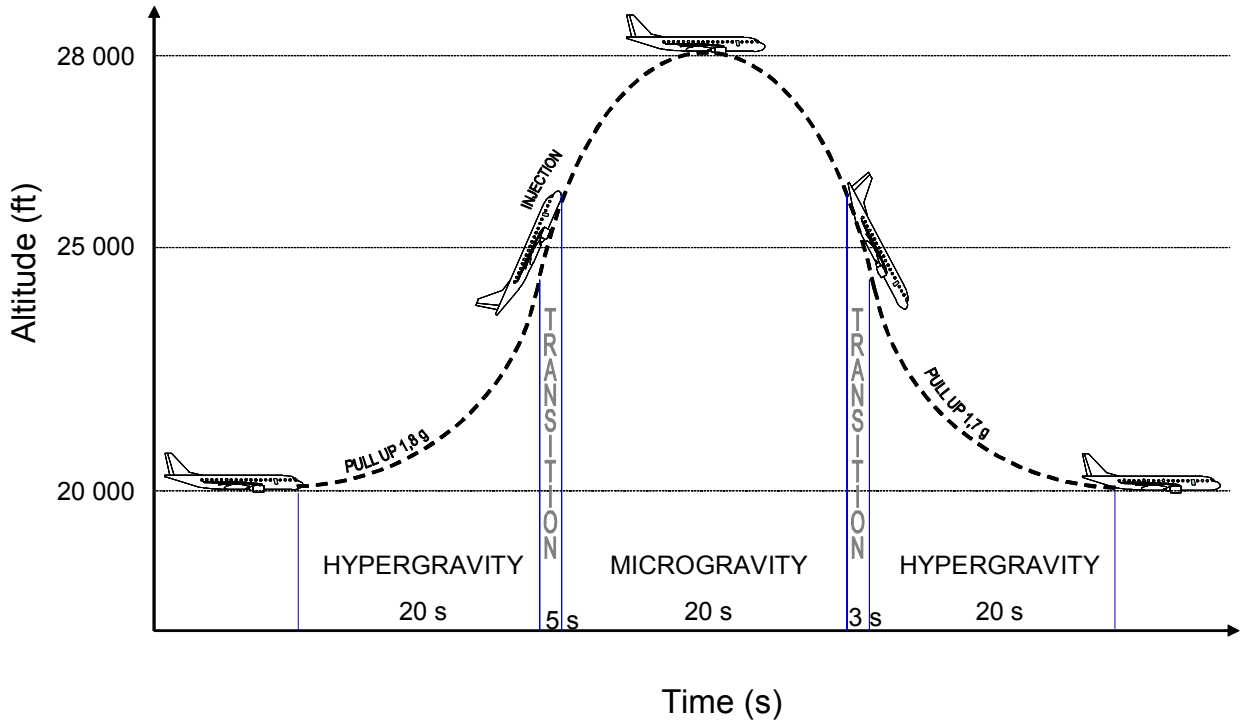

Fig. 8. Schematic representation of a parabolic manoeuvre.

The time delay between successive parabolas is about two minutes. A typical flight consists of 30 parabolas. The average cabin pressure in-flight is 80% of the normal atmospheric pressure at sea level, with only minor fluctuations during the parabolic manoeuvres.

Because of the short duration of micro- and hypergravity exposures, only systems with short time constants can be studied. The experiments described in article II were conducted on an aircraft owned by the Centre National d'Etudes Spatiales with the airport of Bordeaux, France, as a base. The experiments were performed in co-operation with the European Space Agency (ESA), and the Division of Physiology of the University of California, San Diego. Tests were performed on a specially equipped Airbus A-300.

HUMAN CENTRIFUGE

The experiments described in articles III and IV were conducted in the human centrifuge at Karolinska Institutet (Fig. 9). This centrifuge, built in 1950, has a radius of 7.25 m and includes a gondola. The maximal acceleration for equipment testing is 15 G and 9 G for humans (that is, a gondola velocity of 91 $km.h^{-1}$ at 9 G).

The well-being of the subject is routinely controlled by video and audio communication (visual fields, dizziness, motion sickness). ECG and blood pressure are monitored (volume clamp technique, recorded at the finger). When required, O_2 saturation is measured by either a finger or ear probe.

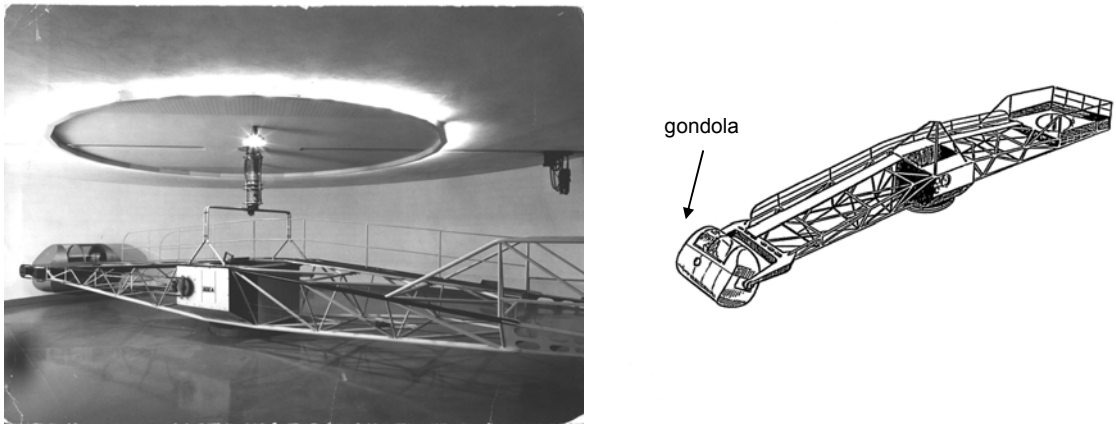

Fig. 9. Left: the human centrifuge at Karolinska Institutet, photographed shortly after its construction. Right: position of the gondola during the rotation of the centrifuge (diagram courtesy of Bertil Lindborg)

SUBJECTS

15 women and 22 men were studied. All were healthy non-medicated non-smokers, apart from one subject in the first series of parabolic flights who was an occasional smoker. Their median age, weight and height were 27 yrs, 70 kg and 1.75 m respectively. Five subjects participated in both series of parabolic flight experiments and three subjects participated in both series of centrifuge experiments.

The subjects participating in the bed rest experiment had undergone extensive medical examination and performed pulmonary function tests before the beginning of bed rest. The parabolic-flight subjects underwent at least clinical examination as part of the general flight requirements. The centrifuge subjects were not clinically examined because only low accelerations were used. However, they answered questions about their state of health (absence of cardiovascular and pulmonary disease), medication and eventual smoking.

Agreement from the Human Ethics Committee at Karolinska Institutet – and of the region where the experiments were performed if outside Sweden – was obtained for each study. Oral informed consent was also obtained, in accordance with the Swedish law.

STATIC AND DYNAMIC SPIROMETRY (ARTICLE I)

Forced expiratory flows and volumes were recorded according to the guidelines of the European Respiratory Society (100, 101) and of the American Thoracic Society (1).

REBREATHING (ARTICLES I AND IV)

Rebreathing (Fig. 10) allows, among other parameters, the computation of functional residual capacity (FRC), cardiac output (Q) and DL_{CO} (109, 110). This method, together with the direct Fick technique, is a gold standard for the measurement of Q (125, 126).

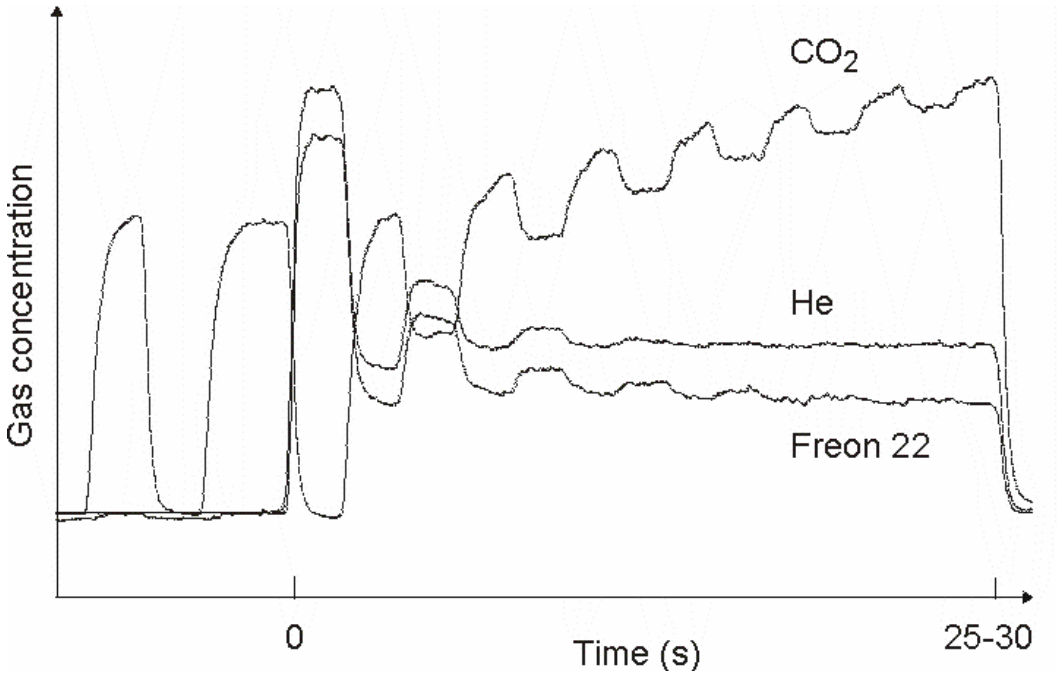

Fig. 10. Typical recording of a rebreathing manoeuvre. Gas concentrations have been rescaled for separation of the curves. The manoeuvre starts at 0 s on the diagram and takes 25-30 s to complete.

The sequence is the following: a 4-L rubber bag is filled with 1.5–2.5 l of rebreathing gas according to the subject's total lung capacity and preference. The subject applies a nose-clip and takes a few normal breaths with the valve in the non-rebreathing mode. They then switch the valve to breathe back and forth in the bag eight times, starting from functional residual capacity (FRC). This takes approximately 25 s. The bag must be emptied at each inspiration. Blood-insoluble gases (helium, He in Fig. 10) are equilibrated between the bag and the subject's lungs at the 4^{th}-5^{th} breath. Blood-soluble inert gases (Freon 22, $CHCl_2$ in Fig. 10) are taken up by the blood at a rate depending on lung perfusion. Gas concentrations are recorded continuously at the mouth.

