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Effects of gravity and posture on the human lung

by

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Cover photo by Lennart Nilsson: alveoli in the lung captured by scanning electron microscopy

To my family

ABSTRACT

The presence of the gravitational force at the surface of Earth affects all of the organ systems in land-living creatures. The function of the lung is particularly susceptible to changes in the direction and magnitude of gravity because of the elastic structure of this organ. Gravity-dependent deformation of lung tissue in turn is an important determinant of gas transfer between the gas and the blood in the lungs. For example, the impaired arterial oxygenation characteristic of patients with acute respiratory distress syndrome (ARDS) become less severe when turned from supine (face-up) to prone (face-down) posture.

In the 1st part of this thesis, we explored if this influence of the direction of gravity also existed in healthy subjects in whom acute lung insufficiency was induced by hypergravity. When exposing healthy subjects to 5 times normal gravity (5 G) in the human centrifuge, the arterial oxygen saturation was 84.6 ± 1.2% (mean ± SEM) in the supine and 89.7 ± 1.4% in the prone posture. Thus, there was a protective effect of prone positioning during hypergravity, due to more effective preservation of alveolar-to-arterial oxygen transport.

In the 2nd part, our goal was to develop and assess a procedure for rapid and non-invasive determination of the lung diffusing capacity and tissue volume, as well as of the distributions of ventilation and perfusion, in order to further characterize this effect of posture on pulmonary function. Our novel approach was first applied to seated subjects exposed to hypergravity, since there are a relatively large number of earlier reports on this situation that could be used for comparison. We employed a combined rebreathing-single breath washout maneuver using soluble and insoluble inert gases. Lung diffusing capacity was reduced by 33% at 3 G, compared to 1 G, most likely as a consequence of a more heterogeneous distribution of alveolar volume with respect to pulmonary-capillary blood volume. The lung tissue volume was increased by 38% at 3 G, probably caused by a sequestration of blood in the dependent parts of the pulmonary circulation, just as occurs in the systemic circulation. We also found that in seated subjects, not only large-scale (apex-to-base), but even smaller-scale (acinar level) heterogeneities in ventilation and perfusion are enhanced by hypergravity.

In the 3rd section of this thesis, I describe application of this novel methodology in studies on recumbent humans exposed to hypergravity (5 G). Lung diffusing capacity was decreased by 46% in the supine posture during hypergravity, but only by 25% with prone posture. These data were in agreement with our previous findings of more extensively impaired arterial oxygenation in supine hypergravity. In addition, the ventilation and perfusion heterogeneities induced by hypergravity were more severe in the supine than in the prone posture. The striking similarities observed between sitting and prone postures probably reflected heart-lung and diaphragm-lung interactions that are more similar than those that occur with supine posture.

We conclude that pulmonary function is more effectively preserved in the prone than in the supine posture upon exposure to hypergravity. Apparently, the differences in cardiopulmonary function associated with these two postures is of little consequence in healthy subjects at normal gravity, but becomes significant under conditions where pulmonary gas exchange is impaired, as in patients with ARDS or upon exposure to hypergravity. We speculate that mammals have developed cardiopulmonary structures and functions that are favourable to a life on four legs.

Keywords: *acceleration, cardiac output, cardiogenic oscillations, closing volume, gas exchange, heart rate, human centrifuge, hypergravity, lung diffusing capacity, prone posture, pulmonary-capillary blood volume, rebreathing, single-breath washout, supine,*

LIST OF PAPERS

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

I. **Rohdin, M.**, J. Petersson, M. Mure, R.W. Glenny, S.G.E. Lindahl, and D. Linnarsson. (2003)
Protective effect of prone posture against hypergravity-induced arterial hypoxaemia in humans.
Journal of Physiology 548: 585-591.

II. **Rohdin, M.**, and D. Linnarsson. (2002)
Differential changes of lung diffusing capacity and tissue volume in hypergravity.
Journal of Applied Physiology 93: 931-935.

III. **Rohdin, M.**, P. Sundblad, and D. Linnarsson. (2003)
Effects of hypergravity on the distributions of lung ventilation and perfusion in sitting humans assessed with a simple two-step maneuver.
Journal of Applied Physiology Dec 12, 2003; 10.1152/japplphysiol.00627.2003.

IV. **Rohdin, M.**, J. Petersson, P. Sundblad, M. Mure, R.W. Glenny, S.G.E. Lindahl, and D. Linnarsson. (2003)
Effects of gravity on lung diffusing capacity and cardiac output in prone and supine humans.
Journal of Applied Physiology 95: 3-10.

V. **Rohdin, M.**, J. Petersson, M. Mure, R.W. Glenny, S.G.E. Lindahl, and D. Linnarsson.
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From an evolutionary point of view the human lung appears to still be functionally adapted for life on four legs.

CONTENTS

LIST OF ABBREVIATIONS

$A\text{-}aD_{O_2}$	Alveolar-to-arterial difference in the partial pressure of oxygen
Ar	Argon
ARDS	Acute respiratory distress syndrome
BTPS	Body temperature, ambient pressure, saturated with water vapor
CO	Carbon monoxide
DL_{CO}	Lung diffusing capacity as assessed with carbon monoxide
ECG	Electrocardiogram
F_{IO_2}	Inspired fraction of oxygen
FRC	Functional residual capacity
G	Magnitude of the gravitational force at the surface of the Earth
HR	Heart rate
LTV	Lung tissue volume
MAP	Mean arterial pressure
$\dot{Q}$	Perfusion
P_{aO_2}	Arterial partial pressure of oxygen
P_{AO_2}	Alveolar partial pressure of oxygen
P_{aO_2}/ F_{IO_2}	Arterial partial pressure of oxygen / inspired fraction of oxygen
P_{aCO_2}	Arterial partial pressure of carbon dioxide
REB	Rebreathing
RV	Residual volume
S_{aO_2}	Arterial oxygen saturation
SBW	Single-breath washout
STPD	Standard temperature and pressure, dry
SV	Stroke volume
$\dot{V}$	Ventilation
V_A	Alveolar volume
VC	Vital capacity

INTRODUCTION

BACKGROUND

The presence of the gravitational force at the surface of the Earth influences all living organisms in a variety of ways. The transition of vertebrates from the aquatic to the terrestrial environment required several structural and functional adaptations to gravitational stress. Although such gravity-induced homeostasis has evolved in the response to the effects of Earth's gravity alone, this evolution has produced a remarkable physiological reserve capacity, *i.e.* the ability to rapidly accommodate to several multiples of G (24) or the total absence of gravity (93).