THE REBREATHING – BREATH-HOLDING – EXPIRATION MANEUVER AS A MEANS TO STUDY PULMONARY PERFUSION DISTRIBUTION AND CARDIO-PULMONARY INTERACTIONS (ARTICLES II AND IV)

Cardiogenic oscillations of expired soluble gas concentrations

Perfusion distribution was assessed with the following protocol (Fig. 11): after an expiration to residual volume (RV), a rapid rebreathing was performed (5 s) to mix respired gases between the rebreathing bag and the lungs, and ended with an inhalation which emptied the bag; then the subject held his/her breath for 10 s, when the blood-soluble gas was removed from the alveolar space by uptake to the perfusing blood; finally, the subject exhaled slowly to RV at a flow corresponding to the volume of the rebreathing bag emptied in 10 s. COS measured on the recordings of the soluble gas concentrations were thus theoretically representative of perfusion differences: large COS amplitude meaning large perfusion differences, no COS meaning homogeneous perfusion.

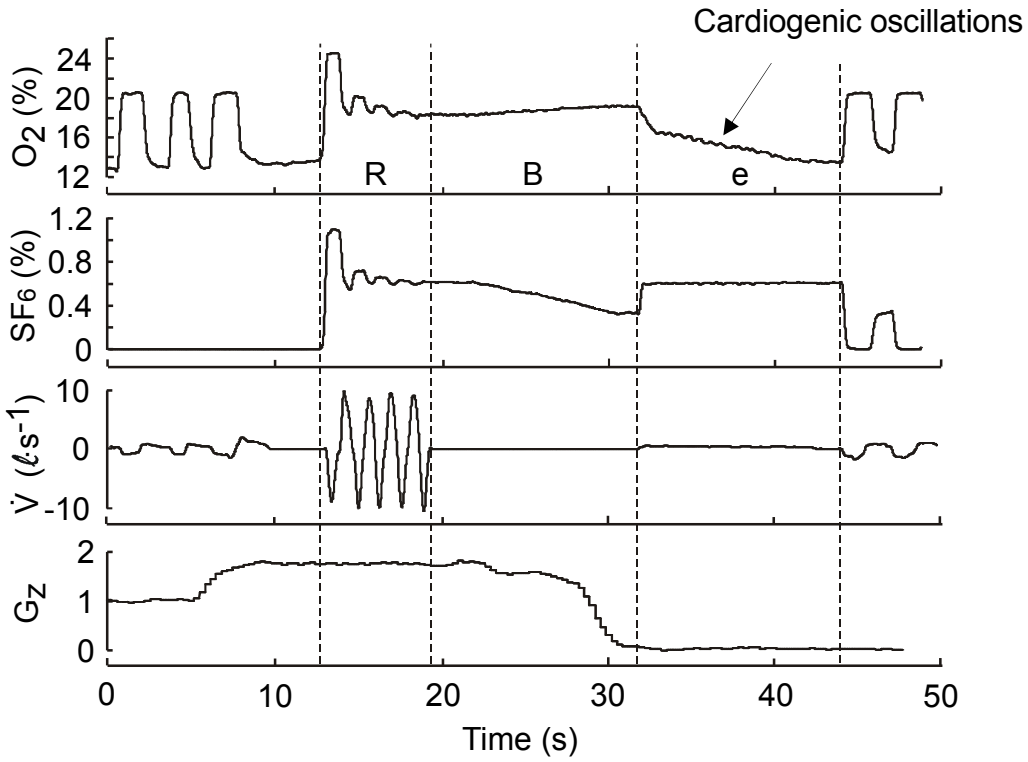

Fig. 11 (reproduced from article II). The rebreathing (R) – breath holding (B) – expiration (e) procedure, typical recording of respired O_2 and SF_6 concentrations and flow obtained during parabolic flight with a simultaneous recording of the gravity vector in the head-to-foot direction (lower panel). Gas concentration readings during breath holding provide no information other than that the gas in the apparatus dead space is drawn in by the sampling flow of the analyzer and is gradually replaced with cabin air.

Phase IV phenomena

These were recorded at the same time as COS, during the maneuver described in Fig. 11 (see also Fig. 3, page 6).

MEAN ARTERIAL PRESSURE

Mean arterial pressure (MAP) was recorded at finger level with a volume clamp technique (Finapres or Portapres) in all series of experiments other than for the first series of article II. However, data are presented only in article III.

EXPERIMENTAL PROCEDURES

ARTICLE I

Six male subjects performed static and dynamic spirometries, and rebreathing manoeuvres before (control or baseline), during (day 113, D113) and after (days of recovery R+0, R+3, R+15) 120 days of HDT. Tests were performed in supine and upright postures.

ARTICLE II

Two sets of experiments were performed during parabolic flight (Fig. 12). Twelve subjects were studied in the first series and six in the second. They performed a rebreathing – breath-holding – expiration manoeuvre during different combinations of HiG and 0 G.

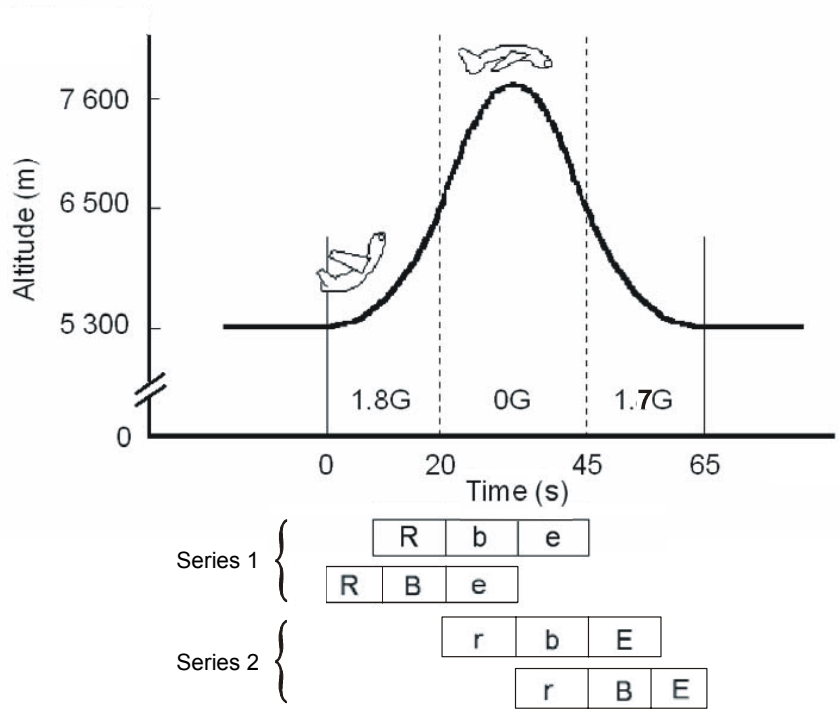

Fig. 12 (reproduced from article II). Time courses of the rebreathing – breath holding – expiration maneuver during the two series of parabolic flight experiments, with the four different timings between the elements of the breathing maneuver and the parabola.

- Series 1: control tests performed at 1 G on the ground, inflight tests with rebreathing at 1.8 G – breath-holding at 0 G – expiration at 0 G (combination Rbe) or rebreathing at 1.8 G – breath-holding at 1.8 G – expiration at 0 G (combination RBe).
- Series 2: control tests performed at 1 G both on the ground and inflight, inflight tests with rebreathing at 0 G – breath-holding at 0 G – expiration at 1.7 G (combination rbE) or rebreathing at 0 G – breath-holding at 1.8 G – expiration at 1.7 G (combination rBE).

ARTICLE III

Nine subjects were studied in the human centrifuge. They wore anti-G suits that were inflated to the following target pressures: 0 (zero IP), 70 (low IP), 140 (medium IP) and 210 mmHg (high IP). Rebreathing tests were performed at 1 G and 2 G with and without inflation.

ARTICLE IV

Twelve subjects were studied in the human centrifuge, wearing anti-G suits. They performed the rebreathing – breath holding – expiration manoeuvre at 1 and 2 G with the anti-G suit inflated either to 0 or to 85 mmHg.

OVERVIEW OF THE DATA ANALYSIS

STATIC AND DYNAMIC SPIROMETRY

Forced expiratory flows and volumes were analysed according to the guidelines of the European Respiratory Society (100, 101) and of the American thoracic society (1).

DL_{CO}

The first part of the computation of DL_{CO} was done as described by Sackner et al. (109). A special consideration was that DL_{CO} is influenced by several factors, of which alveolar volume (V_A) is the only which can and must be corrected for (63, 113). Other influencing factors are the degree of hydration of the lung tissue (118), pulmonary capillary blood volume (118), haemoglobin concentration (33), and impaired matching between distributions of alveolar gas volume and the pulmonary capillary blood volume (97).

The parameter K_{CO} is often computed in an attempt to correct for inter-individual differences in V_A: $K_{CO} = \frac{DL_{CO}}{V_A}$, where V_A is the volume of distribution of an insoluble gas such as helium. However, this correction is not appropriate because when lung volume decreases from total lung capacity (TLC) the surface area for gas exchange decreases more than the pulmonary capillary blood volume (66). Thus, K_{CO} provides a less representative evaluation of gas exchange than does DL_{CO} and was not used in the present work. Instead, DL_{CO} was corrected for day-to-day differences of estimated V_A. The following separate algorithms for supine and upright data from Stam et al. (118) were used to recalculate DL_{CO}:

$$volume\text{–}corrected\ DL_{CO} = \frac{DL_{CO}}{(0{,}4 + 0{,}012 * V_A)}$$

V_A is given as a percentage of TLC for each subject, posture, and test day. V_A is estimated as FRC+1/3 rebreathing bag volume. We reason the following way: rebreathing starts at FRC; during the manoeuvre, the volume of gas present in the lungs at any time is ideally the bag volume / 2 (assuming that inspiration time is 50% of respiration) but inspiration was often shorter during the tests and we adopted a bag volume / 3 instead.

Diffusing capacity has two components, the membrane component, diffusing capacity of the alveolo-capillary membrane (D_m), and a capillary blood volume component (V_c):

$$\frac{1}{DL} = \frac{1}{D_m} + \frac{1}{\theta . V_c}$$

θ depends on the alveolar pressure of O_2 and can be computed by using gas mixtures containing different O_2 concentrations. Unfortunately, the distinction between the membrane and blood components of DL_{CO} was not possible because of too few correct measurements using mixtures with different O_2 concentrations.

Q, SV, MAP AND FRC

Q and FRC were computed from the rebreathing tracings as described by Sackner et al. (109). SV was calculated by dividing Q by HR. MAP at heart level (MAPh) was computed from beat-

by-beat pressure recordings corrected for the hydrostatic pressure difference between heart and finger levels.

COS

The gas mixtures contained Freon 22 or C_2H_2 (blood-soluble inert gases), methane, sulphur hexafluoride (SF_6), argon or He (insoluble inert gases), O_2 and balance N_2. Ideally, the blood-soluble inert gases would be used to study the heterogeneity of perfusion distribution.

Several problems arose: first, because the gas analysers were too sensitive to gravity and/or pressure and/or acoustic transients during the parabolic flights, the recordings of Freon, acetylene and methane were disrupted and not analysable. Thus, O_2 was used as soluble gas and SF_6 as insoluble gas. SF_6 concentrations during the slow expiration were used as an index of the mixing between the rebreathing bag and the lungs. The wash-in of foreign gases did not lead to an entirely homogeneous distribution of the gases because the tracings of SF_6 showed the presence of COS and of a phase IV. Had SF_6 been correctly mixed between the rebreathing bag and the lungs, none of these would have been present. This imperfect gas mixing after rebreathing had to be corrected for and that is detailed in article II.

The experiments of article II were performed using SF_6 as insoluble gas, whereas He was used for article IV (gas mixture available at that time). Thus, in these articles, the abbreviations $COS_{[O2/SF6]}$ and $COS_{[O2/He]}$ refer to cardiogenic oscillations of expired blood-soluble gas concentrations representative of perfusion heterogeneity, recorded after the rebreathing – breath-holding maneuver. Here, for clarity, as these two parameters represent the same thing with the only dissimilarity of different gases used, they will be grouped under the term $COS_{[O2]}$.

The computation of COS amplitude is described in article II.

PHASE IV PHENOMENA AND COS_{FLOW}

The computation of phase IV phenomena is described in article II. P_4 and closing volume (CV) for O_2 / SF_6 or O_2 / He recorded after the rebreathing – breath-holding maneuver, are termed here, in analogy with COS, $P_{4[O2]}$ and $CV_{[O2]}$.

The computation of COS_{flow} amplitude is described in article IV.

STATISTICS

A one- or two-way ANOVA was performed with the software STATISTICA (versions 5.1 and 6; Statsoft, Tulsa, OK) when applicable. A different analysis was used if the pre-requisites for ANOVA where not fulfilled: when sphericity was not verified, the P value was corrected with Huyn-Feldt and Greenhouse-Geisser epsilons; when there was not enough variance in the data a t-test was applied. Significance was accepted at the $P < 0.05$ level. In case of significance, a Tukey HSD post hoc test was applied to locate the differences for pair-wise comparisons.

MAIN RESULTS

ARTICLE I

Mid-maximal expiratory flow ($FEF_{25-75\%}$) was the only spirometric parameter where a difference was found between postures. $FEF_{25-75\%}$ showed lower values in the supine posture. The supine values were decreased by about 20% between baseline and D113, R+0, and R+3, and then increased between R+3 and R+15. At R+15, there was no difference compared to baseline level. The upright values did not change with time. Surprisingly, there was no interaction effect between time and posture.

There was no change in *peak flow (PF)* with time.

Vital capacity (VC) was decreased by 12% on day R+0 and by 15% and 16% on days R+3 and R+15 respectively.

Forced vital capacity (*FVC)* was decreased by 16% between baseline and R+15 and by 5% between D113 and R+15. Also, FVC tended to decrease between baseline and R+3 (P = 0.07). No difference was found between baseline and D113.

Forced expiratory volume in one second (*$FEV_{1.0}$)* was decreased by 14% between baseline and R+15 and tended to be lower than baseline on R+0 and R+3 (P = 0.06 and P = 0.05, respectively).

Functional residual capacity (FRC) did not change with time. However, upright *FRC* values were always larger than supine; in five subjects out of six, there was a 0.6-0.7 l difference between postures throughout the study.

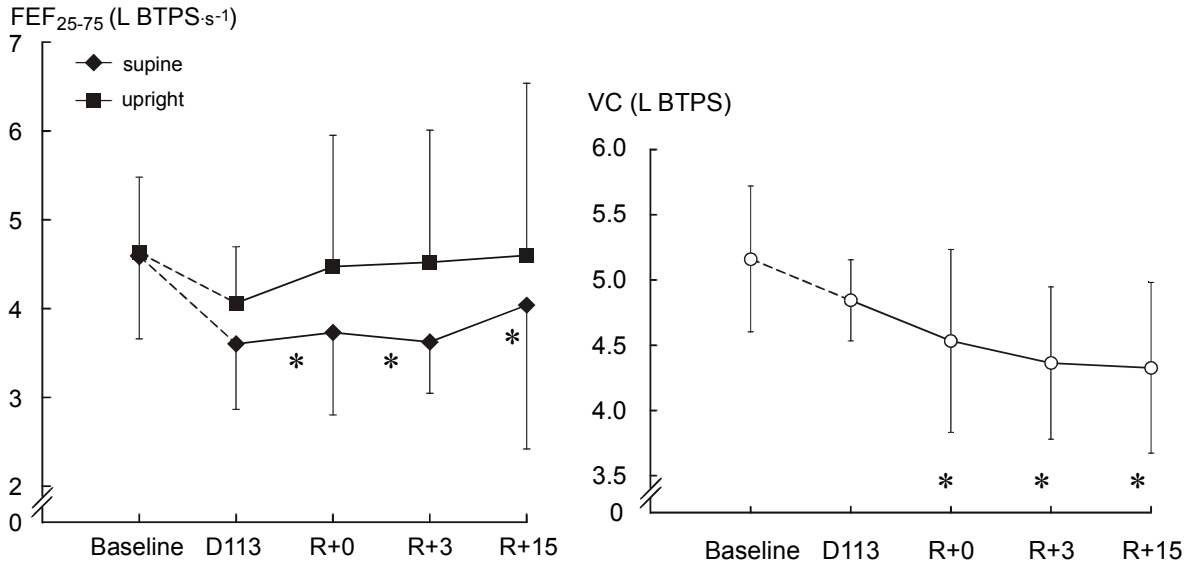

Fig. 13. Mid-maximal expiratory flow ($FEF_{25-75\%}$) and vital capacity (VC) measured before, during and after 120 days of bed rest (n = 6). D, days of bed rest, R, days of recovery. Values are mean ± SE. VC data from upright and supine tests have been pooled. FRC values from supine and upright tests are shown separately. *: P<0.05 between experimental day and baseline.

Volume-corrected DL_{CO} (Fig. 14) decreased by 20% and 15% between baseline and R+0 and between baseline and R+15 respectively. There was also a decreasing trend between baseline and D113 (P = 0.07). During the recovery period, the time course of the volume-corrected DL_{CO} was comparable to that of DL_{CO} except that volume-corrected DL_{CO} was significantly lower

than control on R+15. Supine values were larger than upright and their time courses were similar.

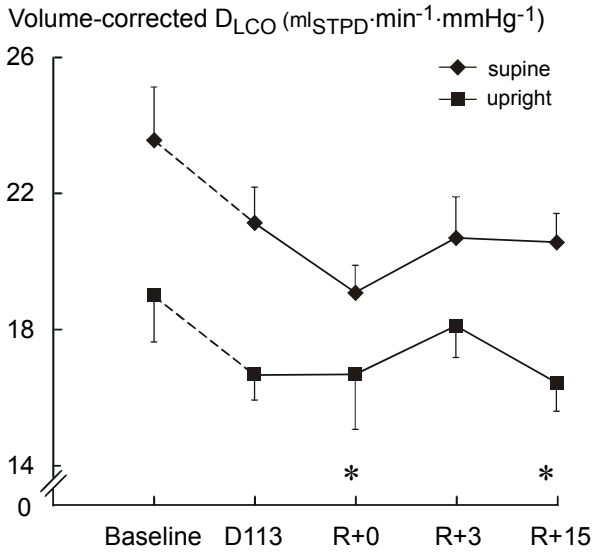

Fig. 14. Diffusing capacity for carbon monoxide (DL_{CO}) corrected for alveolar volume recorded before, during and after 120 days of bed rest, in the upright and supine postures (n = 6), in the same conditions as in Fig. 13. Same significance symbols.

Cardiac output (Q) values were larger supine than upright by about 2 l/min and the time course in these two postures was comparable. Q tended to decrease between baseline and R+0 (P = 0.09). Values increased by 11% between D113 and R+3, by 17% between R+0 and R+3, and by 15% between R+0 and R+15.

ARTICLE II

$COS_{[O2]}$ amplitude demonstrated a gradual increase with the gravity level during breath holding but was not influenced by the gravity level during expiration.

Series 1:

$COS_{[O2]}$ amplitude was lower in rebreathing in HiG – breath holding at 0 G – expiration at 0 G (Rbe) than in rebreathing in HiG – breath holding in HiG – expiration at 0 G (RBe) and tended to be lower in Rbe than at control (P = 0.051).

Values for *$CV_{[O2]}$* and *$P_{4[O2]}$* were always larger during control than inflight, where expirations took place at 0 G. In fact, no significant closing volumes and P_4 were found inflight.

Series 2:

There were no differences in the parameters measured during 1 G ground and 1 G in-flight conditions.

$COS_{[O2]}$ amplitude during rebreathing at 0 G – breath holding at 0 G – expiration in HiG (rbE) was lower than during all of the other conditions. Moreover, $COS_{[O2]}$ *amplitude* was lower during controls than during rBE.

$CV_{[O2]}$ during rbE was lower than during 1 G flight and rebreathing at 0 G – breath holding in HiG – expiration in HiG (rBE), whereas there was no difference between the control and rBE values. $CV_{[O2]}$ was 43% lower in rbE than in control and 26% larger in rBE than in control.

$P_{4[O2]}$ was larger in rBE than during the other conditions. Moreover, 1 G flight values tended to be larger than values in rbE (P = 0.070). P_4 during rbE was 55% lower than control and during rBE 83% larger than control. $P_{4[O2]}$ exhibited, on the average, a positive deviation from phase III. The 95% confidence interval for $CV_{[O2]}$ and $P_{4[O2]}$ did not include zero during any of the conditions examined although it was close to doing so in the case of rbE.

A plot of data from articles II and IV suggests a linear relationship between the gravity level during breath holding and the amplitude of $COS_{[O2]}$ (Fig. 15). This linear relationship is also found for $CV_{[O2]}$ and $P_{4[O2]}$.