Pulmonary gas exchange is obviously essential to human survival and the lung is particularly susceptible to changes in the magnitude and direction of gravitational forces (42, 60), due to the pronounced difference in the densities of air and blood/tissue and to the extensive distensibility of the pulmonary tissue. Thus, the normal gravitational force affects the distributions of ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) in the lung. In the lung of upright humans in normal gravity; the pleural pressure gradient leads to increased $\dot{V}$ further down in the lung (21, 30, 74). The hydrostatic pressure gradient gives rise to a similar, but steeper apico-basal gradient of pulmonary $\dot{Q}$ (119). Since this gradient in $\dot{Q}$ is steeper than that for $\dot{V}$, the $\dot{V}/\dot{Q}$ ratio is relatively high at the apex of the upright lung and low at its base. The relatively more ventilated apical lung units largely determine the composition of the alveolar gas; while the more highly perfused basal units exert the greatest influence on the composition of the pulmonary end-capillary blood (117). This situation results in a measurable alveolar-to-arterial oxygen difference in the partial pressure of oxygen. Even though there are apico-basal gradients in the distributions of both $\dot{V}$ and $\dot{Q}$, locally they are well matched, so that the variation in the $\dot{V}/\dot{Q}$ ratio is less than for those of $\dot{V}$ or $\dot{Q}$ alone (72).

Increased gravitational forces, known as hypergravity, are generated when the body is subjected to linear or angular acceleration, *e.g.* when traveling in a car, an airplane or a space shuttle. When a human being is exposed to increased gravitational force in the head-to-feet direction, the increased weight of the lungs enhances the apico-basal or large-scale differences in ventilation and perfusion (20, 21, 42, 59). Since efficient pulmonary gas exchange is dependent on close matching between ventilation and perfusion and since hypergravity worsens this matching, arterial deoxygenation is observed (40, 42).

In efforts to investigate physiological responses to gravity, the human centrifuge offers a unique environment, since acceleration acting on a mass produces an inertial force that cannot be distinguished from that of gravity. A limited number of exposures to hypergravity do not cause adaptation, but rather rapid physiological accommodations based on existing homeostatic processes. The accommodation in humans is amazing: exposures to gravitational forces three times that of the Earth's are tolerated well employing adaptive physiological mechanisms developed at normal gravity. However, exposure of a seated human being (without an anti-G suit or straining maneuver) to more than 3 G may result in black out due to impaired arterial pressure in cerebral level, but in the supine posture, arterial desaturation appears to be a larger problem (112). Human tolerance to hypergravitational

forces exerted in different directions appears limited by different physiological mechanisms. The over-all aim of this thesis has been to utilize hypergravity as a tool to improve our understanding of the effects of gravity and posture on human pulmonary function.

The first portion of the thesis examines the differences in arterial oxygenation between prone and supine humans exposed to hypergravity (Paper I). The underlying motivation was that arterial oxygenation in patients with acute respiratory distress syndrome (ARDS) is improved when they are turned from a supine to prone posture. Our hypothesis was that a similar effect of the direction of gravity would also be observed in healthy human beings in whom acute lung insufficiency is induced by hypergravity. To our knowledge, there is no other model system in which an increased hydrostatic pressure gradient and lung compression can be used to induce *reversible* acute lung insufficiency in healthy subjects. Thus, our goal was to use exposure to hypergravity as an experimental tool to gain further insight into the normal physiological effects of gravity on the respiratory and cardiovascular systems.

When characterizing human cardiopulmonary adaptations to different gravitational conditions, *e.g.* hypergravity or microgravity, it is important to develop non-invasive procedures that can be employed in the human centrifuge, during parabolic flights and in a space vehicle. **In the second portion** of the thesis, we modified available non-invasive procedures to allow measurements under both normal and hypergravitational force (Papers II and III). For this purpose, we chose a novel combination of a rebreathing (REB) maneuver followed by a single-breath washout (SBW). The REB maneuver enabled us to assess the lung diffusing capacity, lung tissue volume, cardiac output, oxygen uptake and functional residual capacity; while the SBW procedure allowed simultaneous assessments of small- and large-scale heterogeneities in pulmonary ventilation and perfusion. In our first experimental application of this novel approach, we studied seated subjects, since a relatively large amount of previous results in this condition are available. Generally, previous investigations have involved the use of different methods on separate experimental occasions for assessment of the distributions of $\dot{V}$ and $\dot{Q}$ in the lungs. Our approach allowed such assessments to be performed rapidly and simultaneously. Furthermore, because it is non-invasive, multiple repetitions at several G levels could easily be carried out.

In **the third portion** of this thesis, we utilized our novel combined REB-SBW maneuver to further analyze the mechanisms by which pulmonary function is more efficiently preserved in prone than in supine healthy subjects exposed to hypergravity (Papers IV and V).

ACCELERATION

Acceleration involves a change in the rate of movement of an object along a straight line (linear acceleration) and/or a change in the direction of travel (radial acceleration). The acceleration due to the Earth's gravity, termed the gravitational constant and designated by the symbol 'g', has a value of 9.81 m/s^2. The unit of the ratio of an applied acceleration to the gravitational constant is the 'G' (capital letter) (41) and is given by the equation G = applied acceleration / g. Thus, for example, an acceleration of 5 G is 5 x 9.81 = 49.05 m/s^2.

GRAVITY-INDEPENDENT HETEROGENEITIES IN $\dot{V}$ AND $\dot{Q}$

In the case of the normal upright lung, gravity has been suggested to be the dominant factor determining the distributions of pulmonary ventilation and perfusion (74, 119). However, in order to test this dogma, experimentation under conditions of microgravity was required. Studies on human beings subjected to transient microgravity during parabolic flights (73) or to sustained microgravity in connection with space flight have revealed persisting heterogeneities in ventilation (47, 118) and perfusion (94) even in the absence of gravity. In agreement with these findings, high-resolution studies in laboratory animals using radiolabeled microspheres (43, 44, 81) and single photon emission computed tomography (SPECT) (48, 72) performed during the last two decades, have demonstrated that gravity-independent influences on heterogeneities in pulmonary $\dot{V}$ and $\dot{Q}$ are substantially greater than previously realized. However, even though there have been a number of speculations, there is at present no consensus concerning the origin of such gravity-independent heterogeneities in $\dot{V}$ and $\dot{Q}$ (for review, see (50, 95)).