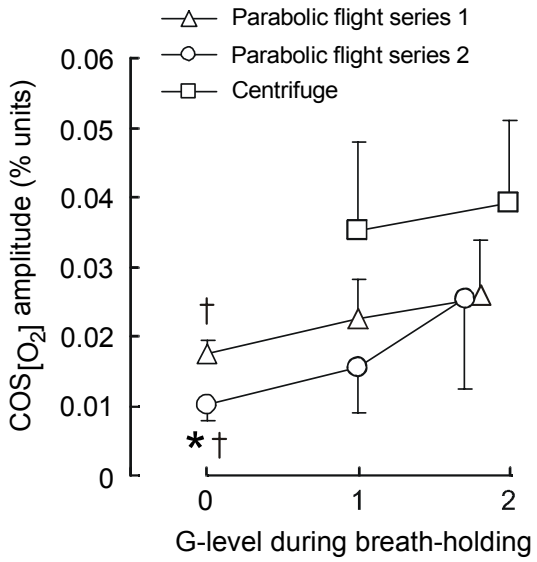

Fig. 15. $COS_{[O2]}$ amplitude measured at different levels of gravity during the breath holding part of the rebreathing – breath holding – expiration manoeuvre (0 G, 1 G, 1.7-2 G), data from three series of experiments (articles II and IV). Statistics were performed separately for each experiment. Significances at the P = 0.05 level are shown as follows: *, different from 1 G; †, different from 1.7-1.8 G.

ARTICLE III

Stroke volume (SV) (Fig. 16 and 17A) decreased at 2 G compared to 1 G. All inflation pressure (IP) levels increased SV at 1 G. The lowest IP gave comparable SV values at 2 G to that at 1 G without inflation. There was no benefit in terms of SV of increasing the IP further at 2 G.

Cardiac output (Q) (Fig. 16) did not differ with G-level although its value at 2 G was 13.4% lower than that at 1 G. Q increased with IP (P = 0.0042) but only at 2 G.

Heart rate (HR) at 1 G was always lower than at 2 G and the difference between 1 G and 2 G did not change with IP. HR also changed with IP (P = 0.024) and in particular decreased at low IP.

Mean arterial pressure at heart level (MAPh) increased with IP (P < 0.001) but did not change with the G-level.

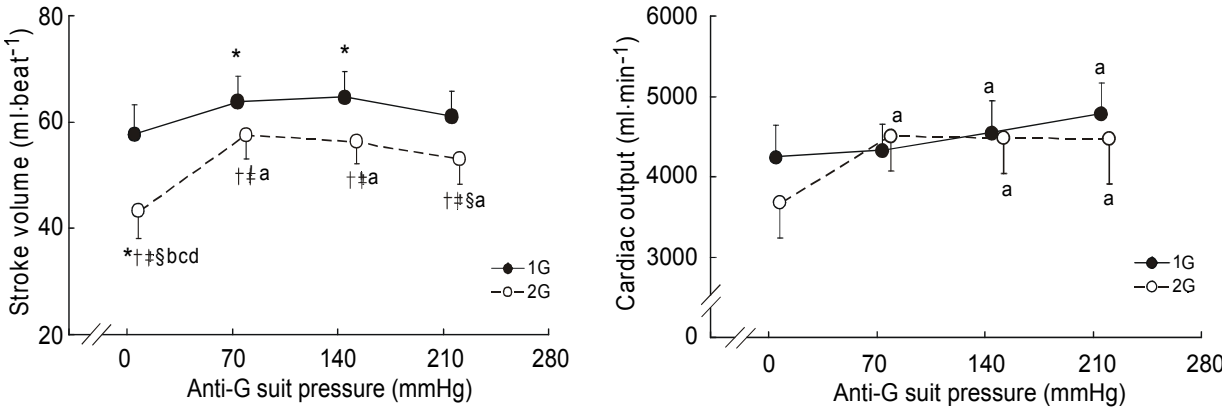

Fig. 16. Cardiac output (left) and stroke volume (right) measured at normal gravity (1 G) and in moderate hypergravity (2 G) with full-coverage anti-G trousers inflated to the target pressures 0, 70, 140 and 210 mmHg. The obtained pressures at 2 G were a bit different than the target pressures. Values are means ± SE. Significances at the P = 0.05 level are shown as follows: *, †, ‡, § compared to 1 G at 0, 70, 140 and 210 mmHg of inflation respectively; [a], [b], [c], [d] compared to 2 G, same inflation pressures.

ARTICLE IV

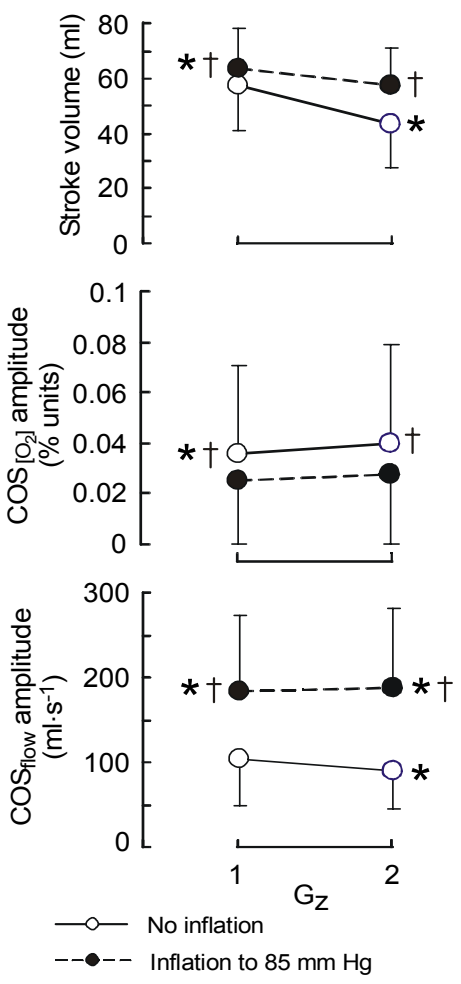

Fig. 17A. Stroke volume measured with and without inflation of an anti-G suit, at normal gravity (1 G) and at 2 G. Significances at the P = 0.05 level are shown as follows: *, different from 1 G without inflation; †, different from 2 G without inflation.

Fig. 17B. Cardiogenic oscillations of O_2 concentrations ($COS_{[O2]}$) recorded after a rebreathing – breath holding – expiration manoeuvre, at 1 G and at 2 G, with and without inflation of an anti-G suit. Significances as in Fig. 17A.

Fig. 17C. Cardiogenic oscillations of expired flow (COS_{flow}) recorded in the same conditions as for Fig. 17B. Significances are shown as in Fig. 17A.

COS_{flow} amplitude (Fig. 17C) was 86% higher at 1 G + inflation than at 1 G control but did not change with the G-level.

$COS_{[O2]}$ amplitude (Fig. 17B) did not change with the G-level but decreased when the anti-G suit was inflated. Values at 1 G + inflation were 25% lower than at 1 G control. Moreover, $COS_{[O2]}$ amplitudes at 2 G + inflation were 18% lower than at 1 G control, a trend that approached significance ($P = 0.053$).

DISCUSSION AND PERSPECTIVES

INFLUENCE OF MICROGRAVITY ON LUNG MECHANICS

Lung volumes and forced expiratory flows

The major findings of article I are post-HDT reductions in VC, forced expiratory volumes, DL_{CO} and Q. The spirometric parameters recovered slowly or not at all during the first 15 days after HDT, in contrast to the rapid initial recovery of DL_{CO} and Q.

Forced expiratory flows and volumes.

Peak flows recorded at high lung volumes during a dynamic expiration largely represent events occurring in the trachea and large bronchi. Alternatively, flows recorded at low lung volumes represent events occurring in small intra-thoracic airways (81).

Expiratory flows recorded at high lung volumes are more effort-dependent than flows recorded at low lung volumes. For instance, PF is effort dependent (69) but only when alveolar pressure is less than that required to achieve flow limitation (123). Above that level, PF is flow limited (69). Below that level, PF increases with high lung volumes at the start of expiration (62) because of increased elastic recoil and decreased upstream frictional pressure loss due to enlarged airway dimensions (94, 124). Equally important, PF increases with a rise in expiratory effort: a fast acceleration of flow causes maximal flow to be reached earlier during expiration, *i.e*., at a higher lung volume. After 25-30% of VC has been expired, flow is independent of muscular effort as long as the effort is above certain levels (81).

In small airways, flow is laminar whereas it is at least partially turbulent in large airways. During expiration, the driving pressure, sum of the pleural pressure and lung elastic recoil, encounters frictional losses down the airways (*i.e*., aborally) and decreases until reaching atmospheric pressure at the airway opening. The point where the driving pressure falls to pleural pressure is defined as the equal pressure point (EPP) (81). Downstream of EPP, airway pressure is less than pleural pressure, which leads to airway collapse (the dynamic airway compression phenomenon).

Dynamic airway compression begins at the start of expiration and EPP are located between the thoracic outlet of the trachea and the lobar bronchi. Nevertheless, dynamic airway compression is not a limiting factor for PF (81). As flow falls off and lung volume decreases the frictional resistance of the segment predominates. Dynamic airway compression is largest between 25% and 75% of expired volume, thus creating an effort-independent flow restriction (81). Thus, $FEF_{25-75\%}$ is influenced by lung elastic recoil and airway resistance rather than muscular effort (96).

During the very last portion of the forced expiration, at least in young individuals, the rising opposition of the chest wall to further volume change opposes the falling static recoil. This opposition is sufficient to allow the EPP to move back up the tracheo-bronchial tree, and flow is again determined by effort (81).

Thus, VC is influenced by muscular effort (inspiratory and expiratory muscles) and by lung elastic recoil (7, 57, 80, 81, 121).

All these experiments were performed with subjects studied in the same posture. However, when going from the upright to the supine posture, variations in central blood volume (CBV) must be taken into account: CBV increases, limiting the capacity of the lungs to expand (see Table 1, Page 7).

Surprisingly, in the present experiment there were no variations of the spirometric parameters with posture. This can be so because, after baseline, the decrease in plasma volume caused by HDT (34) will lead to less blood moved from the legs to the thorax upon assuming

the supine posture. Thereby, the effect on lung volumes and expiratory flows will be limited. Thus, changes in central blood volume during HDT cannot account for the changes of the spirometric parameters.

Although PF was not influenced by HDT, VC was reduced by a mechanism characterised by a slow recovery. PF is measured with a fast forced manoeuvre, whereas the VC manoeuvre is slow. There, a comparison with studies of leg muscles during HDT is interesting: these studies have shown a muscle deconditioning (3) that is characterized by a decrease in the amount of slow fibres and an increase in the number of hybrid fibres (containing both slow and fast fibres) (122). As far as the leg is concerned, it is not certain whether these changes are the cause of muscle deconditioning (122). However, if such fibre changes were to occur in the respiratory muscles, they could explain the observed decrease in VC with a normal PF during HDT. Another non-exclusive possibility is that the decrease in VC is caused by a decrease in lung elastic recoil.