On earth, gravity is a constant force that cannot be eliminated, rendering the study of gravitational and non-gravitational effects on pulmonary function difficult. For our investigations on the relative influences of gravitational and non-gravitational mechanisms on the distributions of ventilation and perfusion, it was ideal to examine pulmonary function in the absence of gravity, *e.g.* in astronauts during a space flight. Employing methods similar to those described here, we thus examined these parameters during a 16-day space flight. However, in deference to the tragic accident of the Columbia space shuttle, these findings will be published at a later time.

LUNG FUNCTION IN PRONE AND SUPINE HUMANS

Since the apico-basal heterogeneities in $\dot{V}$ and $\dot{Q}$ in the lungs of upright humans exposed to normal gravity are caused primarily by the Earth's gravitational force, it is reasonable to assume that these heterogeneities would be attenuated in recumbent subjects, because of the reduced distance between the dependent and non-dependent parts of the lung. Large-scale pulmonary $\dot{Q}$ distribution is, indeed more homogenous when supine (2). However, upon applying a single-breath oxygen test to human subjects in different postures, Cortese et al. (29) observed a more pronounced phase III slope in the supine than in the upright posture, indicating a more heterogeneous overall distribution of $\dot{V}$. Utilizing a SBW involving 4% SF_6 and He, Grönkvist et al. (46) also reported an increased overall ventilatory heterogeneity in supine compared to upright subjects. This finding contributed to their conclusion that in supine subjects there is a markedly greater convection-dependent inhomogeneity (CDI) between well-separated regions of the lung (interregional CDI), as well as a less dramatic increase in convection-dependent inhomogeneity within and/or between more peripheral lung units (intraregional CDI) (46).

If the gravitational force were the only determinant of the distributions of $\dot{V}$ and $\dot{Q}$ in the human lung and if the thoracic contents and boundaries were homogenous structures, then the distribution of these parameters from dependent to non-dependent regions of the lung in prone and supine subjects should be identical. However, investigations on animals (27, 57, 60) and humans (2, 3, 29) have revealed more homogenous distributions of $\dot{V}$ and $\dot{Q}$ in the

prone than in the supine posture indicating an influence by factors other than gravity. The mechanisms underlying these differences in pulmonary function of prone and supine subjects remain to be elucidated (79).

In agreement with the findings on $\dot{V}$ distribution described above, abundant evidence from both animal (61, 62, 80, 84, 124) and human (71) experiments reveals that, under conditions of normal gravity, the vertical gradients of pleural pressure and alveolar size are much smaller (if not non-existent) in the prone than in the supine posture. Furthermore, in connection with prone ventilation the physiological dorso-ventral gradient of lung inflation is abolished in animal models (57, 124). Moreover, Amis et al. (3) demonstrated that, in humans, regional ventilation increases from the upper to the lower regions of the lung in the supine posture but is uniform with prone posture.

Studies on dogs (11, 12, 43) and in humans (83) have revealed a higher degree of perfusion in dorso-caudal regions of the lung which is independent of the direction of gravity, implying the involvement of an anatomical component and/or higher conductance in the vessels in these regions. Such factors will counteract the effect of gravity, leading to a more homogenous distribution of perfusion in the prone posture (83). However, preliminary data from a recent study employing SPECT indicate small differences in the vertical distributions of $\dot{V}$ and $\dot{Q}$ in the prone and supine postures when imaged in both postures (88, 89). The are several methodological differences between the studies by Nyrén et al. (83) and Petersson et al. (88, 89): a) only Petersson and coworkers corrected for attenuation and scatter using algorithms based on transmission images; b) the same researchers analyzed the entire lung, whereas only three sections were examined in the former study (83); and c) image acquisitions were performed by Petersson et al. with the subject in both supine *and* prone postures, whereas only the supine posture was studied by Nyrén and coworkers.
Jones et al. (58) used electron-beam computed tomography to study the effects of prone positioning on regional pulmonary perfusion in six healthy subjects. Regions of interest were placed along the nondependent to dependent axis and relative perfusion calculated. When corrected for the redistribution of lung parenchyma, the gravitational gradient of pulmonary perfusion along the nondependent to dependent axis did not differ between supine and prone postures (58).

Nitric oxide (NO) is a potent vasodilator and has been implicated as a mechanism that improves matching between the pulmonary ventilation and perfusion distributions. On the basis of observed regional differences in the *in vitro* responses of arteries from the dorso-caudal and cranio-ventral regions of horse lung, Pelletier et al. (86) concluded that the regional differences in endothelium-mediated relaxation are caused by differences in endothelial release of NO, possibly resulting in preferential perfusion of the dorso-caudal regions. Preliminary data from human experiments indicate that there are higher levels of NO syntetase activity in dorsal lung parts (S. Nyrén, personal communication). Furthermore, when blocking the NO production with L-NMMA, pulmonary perfusion was more directed to anterior lung parts when supine but unchanged when prone.

Data on the topographical distribution of pulmonary perfusion under conditions of hypergravity in recumbent humans are scarce (53). Pulmonary perfusion becomes more heterogeneous with increasing G force in animals (45, 49) and in humans (42, 53). Perfusion distribution was studied in pigs with fluorescent microspheres during parabolic flights by

Glenny et al. (45), who found that perfusion heterogeneity was significantly less in the prone than in the supine posture during 1- and 1.8 G conditions. Interestingly, Hoppin et al. (53) found strikingly similar perfusion distributions in humans between 1, 4 and 8 G supine using lateral radioisotope scanning, with injection of a perfusion marker at 1, 4 and 8 G, but data acquisition at 1 G only. However, the authors concluded that the vascular architecture must have been markedly distorted at 4 and 8 G, thereby implying that perfusion distribution must have been equally skewed towards dependent lung regions relative to external landmarks. To our knowledge, no comparisons between the topographical distributions of $\dot{V}$ and $\dot{Q}$ in recumbent humans during exposure to hypergravity have been reported.

PRONE POSITIONING IN PATIENTS

Patients with ARDS exhibit a pronounced and rapid improvement in arterial oxygenation when turned from a supine (face-up) to a prone (face-down) posture (78). Bryan (22) was first to suggest that prone positioning of anesthetized and paralyzed patients should result in enhanced expansion of dorsal lung regions and, thereby, an improvement in oxygenation. Subsequently, several studies have demonstrated improved arterial oxygenation in prone severely hypoxemic patients with acute lung injury (ALI)/ARDS (32, 62, 63, 77, 78, 92). This effect of prone positioning of such patients is remarkably rapid (36), suggesting that the underlying disease process is not being reversed but rather that the diseased lungs are being used more efficiently for oxygen transfer.

However, the physiological mechanisms underlying such improvement of arterial oxygenation have not yet been elucidated (79), in part because the performance of well-controlled experiments with patients in an intensive care unit involves several ethical and practical problems. The homogenously distributed lung edema in patients with ARDS increases the hydrostatic pressure gradient down the lung. As a result, the lung tends to collapse under its own weight, creating severe disturbances in ventilation and perfusion (16, 38, 87).

Upon exposure of healthy human beings to hypergravity in a human centrifuge, the intrathoracic hydrostatic pressure gradients also increases resulting in impaired gas exchange (9, 40, 42). The similarities between lung function in patients with ARDS and hypergravity-induced acute lung insufficiency include pronounced increases in the tissue densities and hydrostatic pressure gradients within the lung, as well as elevations in the weight of the heart and its pressure on underlying pulmonary tissue (69, 121). Our hypothesis was that the protective effect of prone positioning would also be seen in healthy humans exposed to hypergravity.

AIMS

The principal aim of this thesis was to characterize the effects of posture and of different levels of gravitational force on human pulmonary function.

Specific aims were as follows:

♦ to determine whether subjects with hypergravity-induced acute lung insufficiency preserve arterial oxygenation more efficiently in the prone than in the supine posture, in analogy with the protective effect of prone positioning in patients with ARDS (**Paper I**).

♦ to adapt a non-invasive procedure for assessment of the lung diffusing capacity, lung tissue volume, oxygen uptake, functional residual capacity, and cardiac output in sitting humans during exposure to normal and hypergravity (**Paper II**).

♦ to develop and evaluate a non-invasive procedure for simultaneous measurement of heterogeneities of small- and large-scale pulmonary ventilation and perfusion in sitting humans under conditions of normal and hypergravity (**Paper III**).

♦ to compare the lung diffusing capacity, lung tissue volume, oxygen uptake, functional residual capacity, and cardiac output in prone and supine humans during exposure to normal and hypergravity (**Paper IV**).

♦ to characterize differences in the heterogeneities in small- and large-scale pulmonary ventilation and perfusion between prone and supine humans under conditions of normal and hypergravity (**Paper V**).

METHODOLOGICAL CONSIDERATIONS

SUBJECTS

9 or 10 male and female volunteers participated in each of the investigations presented here. The experiments in Paper II were performed in conjunction with those in Paper III, using the same subjects, which was also the case for Papers IV and V. The ages, heights, and body masses of our subjects ranged from 21-32 years, 163-193 cm, and 55-90 kg, respectively. None of the subjects had a history of cardiopulmonary disease or were taking medication at the time of the study. They were also instructed not to drink coffee or use nicotine-containing products on the day of the experiment.

ETHICAL CONSIDERATIONS

The subjects received written information concerning the procedure they were to undergo and informed verbal consent was obtained. The experimental protocols had been previously approved by the Regional Ethics Committee of Karolinska Institutet (Stockholm, Sweden).

THE HUMAN CENTRIFUGE FACILITY

The experiments were conducted using the human centrifuge at Karolinska Institutet. This centrifuge has two arms; one with a platform (Papers I, IV and V) and the other with a gondola (Papers II and III).

The platform used in papers I, IV and V (Fig. 1)

For these investigations a support structure was mounted on the platform. The supine or prone subject was secured on the surface by a five-point safety belt to a padded support surface that could be adjusted so as to be perpendicular to the resultant of the normal-G and centrifugal-G vectors. The head and torso of the subject were covered with a cowling in order to reduce air drafts, noise, and visual inputs. The rotational radius of the centrifuge at the middle of the support surface was 7.2 m.

Fig. 1. The human centrifuge facility at Karolinska Institutet used in this thesis. This platform was used to perform the experiments with recumbent subjects (Papers I, IV, and V).

The gondola used in papers II and III (Fig. 2)

The rotational radius to the center of the gondola was 7.2 m and the roll angle of the gondola was automatically adjusted so that the gondola floor was perpendicular to the resultant of the normal-G and centrifugal-G vectors. Because of the 28° tilt of the backrest supporting the seated subject, the magnitudes of the G-vector in the head-to-feet direction at forces of 1, 2 and 3 G were in reality 1 G * cos 28° (0.88 g), 2 G * cos 28° (1.77 g) and 3 G * cos 28° (2.65 g), respectively. The small errors introduced by rounding off to the nearest integer for G were neglected throughout the text.

Fig. 2. The gondola of the human centrifuge at Karolinska Institutet was used for the experiments with seated subjects (Papers II and III).

EQUIPMENT AND MEASUREMENTS

Slip rings located at the center of rotation were employed for power supply, as well as for transmission of physiological and audiovisual signals between the platform or gondola and a nearby control room. The instrumentation for respiratory measurements included a quadrupole mass spectrometer and a wide-bore, 3-way solenoid valve with a 4-liter rebreathing bag. The subject wore a nose clip and breathed through a mouthpiece. Located between the mouthpiece and the solenoid valve was a unidirectional impeller flowmeter (Papers II and III) and an inlet for gas sampling via a 10-m capillary tube attached to the mass spectrometer at the center of the centrifuge. The recumbent subjects (Papers I, IV and V) breathed through a pneumotachometer, coupled to a pressure transducer with its membrane mounted parallel to the plane of rotation (*i.e.*, the horizontal plane), in order to eliminate the influence of centrifugal G-forces on this transducer. The instrumental dead space was 150 ml.

The subject's electrocardiogram was monitored employing a clinical monitoring system with chest electrodes. The latency between the flow meter and the response of the mass spectrometer following sudden and simultaneous changes in gas composition and flow direction at the inlet of the sampling capillary and was found to be ~3 s (10).