The most likely explanation to the reductions in FVC and $FEV_{1.0}$ is that of scaling because VC was reduced with time. Thus, MEFV manoeuvres were performed at a somewhat lower volume, with an associated lower elastic recoil and airway conductance. The decrease in $FEF_{25-75\%}$ in the supine posture from D113 to R+3 is possibly due to a decrease in lung elastic recoil. This decrease may only become apparent in a situation where airway resistance is increased due to a relatively larger thoracic blood volume, such as in the supine posture.

To answer these questions, further studies including measurements of respiratory muscle fibres (biopsies) and of lung elastic recoil (estimated from oesophageal pressure) during HDT are required.

DL_{CO}

The consistent difference between supine and upright measurements of DL_{CO} points to the well-established relationship between pulmonary capillary blood volume and DL_{CO}. It might also be reasoned that time-dependent changes of DL_{CO} are a function of the plasma and blood volumes reductions during HDT. The slightly larger values on R+3 than on R+15 could be a function of two parallel processes, the first determined by plasma volume and a second much slower related to lung tissue properties. An alternative explanation is that the initial recovery of plasma volume after HDT is accompanied by hemodilution and no effective content in the pulmonary capillaries, because 2-3 weeks are necessary for red blood cell synthesis. Data reported by Fortney et al. (35) show clearly a hemodilution during the first 2 weeks after HDT.

It would be of interest, during another long-term HDT experiment, to simultaneously perform plasma and blood volume measurements, and numerous rebreathing tests with two gas mixtures of different O_2 content. These rebreathing tests would permit the computation of the tissue and blood components of DL_{CO}. From that point of view, it is unfortunate that the small number of tests available here did not enable such calculations.

Significance

The changes in lung volumes and expiratory flows, Q and DL_{CO} observed during HDT are not of such a magnitude that they will limit the daily activities of the subjects after HDT. The quality of life of these subjects is rather likely to be impaired by orthostatic hypotension, a common side-effect of HDT and space flight (22), at least during the first week or weeks of recovery.

On the other hand, the finding of impairment in lung function, of (possibly) lowered haemoglobin content and of a decreasing trend for Q during and shortly after HDT will probably concur in a decreased maximal O_2 uptake. Previous studies have shown that work capacity is altered after HDT (20, 61) because of dramatic reductions in maximal SV, Q, and O_2 uptake. In

a parallel study, during the same experiment and on the same subjects (116), a rapid, preload-dependent reduction in SV, and a more slowly developing cardiac dysfunction were observed. Cardiac dysfunction was most evident during 30 min of supine 50W exercise, which is a low work load. Thus, any sustained physical work, even of low intensity, will be more difficult to perform after 120 days of HDT.

Cardiopulmonary interactions at 0 G

The mechanical action of cardiac pumping on the lung tissue can be assessed from COS_{flow}, since COS is generated from a combination of heart-synchronous sequential emptying of pulmonary units and of gas composition differences between these units.

At 1 G, during the rapid ejection phase of the ventricles, atrial pressure decreases, the atrio-ventricular groove moves down toward the apex, and blood flows into the atria ("ventricular systolic suction" phenomenon) (14). During systole at rest, 60-70 ml of blood (SV) is ejected from the left ventricle and thus leaves the thorax (117). This amount is partly simultaneously compensated for by left ventricular systolic suction, the remainder coming to the left atria during diastole (14). Thus, at 1 G there probably exists a temporary systolic negative blood balance in the thorax as a whole. COS_{flow} is likely to be initiated by these cyclic changes in the overall intra-thoracic (= central) blood volume (13, 23, 55). Thus, during systole, the transient volume reduction in the thoracic cavity results in an inflow of air if the airways are open (13).

When going from 1 G to short-term 0 G, the venous return to the heart increases, leading to increased preload and central blood volume (CBV). As a consequence, SV and Q increase (Table 1). This must cause a larger capillary recruitment (95, 127), even though capillary recruitment has not been studied directly at 0 G. As a result, perfusion differences should be lower than at 1 G.

Another consequence of the increase in CBV at 0 G is that there is no requirement to pump blood into the thorax during ventricular systolic suction because the amount available in the thorax would be sufficient. This would result in a more negative intra-thoracic blood balance during systole. Thus, COS_{flow} should increase. Moreover, lung units would empty more easily because of an increased mechanical action on alveolar emptying due to the larger SV at 0 G.

Thus, it is probable that perfusion differences decrease and that the remaining differences are easy to see with $COS_{[O2]}$ and with phase IV phenomena for O_2 because of increased sequential emptying.

Consequences of going from 1 G to sustained 0 G are probably a bit different, because of the combination of a decrease in plasma volume with increased Q and SV: capillary recruitment should be less than in short-term 0 G but the mechanical influence of SV on alveolar emptying should be comparable to that in short-term 0 G. Thus, one would expect to see larger $COS_{[O2]}$ and phase IV phenomena for O_2 than in short-term 0 G but these would still be smaller than at 1 G.

As for HDT, plasma volume, SV and Q decrease (Table 1). CBV should be larger than in the upright posture but smaller than at 0 G because of the decreased overall plasma volume. Because of this, capillary recruitment should increase but less than at 0 G. Another factor, which should limit capillary recruitment, is the smaller SV. Accordingly, this smaller SV would influence alveolar emptying less than at 1 G. Thus, even though perfusion differences should be only mildly lower than at 1 G, they would appear lower than they really are because of a decreased sequential emptying. From this point of view, HDT is probably not a realistic simulation of a microgravity state.

MECHANISMS GENERATING CARDIOGENIC OSCILLATIONS

Effects of anti-G suit inflation or/and exposure to 2 G

The experiments described in article III support the notion that anti-G suit inflation acts in two ways. First, it displaces a finite amount of blood from the periphery to the central circulation and increases preload (59, 133). These changes are already maximal at low IP. Second, it increases afterload (46, 59, 133) in proportion to IP. In terms of Q, the direct and secondary effects of arterial compression cancel out the benefits of increased preolad.

We found that ~ 85 mmHg of inflation of a full-coverage anti-G suit counteracts the effects of 2 G on SV. At 1 G and at the same IP, SV is increased. At ~ 85 mmHg of inflation, arterial occlusion in tissues covered by the anti-G suit likely does not occur.

Because central venous pressure (CVP) was not measured in article III, the effects of anti-G suit inflation on systemic vascular resistance (SVR) are not discussed. Nevertheless, such information would be of great interest. For completeness, a tentative discussion of this matter is presented:

$$SVR = \frac{MAP - CVP}{Q} \quad (72) \text{ (Equation 1)}$$

has often been approximated as $SVR = \frac{MAP}{Q}$ (12, 32, 64, 84, 92, 106, 114) (Equation 2)

This approximation can be made in the sitting position at 1 G because CVP approaches zero. At 2 G, CVP values are slightly higher (32, 92) but are still low enough for SVR to be estimated by Equation 2 with an acceptable potential error. However, when an anti-G suit is inflated at 1 G, CVP is increased to a large degree (12, 106, 114). Moreover, the combined effects of anti-G suit inflation and exposure to 2 G on CVP are unknown. In these conditions at least, neglecting CVP cannot be justified.

Effect of hypergravity.

The measurement of CVP is invasive and not easily combined with HiG experiments in a centrifuge. For these reasons, there are no recordings of CVP in the experiments described in article III. Nonetheless, we can try to estimate SVR from mean CVP recordings obtained elsewhere in the literature: we adopt a CVP of 1.5 mmHg at 1 G (12, 32, 64, 84, 92, 106, 114) and of 3.4 mmHg at 2 G (32, 92). From these values, we can compute one SVR value for all subjects together at 1 G and at 2 G (Table 3) and find an approximately 11% increase in SVR from 1 G to 2 G, which is in accordance with the data of Lindberg *et al.* (75). It seems logical that SVR should increase in hypergravity as a counter-regulatory baroreflex response to a decrease in arterial blood pressure at carotid level (76).

Effect of anti-G suit inflation.

We found no reports of SVR in these conditions which have taken possible CVP changes into account. The SVR values calculated without CVP were all reported to increase with inflation (16, 38, 41, 46, 75, 133). However, CVP increases when an anti-G suit is inflated, so the SVR values on these reports must be disregarded.

There are no reports of CVP when a full-coverage anti-G suit is inflated. Thus, we adopt values measured with five-bladder suits, which offer less G-protection than full-coverage anti-G suits (26, 48). The mean inflation pressure and the mean CVP reported are 100 mmHg and 24

mmHg respectively (12, 106, 114). We reason that the effect of 100 mmHg of inflation of a five-bladder suit on CVP is probably not very different from that of 85 mmHg in the full-coverage anti-G suit. Results are presented in Table 3.

CVP during the combination of 2-G exposure and inflated anti-G suit was estimated as the difference between 1 G and 2 G added to the effect of inflation, *i.e.* 24 + 1.9 = 25.9 mmHg (Table 3).

Inflation pressure (mmHg)	*Estimated CVP (mmHg)*		*Q (l.min-1)*		*MAPh (mmHg)*		*Estimated SVR (resistance units)*	
	1 G	*2 G*	*1 G*	*2 G*	*1 G*	*2 G*	*1 G*	*2 G*
0	1.5	3.4	4.3	3.7	75.2	74.0	17.3	19.2
85	24	25.9	4.3	4.5	86.0	82.4	14.3	12.6

Table 3. Systemic vascular resistance (SVR) estimated from central venous pressure (CVP) data reported in the literature and from our own measurements of mean arterial pressure at heart level (MAPh) and cardiac output (Q). Q and MAPh are means reported from article III.

We suggest that two mechanisms can explain the proposed decrease in SVR when an anti-G suit is inflated. First, tissue compression most likely increases afterload, which tends to increase arterial pressure, leading to arterial baroreceptor stimulation. Sympathetic activity is accordingly inhibited. This, in turn, decreases SVR in the vascular beds outside the anti-G suit. Second, the volume displaced from tissues underneath the anti-G suit is likely to be transmitted to both the venous and arterial sides of the systemic circulation outside the trousers. Thus, arterial distension might occur there, which would decrease SVR.

A summary of the effects of anti-G suit inflation is presented in Fig. 18. The part on $COS_{[O2]}$ and COS_{flow} is discussed under *Influence of gravity on cardiopulmonary interactions* below.