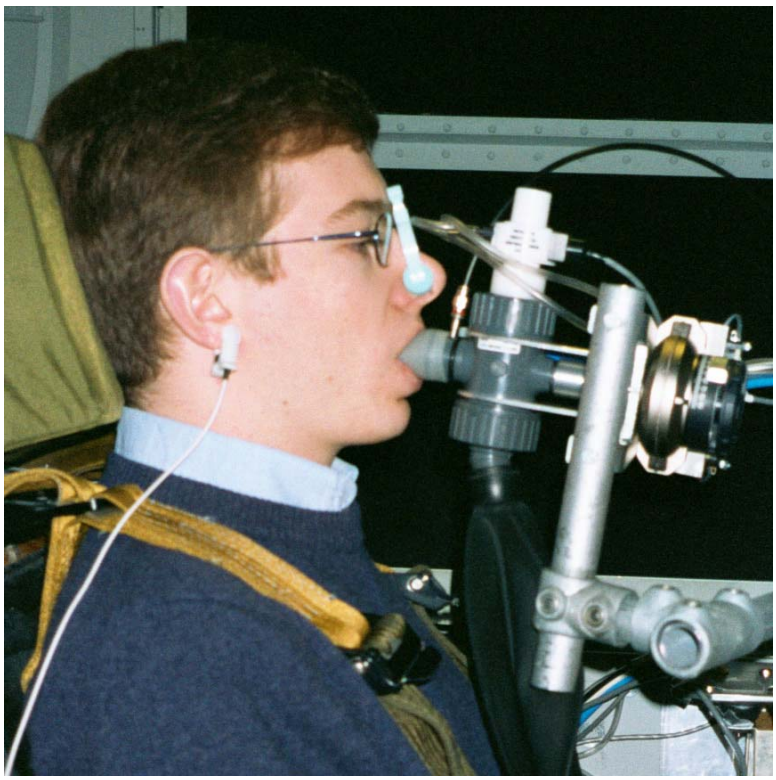

Fig. 3. A seated subject and parts of the experimental setup (Papers II and III). Note that the flow meter is placed in a different position from that in the experiments and in Fig. 4.

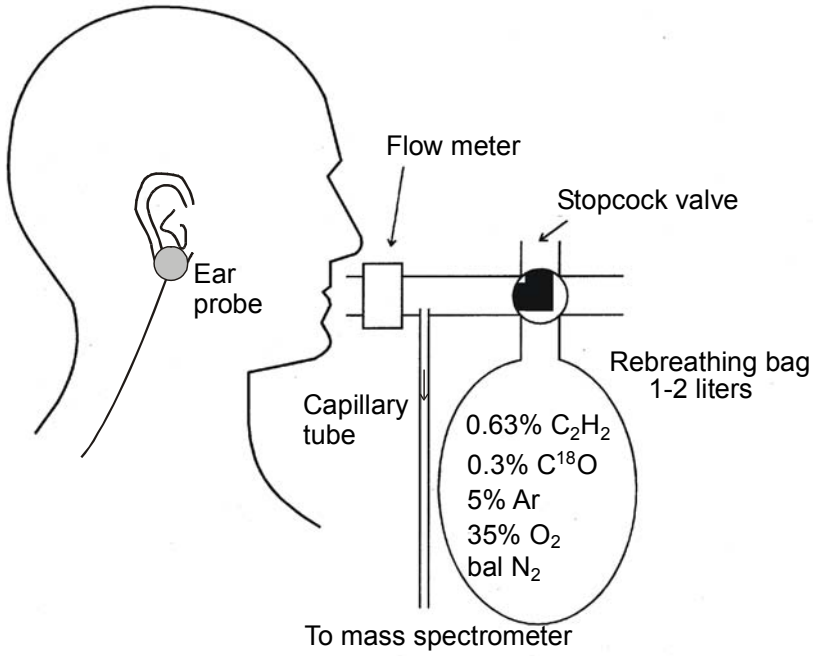

Fig. 4. Schematic drawing of parts of the experimental setup used with seated subjects (Papers II and III).

Determination of arterial oxygen saturation by pulse oximetry (Papers I, IV and V)

The ear probe worn by the subjects for pulse oximetry was held in place by an elastic bandage and the ear lobe pretreated with capsaicin ointment to obtain vasodilatation in order to ensure a satisfactory signal. Our laboratory (Paper I) has found excellent agreement between this technique and assay of arterial samples taken concomitantly under conditions of hypergravity.

Determination of arterial oxygen saturation using a radial artery catheter (Paper I)

A radial artery catheter was placed in the subjects under local anaesthesia. Subsequently, a disposable pressure transducer was connected to the arterial line and mounted beside the subject at a level corresponding to 50% of his/her reclining anterio-posterior height. This pressure transducer was not affected by the magnitude or direction of the gravitational force. Prior to the centrifuge runs, the arterial catheter was connected to two syringe pumps, modified to be activated only in aspiration mode and only from the control room.

EXPERIMENTAL PROCEDURES

Papers I, IV and V

These experiments were performed at 1 and 5 G, using prone and supine postures and in random order. Each subject participated in a total of four runs, two at each G level and two in each posture. The subject rested on a support surface on the platform of the centrifuge and breathed air through a mouthpiece. Individual runs were separated by at least 10 min, at least 8 of which were spent at normal gravity.

Papers II and III

These experiments were performed four times each at 1, 2 and 3 G, in random order. The resting subject sat in the gondola of the centrifuge (Fig. 2) and breathed air through a mouthpiece (Fig. 3). Repetitions of the combined maneuver were separated by a period of at least 10 min, in order to allow elimination of test gases, at least 8 of which at normal gravity.

Determination of arterial oxygen saturation using radial artery catheter (Paper I)

Approximately 6 min after the desired G level was attained, blood sample was taken from the radial artery catheter for gas analysis and hematocrit determination. The first 6 ml of blood were drawn in a separate syringe and discarded and the subsequent 2-ml sample was collected in a second syringe of glass for analysis. Samples were stored on ice and analyzed in quadruplicate within 1 hour after being taken.

Rebreathing (REB)-single breath washout (SBW) maneuver (Papers II-V)

Approximately 1 min (Papers II and III) or 4.5 min (Papers IV and V) after reaching the desired G level, the subject performed one combined REB-SBW maneuver. This involved expiring to functional residual capacity (FRC), and then rebreathing the entire volume of the bag eight times at a rate of 3 s/breath. After a final inhalation from the rebreathing bag, a rotary valve was switched and the subject exhaled completely to residual volume (RV) at a constant flow rate of 0,5 l/s. In order to allow this rate to be maintained, a flow meter provided visual feed back to seated subjects and recumbent subjects received corresponding acoustic feed back. Gas tracings recorded during this expiration to RV were analyzed for deviations in end-expiratory concentration (phase IV amplitude), which, if present, would indicate poor intrapulmonary gas mixing at the end of the rebreathing period. Finally, the subject inhaled one vital capacity (VC) of atmospheric air and performed a second expiration to RV, both at a rate of 0.5 l/s.

The gas mixture used for rebreathing contained 35% oxygen (O_2), 5% argon (Ar), 0.63% acetylene (C_2H_2), 0.3% carbon monoxide ($C^{18}O$), 3% sulphur hexafluoride (SF_6), and 5% helium (He), with the remainder being nitrogen (N_2). The volume of the rebreathing bag varied between 1 and 2 liters, depending on the stature and the preference of the subject.

DATA ANALYSIS

Data analysis was performed offline with an Acknowledge 3.2 Biopac digital data handling system. These offline computations included algorithms designed to correct for total dry pressure (110) and computation of calibrated values for all fractional concentrations of dry gas. In addition, concentration readings were corrected for the response latency of the mass spectrometer system (10) and gas volumes and flows were converted to STPD (standard temperature and pressure, dry) or BTPS (body temperature, ambient pressure, saturated with water vapour), where appropriate.

Alveolar-to-arterial differences in P_{O_2} (A-aD_{O_2})

We computed the A-aD_{O_2} (P_{AO_2}-P_{aO_2}) by utilizing the alveolar gas equation (99-101) to estimate P_{AO_2} and employing P_{aCO_2} as an estimate of P_{ACO_2} with an assumed R value of 0.8.

The rebreathing maneuver

In connection with the rebreathing maneuver the **lung diffusing capacity (DL_{CO})** was calculated on the basis of the rate of uptake of $C^{18}O$ and the **cardiac output** was considered to be proportional to the uptake of C_2H_2 (35, 107-109). Since DL_{CO} is dependent on the V_A at which the determination is carried out (103, 113, 114) and since FRC and, thereby, V_A differed between the conditions employed here (IV), a method for comparing DL_{CO} values obtained at different values of V_A had to be devised. Clearly, the mean V_A during a rebreathing maneuver must lie somewhere between FRC (the volume when connected to the rebreathing bag) and FRC plus the volume of the bag with the latter representing the lung volume after inhalation of the contents of the bag.

Thus, DL_{CO} was corrected for the differences in V_A at the different conditions employed, as described by Montmerle et al. (75); and the algorithms of Stam et al. (113) were used to recalculate DL_{CO} as if V_A were 50% of the total lung capacity obtained in the supine posture at 1 G. V_A was estimated as being the FRC + 1/3 the volume of the rebreathing bag, and the total lung capacity as VC + RV (the latter being obtained from anthropometric data, according to Quanjer et al. (97)). The residual volume appears to be unaffected by the size and direction of acceleration (26, 40).

Lung tissue volume was estimated as described by Sackner et al. (107) on the basis of extrapolation of the disappearance curve for C_2H_2 back to the ordinate at time zero. **Functional residual capacity (FRC)** was calculated from the dilution of the insoluble gas Ar in the total volume of the lung-bag system, where all Ar readings were offset by the Ar concentration in atmospheric air. **Oxygen uptake** was calculated from the linear slope of the end-tidal O_2 values obtained during rebreathing and the total volume of the lung-bag system (15). **Onset of alveolo-capillary exchange:** the intercept of the CO regression line with the initially inspired CO level was used to determine the time-point at which the inhaled gas mixture reached the alveoli, *i.e.*, the onset of alveolo-capillary exchange of the inhaled foreign gases or time zero (107).

Heart rate (HR) was determined from the electrocardiogram recorded during the period 15-5 sec. prior to the initiation of the rebreathing maneuver. **Stroke volume** was calculated by dividing cardiac output with HR, assuming that the cardiac output during the SBW maneuver was the same as during the preceding REB manuever.

Analysis of expirograms (SBW)

Three different types of expirograms were generated: a) The Ar concentration in expired air was plotted as a function of expired volume (Paper IV, Fig. 1). The Ar concentration at the end of the rebreathing maneuver and before the VC inhalation was defined as 100% and the Ar in atmospheric air was defined as 0%. The resulting

expirogram is analogous to a conventional SBW expirogram, in which an evenly distributed resident gas (classically, N_2) is diluted with one VC of another gas (classically, pure O_2). b) The CO_2 concentration in expired air was plotted in a similar manner, again by defining the pre-inspiratory level as 100% and the CO_2 level of atmospheric air as 0% (Paper IV, Fig. 1). c) Finally, the ratio of the concentration of expired CO_2 to that of expired Ar (as defined above) was plotted as a function of expired volume (Paper IV, Fig. 2). Hereafter, the terms Ar and CO_2 will be used to mean %Ar and %CO_2 as defined above, where not otherwise stated.

In our analyses, the alveolar portion of the expirogram was divided into two parts, phase III and phase IV (4, 74). **Vital capacity (VC)** was defined as the maximal expiratory volume. The beginning and end of the alveolar plateau were identified using a cursor and the **phase III slope** determined using least-squares best-fit line. The onset of airway closure was defined as the end of phase III and onset of phase IV, although not with an iterative process as done by Guy et al. (47). **Closing volume (CV)** was calculated from this point to the end of the expiration and was also expressed as a percentage of the VC. **Phase IV amplitude** was calculated as the vertical distance between the extrapolated phase III slope and the maximal deviation in concentration at the end of phase IV. From the four repetitions at each G level, we used the data from the two experiments in which the expired VC was largest or, if these two VC values differed by more than 0.5 liter, only the experiment with the largest VC (Paper III).

With respect to **cardiogenic oscillations (COS)**, we selected the two largest consecutive COS during phase III on the basis of plots of Ar or CO_2 concentrations or the CO_2/Ar ratio against volume. We used the R-R interval to obtain the local maxima and minima, in relationship to the line already fitted to phase III. Finally, since COS are affected by the size of the SV (59), we normalized our COS values with regard to changes in SV.

STATISTICAL PROCEDURES

Papers I, IV and V

Analysis of variance (Statistica 6.0, Statsoft, Tulsa, OK, USA) with repeated-measures design with two independent factors (gravity (in the anterior-posterior or the posterio-anterior direction) and posture) was applied to test for significant differences between changing G levels and posture, as well as for interactions between these parameters.

Papers III and IV

Analysis of variance with repeated-measures design with one independent factor (gravity in the head-to-feet direction) was used to test for significant differences between changing G levels with respect to respiratory parameters. In addition, planned comparison was employed as a post-hoc test. The two contrasts were linear and quadratic. In order to calculate percentage changes, the data were normalized to the corresponding average 1-G values for each subject.

P values of <0.05 were considered statistically significant, and all statistical analyses were two-sided. The data are presented as means ± SEM, unless otherwise stated.