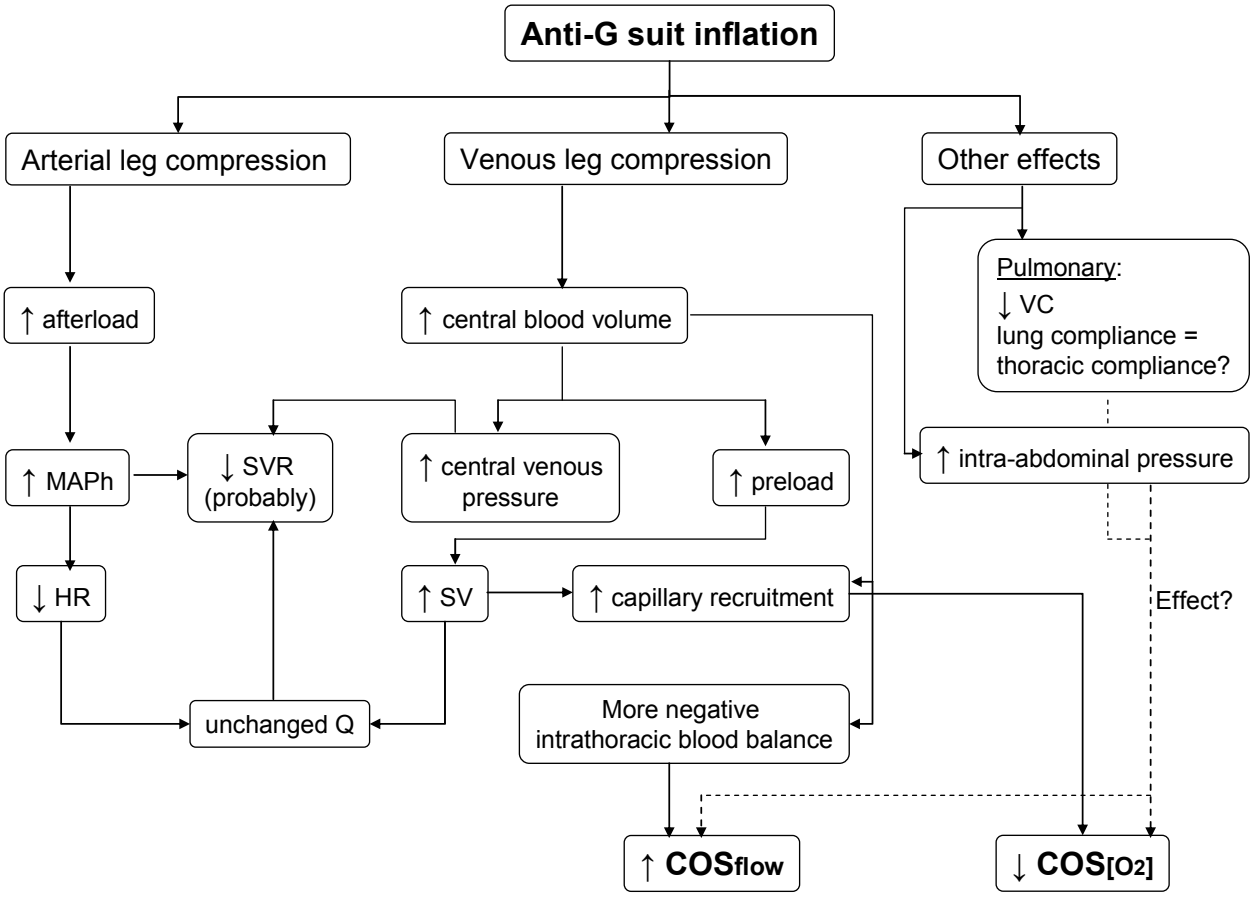

Fig. 18. Summary, cardio-pulmonary effects of anti-G suit inflation.

Timing between the cardiac cycle and COS

Dahlström *et al.* studied subjects who took a single breath of N_2 after several minutes of O_2 breathing. Thus, the subjects started the manoeuvre with a quasi-homogeneous ventilation distribution. The authors could relate the different parts of $COS_{[N2]}$ to the various phases of cardiac pumping (23).

The first descending slope was in phase with left auricular systole, when a reflux of blood into the pulmonary venous system is produced (P wave on the ECG). The slope was then in phase with ventricular systole (QRS wave). Moreover, it was observed ex-vivo that the expansion of pulmonary vessels produced a shift of gas from well-ventilated regions to low-ventilated areas. Because the first slope was descending, it was concluded that gas with low content in N_2, *i.e.* coming from lung units with a low turnover, is added to the expired gas during ventricular systole. Thus, lung vessels probably push certain volumes of gas from the deepest parts of the system, i.e. farthest away from the mouth, to more superficial regions.

The following upslope was in phase with left auricular diastole and thus the emptying of the pulmonary veins (first half of the T wave on the ECG). Then, a descending slope appeared, in phase with the second phase of the T wave. The last upslope corresponded to ventricular diastole, where the volume of the pulmonary vascular bed decreases (interval between T and P waves). Therefore, the authors concluded that highly ventilated alveoli emptied during the last upslope and delivered a high amount of N_2.

Furthermore, Arieli *et al* (5) concluded that COS of expired gas concentrations resulted from differential emptying rates from lung units with differing time constants in their response to pressure waves generated by the heart.

Heart volume changes during the cardiac cycle and ventricular systolic suction

Observations on animals (dog, frog, turtle, pig) have demonstrated that total heart volume is nearly constant throughout the cardiac cycle (volume changes are reciprocal between the atria and ventricles (54, 56, 115)). During the rapid ejection phase, the atrial length increases due to ventricular systolic suction (14). Thus, external volume changes of the heart as such are not likely to have any large impact on the rate of alveolar emptying (54, 56, 115).

Dynamics of the heart and big vessels

It has been shown that the heart rotates around the left ventricular long axis (78). Also, manual compression of a rubber bulb connected to the pulmonary vessels of excised human lungs generates an oscillation on the concentration of expired N_2. This oscillation is comparable whether the bulb is attached to the venous or to the arterial system (23).

The aorta is elastic and dilates when receiving a large amount of blood, as during systole. In the mechanically ventilated dog, pulmonary vascular resistance is greater in the dependent lung. This is probably because of non-uniform lung distension due to cardiac and abdominal weight and possibly to local hypoxic vasoconstriction. Moreover, pulmonary vascular resistance is lung volume-induced (18). Vascular resistance has also been found to increase along the dorso-ventral axis in the isolated supine lung, but this is not a consistent finding (9).

Influence of increased gravity on cardiopulmonary interactions

The G-level of the hypergravity experiments described in this thesis was between 1.7 (parabolic flight) and 2 G (human centrifuge). The pulmonary and cardio-vascular effects of these two G-levels are probably quite similar.

We found dissociated responses of COS_{flow} and $COS_{[O2]}$ to the inflation of the anti-G suit at 1 G and 2 G (Fig. 17). Although cardiac pumping nearly doubled COS_{flow} when the anti-G suit was inflated, suggesting a marked increase of the heart–synchronous mechanical agitation of the lungs, $COS_{[O2]}$ decreased by 25%–30%. Another important finding is that none of these parameters changed with the G-level.

$COS_{[O2]}$ are influenced by lung and thoracic compliance (74). The effect of thoracic blood volume movements on the parenchyma could be damped by stiffness of the lung tissue but enlarged by decreased thoracic compliance. It is possible that the absence of significant effect of 2 G on $COS_{[O2]}$ and COS_{flow} be explained by these two effects cancelling each other out. Differences in compliance between lung regions are probably also of importance; Colebatch et al. found that COS_{flow} amplitude decreases as airway resistance increases (19). It is unclear from which alveolar populations COS_{flow} originate, and our data do not give any topographical information. Proximity to the heart (128, 132) is one but not the only factor which determines the extent of heart-synchronous airway flow oscillations. In that perspective, measurements of thoracic and lung compliance with an anti-G suit at 1 G and at 2 G are required.

When an anti-G suit is inflated, central blood volume increases (129) and may become large enough for systolic suction into the right heart to be accounted for to a larger extent by blood already located in the thoracic cavity. This would attenuate the impact of ventricular systolic suction on the rate of influx of blood to the thorax. Acting in a similar direction, the venous blood volumes in the legs and abdomen decrease, dramatically reducing the blood volume accessible for systolic suction into the thorax. This would in turn increase the systolic negative

blood balance in the thorax, and together with a 10%–30% increase in SV (88), would increase COS_{flow} amplitude. Anti-G suits also affect the lungs: it seems logical that the chest wall and the lung would become stiffer because of the upward movement of the diaphragm (43). Thus, it is probable that other effects of anti-G suit inflation than SV *per se* have a much greater impact on the outcome of COS_{flow}.

SV is, by definition, the *primum movens* of the generation of any heart-synchronous event. SV probably influences the generation of $COS_{[O2]}$ in two entirely opposite ways (Fig. 19). First, SV induces intrathoracic blood volume pulsations, which mechanically influence the emptying of compliant lung units (and thereby increase COS_{flow}). Thus, if all other factors were to remain constant, an increase in SV would tend to increase $COS_{[O2]}$. Second, an increase in SV and thereby pulmonary blood flow increases capillary recruitment, which decreases the differences in pulmonary perfusion and lowers the amplitude of COS. Inflation of the anti-G suit will increase capillary recruitment by increasing SV but also by increasing vascular pressures in the pulmonary circulation (107, 108). The dominating factor behind $COS_{[O2]}$ amplitudes must therefore be differences in gas composition between asynchronously emptying lung units rather than the mechanical agitation of the lung tissue.