RESULTS

LUNG FUNCTION IN PRONE AND SUPINE HUMANS AT 1 AND 5 G

Arterial oxygenation

All three indices of arterial oxygenation employed here (*i.e.,* P_{aO_2}, arterial O_2 saturation (S_{aO_2}) and S_{aO_2} obtained with pulse oximetry) indicated that hypergravity-induced impairment of arterial oxygenation was significantly greater in the supine than in the prone (Paper I, Tables 1 and 2, Fig. 1). This fact is clearly demonstrated by the significant interaction between posture and gravity for all three variables (Paper I, Table 2). At 5 G, S_{aO_2} (obtained by blood sampling) was 84.4 ± 1.3% (mean ± SEM) with supine and 89.2 ± 1.2% with prone posture ($P< 0.001$). The pulse oximetry data were in close agreement with the values obtained by analysis of arterial samples ($r= 0.98$, $P< 0.001$ at 5 G, prone posture; n=10). The slightly less pronounced decrease in S_{aO_2} at 5 G reported in Paper IV (to 87.5 ± 1.3% in the supine and 91.9 ± 0.6% in the prone posture) may be due to the difference in the duration of exposure to hypergravity prior to the measurements (>6 min in study I versus 4.5 min in study IV).

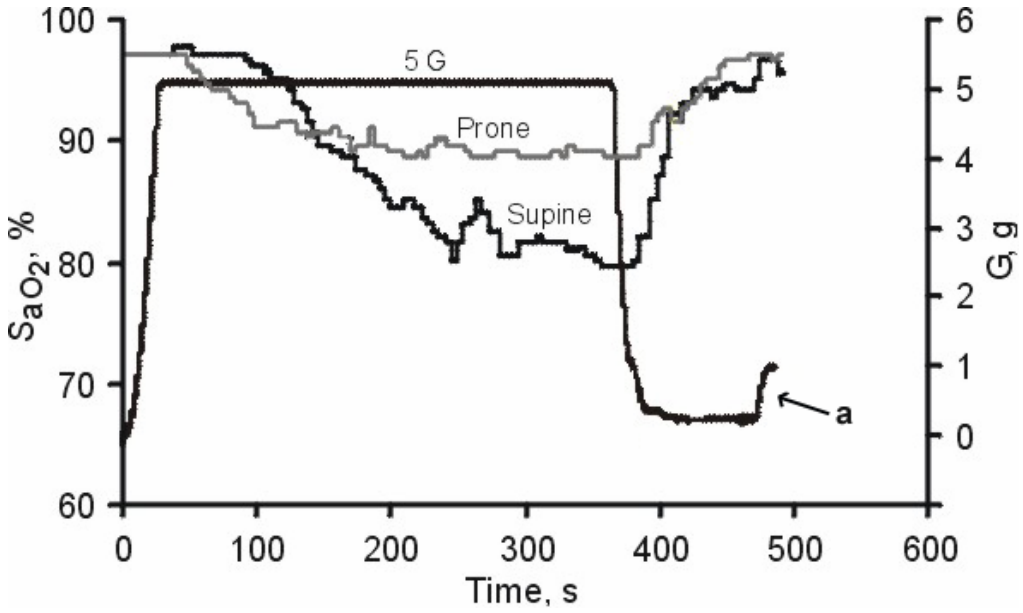

Fig. 5. Arterial oxygen saturation (S_{aO_2}) during the approximately 6-min exposure to five times normal gravity (5 G) in prone or supine postures: representative findings for one individual subject. The angle of the support surface is approximately 78° from horizontal before and during the hypergravity period. The arrow (a) indicates when the support surface is raised to horizontal.

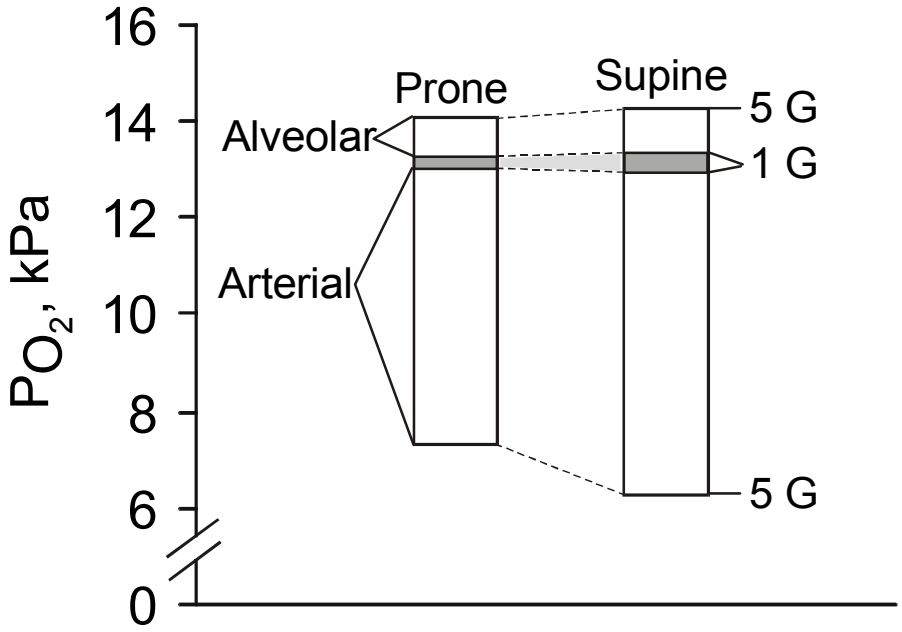

Fig. 6. Alveolar and arterial partial pressures of oxygen at normal gravity (1 G) and after 6 min exposure to five times normal gravity (5 G) in prone and supine postures (n=10).

The estimated mean alveolar oxygen tension (P_{AO_2}) increased with gravity with both postures, to 0.8 ± 0.2 and 1.0 ± 0.2 kPa in the prone and supine posture, respectively (Fig. 6). In both postures, there was also a hypergravity-induced increase of 20% in the end-tidal P_{O2} and a 14% decrease in arterial carbon dioxide tension (P_{aCO2}; table 1). As was the case for arterial P_{O2} and saturation, a significant interaction between posture and gravity was also observed for A-aD_{O_2} (Paper I, Table 2); with prone posture A-aD_{O_2} was 6.6 ± 0.3 kPa higher at 5 G than at 1 G, while the corresponding increase in the supine posture was 8.0 ± 0.2 kPa (Paper I, Table 1 and Fig. 2).