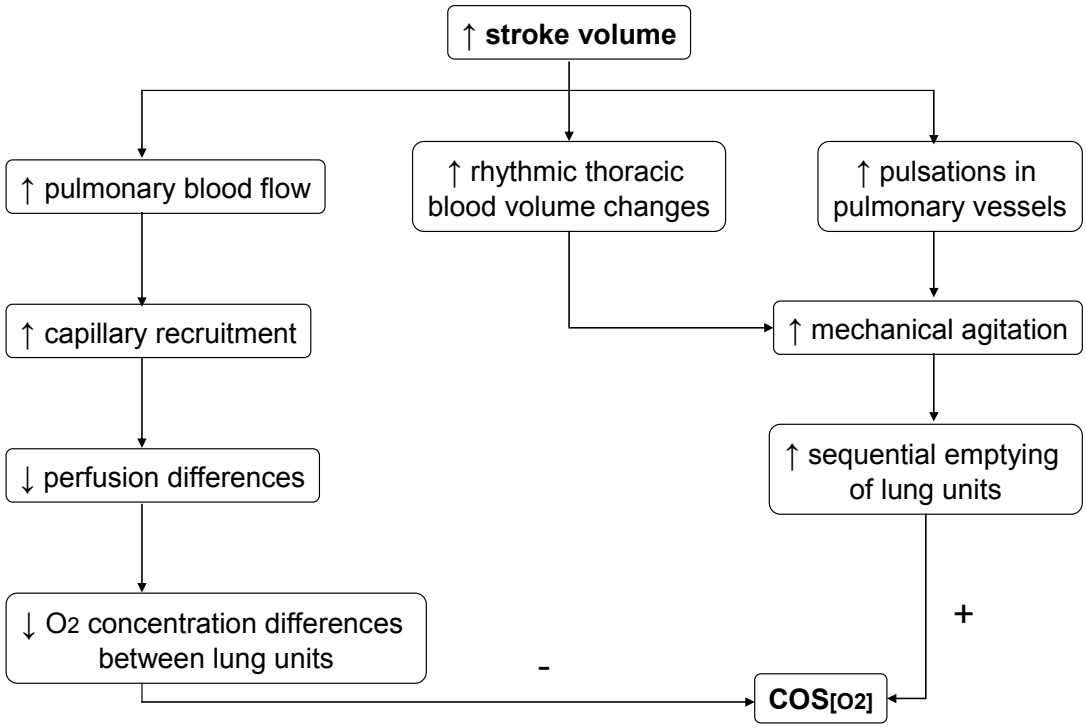

Fig. 19. Summary, effects of an increase in stroke volume on the generation of cardiogenic oscillations of expired O_2 concentrations as an index of pulmonary perfusion heterogeneity ($COS_{[O2]}$). The effects of a decrease in stroke volume are the opposite.

On the use of COS as an index of the inequality of pulmonary perfusion: is there a linear relationship between COS amplitude and pulmonary perfusion distribution?

An advantage of the present protocol was that the combination of different G-levels during breath-holding enabled us to make a distinction between the perfusion effect of SV (breath holding) and the mechanical effect of SV (expiration). If one assumes that the relationship between $COS_{[O2]}$ amplitude and phase IV phenomena for O_2 recorded with that protocol, and perfusion distribution, is linear, we find a much larger degree of gravity-independent

heterogeneity of perfusion distribution than that found in previous topographical studies in humans (119) and in animals (44, 82).

The findings of article IV would speak in favour of a non-linear relationship: we have found that SV influences $COS_{[O2]}$ in two opposite ways, by enhancing sequential alveolar emptying but also by increasing capillary recruitment. Thus, an increase in SV as at 0 G will enhance the sequential emptying of compliant lung alveoli and thus increase $COS_{[O2]}$ amplitude: the differences in gas content between alveolar populations will appear more clearly. On the other hand, a larger SV increases pulmonary blood flow and thus capillary recruitment. This will decrease regional differences in perfusion and in gas content between alveolar populations. In hypergravity, SV decreases and the reverse occurs.

In addition, as discussed above $COS_{[O2]}$ is also influenced by thoracic compliance and by lung compliance (74). However, the effect of their combination on $COS_{[O2]}$ is unclear. Both compliances are influenced by gravity, which further complicates the problem.

Another possible explanation to the discrepancy between our results and previous estimations of overall heterogeneity of pulmonary perfusion is the following: these experiments were performed at 1 G after injection of contrast/radioactive marker during exposure to 0 G or to hypergravity. Thus, what was measured was perfusion per vascular unit and not perfusion per unit lung volume. As the lung tissue is more distorted at 1 G than at 0 G, perfusion heterogeneity at 0 G might be underestimated when assessed from 1 G measurements. Finally, the techniques used had not a resolution down to alveolar level. This might be another cause of underestimation of perfusion heterogeneity.

In conclusion, the assessment from $COS_{[O2]}$ amplitude to overall degree of pulmonary perfusion heterogeneity is probably complex and non-linear.

INFLUENCE OF GRAVITY ON PULMONARY PERFUSION DISTRIBUTION

Intra-regional perfusion distribution ($COS_{[O2]}$)

Having accepted the points raised above, the findings of article II suggest that pulmonary perfusion distribution is mostly gravity-independent in humans. If one assumes that the relationship between $COS_{[O2]}$ amplitude and phase IV phenomena for O_2 recorded with that protocol and perfusion distribution is linear, the gravity-independent part is estimated to be ~ 70-80% for intra-regional distribution and ~ 50% for inter-regional distribution. $COS_{[O2]}$ values were lower in series 2 than in series 1, which is probably a random occurrence as the populations studied were similar.

Nonetheless, there seems to be a linear effect of gravity on indices of intra-regional perfusion distribution, with perfusion differences increasing with increasing G-level (Fig. 15). This was observed by Rohdin et al.(104) between 1 and 3 G with a protocol slightly different from that used here. In the present experiments (articles II and IV), there probably exists a difference between 1 G and 2 G but it is too small to be statistically significant.

Inter-regional perfusion distribution (phase IV phenomena for O_2)

Here also, with the reservations made above in "*On the use of COS…*", in article II, signs of inter-regional heterogeneity of pulmonary perfusion were found following breath holding at 0 G. Moreover, some 50% of the indices of inter-regional heterogeneity in perfusion at 1 G appear to be independent of gravity. The advantage of series 2 over series 1 is that the use of expiration at 1.7 G enhanced sequential emptying. This unmasked differences in O_2 concentrations between pulmonary units. The disadvantage was that perfusion differences increased during expiration at 1.7 G. Thus, the phase IV phenomena recorded at the end of expiration in that case were rather a

combination of 0-G exposure (breath holding) and 1.7 G (expiration) than an index of inter-regional perfusion differences only at 0 G.

In analogy with $COS_{[O2]}$, there seems to be a linear effect of gravity on inter-regional perfusion distribution, with perfusion differences increasing with increasing G-level. Also in analogy with $COS_{[O2]}$, there probably exists a difference between 1 G and 2 G that is too small to be statistically significant. The fact that our results show a greater $P_{4[O2]}$ value at 1.7 G than at 1 G is in agreement with previous findings (104). It was proposed that hypergravity-induced vascular engorgement of dependent pulmonary regions reduces airway dimensions, thereby promoting airway closure (104). Such vascular engorgement would also prevent pulmonary units with a relatively high degree of perfusion from contributing to the expirate, probably more so at 3 G than at 2 G (104). This would mask part of the heterogeneity of perfusion.

An interesting perspective is given by the findings of lower $P_{4[O2]}$ values than expected recorded with breath holding at 0 G and expiration at 1.7 G; because both breath holding and expiration have the same duration, their effect on phase IV phenomena is expected to have the same magnitude but in opposite directions: 0 G should decrease apical-to-basal perfusion differences and 1.7 G should increase them. As a result, $P_{4[O2]}$ values should be only slightly lower than those recorded at 1 G. Yet, we found values only half of what was expected. As an extension, one could suggest that there is a negative $P_{4[O2]}$ at the end of breath-holding at 0 G, which partially offsets the positive $P_{4[O2]}$ that is likely to develop during expiration at 1.8 G (Fig. 20). This would mean, if one still assumes a linear relationship between phase IV phenomena for O_2 and the degree of inter-regional perfusion heterogeneity, that there is a reversed gradient of perfusion distribution at 0 G. Such a reversed difference would indicate a larger perfusion of the apical pulmonary units than of the basal units.

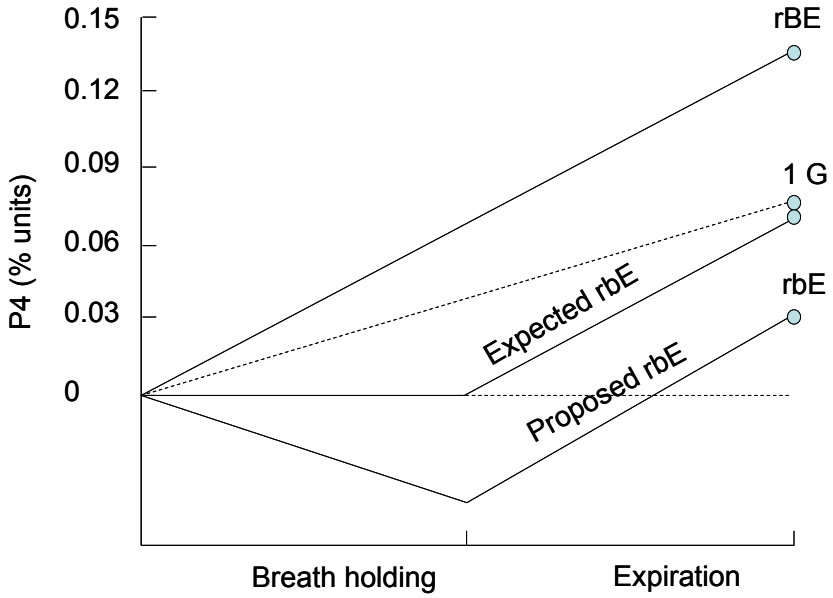

Fig. 20. Suggested explanation to the $P_{4[O2]}$ values lower than expected in rbE (rebreathing at 0 G – breath holding at 0 G – expiration at 1.7 G). Breath holding and expiration both last ten seconds. Thus, if one supposes that perfusion differences decrease at 0 G and increase at 1.7 G, at the end of rbE $P_{4[O2]}$ should approach its 1 G value ("expected rbE"). The real $P_{4[O2]}$ at the end of rbE being twice as small as this value (point "rbE"), it is possible that the effect of 0 G is larger than the effect of 1.7 G and that the pulmonary perfusion gradient is reversed during breath holding (i.e. larger perfusion at the apex than at the base). This reversed gradient would only partly be compensated for by 1.7 G during the following expiration ("proposed rbE").

Topographical studies report that perfusion per unit alveolar tissue increases in the apical parts of the lung at 0 G. Although these reports provide no proof of the existence of a reversed perfusion gradient at 0 G, they do not refute the possibility that it exists (44, 119).

A problem with imaging techniques used in humans so far is their low resolution. However, it is probable that the techniques currently available, for example single photon computerized tomography or magnetic resonance imaging, would detect small changes in the perfusion gradient down the lung. The limitation is that this equipment is bulky and cannot be installed in a plane. Even if that issue were solved, the image acquisition time, between 20-30 min, would render this kind of experiment impossible to perform during parabolic flight or in the human centrifuge (for the centrifuge at least at G-levels larger than 3 G). If measurements were to be made on the ground and injections inflight (119) instead, one would need to administer a large amount of radioactivity to cover the flight duration and transport to the site of image acquisition.

CONCLUSIONS

1) The impairments in lung function (lung volumes and forced expiratory flows) reported during and after spaceflight were not all present during and after long-term bed rest. This shows that as far as the lung is concerned, bed rest is not a perfect simulation of a 0-G state. Peak expiratory flow, a parameter representative of muscular effort, was unchanged. This suggests that, if any impairment in expiratory muscle function occurs, it is to a small extent. On the other hand, mid-maximal expiratory flow, a parameter representative of the properties of the lung tissue, was decreased. We propose that this decrease is due to reduced lung elastic recoil during and after bed rest. DL_{CO}, which is composed of a lung tissue component and of a blood component, showed a time course during bed rest different from that during spaceflight (decrease instead of increase). The decrease in DL_{CO} could follow the time course of haemoglobin concentration measured in other studies (24, 111) or be due to the alteration of the alveolo-capillary membrane. These impairments caused by bed rest do probably not influence daily life after bedrest but may limit maximal work capacity.

2) Indirect estimates of the effects of gravity on the distribution of lung perfusion must be performed under well-controlled conditions. Thus, the present estimation from cardiogenic oscillations of expired gases is also influenced by changes in stroke volume and central blood volume, which are markedly influenced by gravity.

3) Taking the findings under 2) above into account it was found that most of the small-scale perfusion heterogeneity in the human lung remains in the absence of gravity. It is therefore concluded that the traditional concept of gravity as the major determinant of perfusion distribution in the human lung overstates the role of gravity.

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POPULAR SCIENTIFIC SUMMARY

The aim of the present work is to get a better understanding of the effects of gravity on aspects of the human lung. The lung is extremely susceptible to gravity because it is a mixture of air and elastic components. Yet, knowledge of the effects of gravity on the human respiratory system is limited.

For example, decline in the volume of air that the lungs can contain and in the speed at which this air can be exhaled have been observed after space flights of duration up to one year. It is not clear why this has happened.

Another example is the distribution of blood in the lungs. Blood is not homogeneously distributed in the human lungs on Earth. The traditional concept points out gravity as the main factor responsible for this uneven distribution and suggests a 4-zone model: zone 1, upper quarter of the lung, where there is no blood flow; zone 2, second quarter, where blood flow is small; zone 3, third quarter, where blood flow is the highest; and finally zone 4, where blood flow decreases again. However, it is now known that this model is incomplete and that gravity is not the sole factor responsible for the distribution of lung blood flow. Indirect methods using gas mixtures have been designed. However, how much is gravity-*in*dependent has not been quantified.

By answering these questions, one could get a better understanding of the changes that occur in the lungs, heart and vessels of a patient confined to bed. This situation is a partial simulation of a weightlessness state.

Article I studied six healthy subjects lying in bed for 120 days. Tests of lung mechanics found no signs of a decrease in the force of the expiratory muscles. In contrast, it is probable that the elastic properties of the lung were impaired and the function of the lung as a gas exchanger also. These impairments caused by bed rest were of a small magnitude but nevertheless had not completely recovered two weeks after bed rest. Thus, they would probably not influence daily activities after bed rest but may limit the capacity to do physical exercise.

In a further step (articles III and IV, nine and twelve subjects), two series of experiments were performed in increased gravity. We tried to understand how the heart can influence the emptying of lung alveoli and how this interaction is influenced by gravity. An alveolus is the smallest part of the lung and is responsible for taking up oxygen and releasing carbon dioxide. It was found that the volume of blood in the chest is a major influencing factor for the emptying of lung alveoli. This blood volume decreases when gravity is increased and increases in weightlessness.

Article II studied twelve and six subjects during short periods of weightlessness. Indirect estimates of the distribution of blood in the lungs showed that there was still a large unevenness in weightlessness, which could be as large as 50-80% of that at normal gravity.

Conclusion

Lung function is adapted to a life at normal gravity. In contrast, the distribution of blood in the lungs is only partially influenced by gravity. Finally, the blood content in the chest is an essential part of the interaction between the heart beat and the emptying of lung alveoli.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Det här arbetet syftar till att öka vår förståelse av hur tyngdkraften påverkar den mänskliga lungan. Lungor är mycket känslig för tyngdkraften eftersom de är en kombination av luft och elastiska vävnader. Dock finns det begränsad kunskap om effekterna av tyngdkraften på det mänskliga andningssystemet.

Exempelvis har undersökningar av astronauter efter långvarig vistelse i rymden visat nedsatt lungfunktion med låga maximala utandningsflöden. Orsaken till dessa fenomen är fortfarande oklar.

Ett annat exempel är blodfördelningen i lungan. På Jorden är blodflödet inte jämnt fördelat i den mänskliga lungan. Traditionellt har det beskrivits en 4-zon modell, där tyngdkraften är den viktigaste faktorn: zon 1, en övre fjärdedel, där det inte finns något blod; zon 2, en andra fjärdedel, där blodflödet är litet; zon 3, en tredje fjärdedel, där blodflödet är störst; zon 4, längst ner, där blodflödet minskar igen. Man vet nu att denna modell inte är komplett och att det finns andra faktorer som påverkar blodfördelningen i lungan.

Får dessa frågor ett svar kan man kanske förstå bättre vilka ändringar som sker in lungorna, hjärtat och kärlen hos patient som är sängliggande länge. Sängliggandet är ett läge som delvis motsvarar tyngdlöshet.

I artikel I studerades sex försökspersoner som blev liggande i 120 dagar. Tester av lungmekanik visade ingen försvagning av andningsmuskulaturen. Däremot är det troligt att lungans elastika egenskaper försämrades liksom gastransporten mellan lungluften och blodet. Dessa försämringar var måttliga men hade inte helt återhämtats två veckor efter slutet av sängliggandet. Detta innebär att de sannolikt inte påverkar det vardagliga livet efter sängliggandet men den maximala arbetsförmågan var däremot sänkt.

I artikel III och IV studerades nio och tolv försökspersoner. Två serier av tester gjordes vid ökad tyngdkraft. Vi ville studera hur hjärtat kan påverka tömningen av lungalveoler och hur denna interaktion påverkas av tyngdkraften. En alveol är lungans minsta del och svarar för upptagningen av syre och frisättningen av koldioxid. Resultaten visade att blodvolymen i bröstkorgen är viktig för tömningen av alveoler. Denna blodvolym minskar när tyngdkraften ökar och den ökar i tyngdlöshet.

I artikel II studerades tolv och sex försökspersoner under kortvarig tyngdlöshet. Indirekta mått på blodfördelningen i lungan visade att det fanns fortfarande mycket ojämnhet kvar. Ojämnheten kunde vara upp till 50-80% av den som finns vid normal tyngdkraft.

Slutsats

Lungfunktionen är anpassad till ett liv vid normal tyngdkraft. Å andra sidan, blodfördelningen i lungan påverkas enbart delvis av tyngdkraft. Blodmängden i bröstkorgen är en fundamental del i interaktionen mellan hjärtslag och tömningen av lungalveoler.

RÉSUMÉ SIMPLIFIÉ

Le but de cette thèse est de mieux comprendre comment la pesanteur agit sur le poumon humain. Le poumon est un organe très sensible à la pesanteur de par sa composition : c'est un mélange d'air et de tissus élastiques. Pourtant, notre connaissance des effets de la pesanteur sur le système respiratoire humain est limitée.

Il a par exemple été observé après des vols spatiaux ayant duré jusqu'à un an que le volume d'air que contiennent les poumons est diminué, de même que la vitesse maximale à laquelle l'air peut être expiré. L'origine de ces altérations est inconnue.

Un autre exemple est la répartition du sang dans les poumons. Le sang n'est pas distribué de façon homogène, et 4 zones sont traditionnellement décrites dans un modèle où l'apesanteur en est la cause principale: dans la zone 1 (quart supérieur du poumon), il n'y a pas de sang ; dans la zone 2 (deuxième quart), il y a un faible débit de sang ; dans la zone 3 (troisième quart), il y a beaucoup de sang et dans la zone 4 (quart inférieur), la quantité de sang diminue à nouveau. On sait maintenant que ce modèle est incomplet et que la pesanteur n'est pas la seule cause de la répartition inégale du sang dans les poumons. La proportion de la distribution sanguine dépendant de la pesanteur n'a pas été quantifiée.

Si une réponse pouvait être trouvée à ces questions, il serait possible de mieux comprendre ce qui se passe dans les poumons, le coeur et les vaisseaux d'un patient alité. L'alitement prolongé est une simulation partielle de l'état d'apesanteur.

Dans le premier article, six personnes ont été étudiées au cours d'un alitement prolongé de 120 jours. Des tests de mécanique pulmonaire n'ont montré aucun signe d'affaiblissement des muscles respiratoires. En revanche, il est probable que les propriétés élastiques du poumon étaient altérées ainsi que la fonction d'échange gazeux (oxygène, dioxyde de carbone) des tissus pulmonaires. Les changements de la fonction pulmonaire étaient peu importants mais n'avaient pas complètement disparu deux semaines après la fin de l'alitement. Ils n'empêcheraient donc probablement pas de mener une vie normale après l'alitement mais peuvent limiter la capacité à fournir un effort physique intense.

Dans les troisième et quatrième articles, neuf et douze personnes ont été étudiées dans des situations où la pesanteur était accrue. Le but était de comprendre l'action mécanique du coeur sur les alvéoles pulmonaires et comment cette action est influencée par la pesanteur. L' alvéole est la plus petite partie du poumon et l'espace où l'oxygène passe de l'air dans le sang et le dioxyde de carbone du sang dans l'air expiré. Les résultats de ces expériences ont montré que le volume sanguin contenu dans la cage thoracique est un facteur primordial de cette interaction coeur-alvéoles. Ce volume de sang varie en fonction de la pesanteur : il augmente en apesanteur et diminue quand la pesanteur augmente.

Dans le deuxième article, douze et six personnes ont été étudiées durant de courtes périodes d'apesanteur. La répartition du sang dans les poumons a été étudiée de façon indirecte : une large proportion était encore inégalement distribuée en apesanteur. Cette proportion qui est indépendante de la pesanteur pouvait atteindre 50-80% de l'hétérogénéité à pesanteur normale.

Conclusion

La function pulmonaire est adaptée à la vie sur terre. En revanche, la répartition du sang dans les poumons ne dépend que partiellement de la pesanteur. Le volume de sang contenu dans la cage thoracique est une partie essentielle de l'interaction entre les battements cardiaques et le vidage des alvéoles pulmonaires.