Pulmonary ventilation

Hypergravity induced an increase in pulmonary ventilation of 5.6 ± 1.3 l/min with prone and 7.6 ± 1.8 l/min with supine posture (Paper I, Table 1). This increase in ventilation reflected a 60-80% increase in respiratory rate with no change in tidal volume (Paper I, Table 1).

Rebreathing

Lung diffusing capacity, FRC and oxygen uptake

The DL_{CO} under conditions of hypergravity was lower compared with normogravity for both postures (P=0.002), with a significantly lower DL_{CO} value being observed in the supine than in the prone posture at 5 G (P=0.01) (Paper II, Fig. 1). Furthermore, there was an apparent tendency for interaction between posture and gravity with respect to DL_{CO}

(P=0.07), *i.e.*, a slightly larger hypergravity-induced decrease in DL_{CO} with supine than with prone posture.

The FRC decreased under conditions of hypergravity (P<0.001) and was significantly larger with prone than with supine posture at both G levels (8% larger at 1 G and 26% at 5 G, P<0.001). The estimated V_A was also decreased by hypergravity (P<0.001) and was also significantly larger with prone than with supine posture at both G levels (P<0.001). A tendency towards a hypergravity-induced difference in oxygen uptake (P=0.09 for the difference between G levels) was observed, this tendency being towards an increase in the prone, but not the supine posture (P=0.05 for prone versus supine). Furthermore, oxygen uptake was 17% higher with prone than with supine posture at 5 G and in this case as well there was a tendency towards interaction between posture and gravity (P=0.07). No difference in the LTV between postures (P=0.2) or G levels (P=1) was observed. Finally, a surrogate value for the arteriovenous difference in P_{O2}, *i.e.* O_2 uptake/cardiac output, was the same in both postures (P=0.8), but 80% larger at 5 G than at 1 G (P<0.001).

The central circulation

The cardiac output decreased with increasing gravitational force (P=0.001) and at 5 G was lower in the supine than in the prone posture (P=0.007) (Paper II, Fig. 2). The heart rate (HR) was significantly higher in the prone posture at both G levels (P<0.001) and was incrased by hypergravity (P=0.002), there being a tendency for interaction between posture and gravity with respect to this parameter (P=0.07). The stroke volume (SV) was 87.1 ml/heart beat under normogravity and decreased to 44.6 ml under hypergravity (mean value of prone and supine; P<0.001) with no significant difference between the postures (P=0.9).

Single-breath washout

Typical individual expirograms recorded during a SBW maneuver are presented in Paper V, Figs. 1A and B. The VC and parameters extracted from the expirograms are documented in Paper V, Tables 1 and 2 and in Figs. 2-4. In Figures 2-4 previous findings for the seated posture (Paper III) have been included for comparison.

Vital capacity

Although at normogravity the VC values for the two postures were the same, hypergravity decreased this parameter to a greater extent in the supine (-38%) than in the prone posture (-29%) (Paper V, Tables 1 and 2).

Phase III

The COS/SV_{Ar} and $COS/SV_{CO2/Ar}$ ratios increased under conditions of hypergravity and exhibited no difference between the two postures at either of the G levels (Paper V, Table 1, Figs. 2A and B). A tendency towards a steeper phase III $slope_{Ar}$ with supine than with prone posture at normal gravity (P=0.08 for planned comparison) was apparent. The phase III $slope_{CO2/Ar}$ was steeper in the prone than in the supine posture at 1 G (P=0.01). The phase III slope with supine posture was altered dramatically by increasing gravitational force: in the case of Ar, this slope increased to 580% of the control (Paper V, Fig. 3A),

whereas for the CO_2/Ar ratio the slightly positive slope at 1 G changed to a markedly negative slope at 5 G (Paper V, Fig. 3B). Hypergravity-induced changes in the phase III slope were more pronounced in the supine than in the prone posture for both Ar and CO_2/Ar (Paper V, Table 1, Figs. 3A and B).

Phase IV

Under normal gravity the phase IV amplitude$_{Ar}$ in the supine posture was higher than with prone posture (P=0.04) (Paper V, Table 1, Fig. 4A). All of the parameters extracted from the Ar expirograms during phase IV (*i.e.*, CV_{Ar}, CV/VC_{Ar}, and phase IV amplitude$_{Ar}$) exhibited significant interactions between posture and gravity, such that hypergravity had a more pronounced effect on these parameters with prone than with supine posture (Paper V, Tables 1 and 2). Furthermore, the phase IV amplitude$_{CO2/Ar}$ was also more pronounced in the prone than in the supine posture under conditions of hypergravity (Paper V, Table 1, Fig. 4B). In the case of $CV_{CO2/Ar}$ and $CV/VC_{CO2/Ar}$ there were no gravity-induced difference with either posture, but a tendency towards a difference between the prone and supine postures independent of the G level was detected (P=0.07 for $CV_{CO2/Ar}$ and P=0.06 for $CV/VC_{CO2/Ar}$).

LUNG FUNCTION IN SITTING HUMANS AT 1, 2 AND 3 G

Rebreathing

Cardiac output was decreased by 11% at 2 G and by 16% at 3 G compared to normal gravity (Paper III, Table 1). The HR increased by 13 ± 2 and 22 ± 3 beats/min at 2 and 3 G, respectively, with corresponding reductions in the SV of 20.3 ± 2.0 and 29.8 ± 3.8 ml. The DL_{CO} was reduced by 20% and 33% and LTV increased by 26% and 38% at 2 G and 3 G, respectively (Paper III, Table 1, Fig. 4), while oxygen uptake was increased by 5% at 2 G and 16% at 3 G. The arteriovenous difference in P_{O2} (calculated as O_2 uptake / cardiac output) increased by 19% and 39%, respectively. Thus, all of the parameters examined were altered significantly by increased gravitational force , with the exception of the FRC, which remained within 3% of the control value under both conditions of hypergravity. Furthermore, all of the variables (except for FRC) presented a linear effect in the planned comparison.

Single-breath washout

Vital capacity

The VC decreased 8% at 2 G and 14% at 3 G compared with the normogravity control value (Fig. 7).

Phase III

The COS/SV_{Ar} ratio exhibited a significant increase with G force, to approximately 160% of the control value at 3 G (Paper IV, Fig. 3a). As was the case for Ar, $COS/SV_{CO2/Ar}$ was

increased significantly at 2 G, but the further increase at 3 G, if one occurred at all, was considerably more modest than for Ar, (Paper IV, Table 1). Furthermore, tendencies towards an increasingly positive phase III $slope_{Ar}$ (P=0.06) and an increasingly negative phase III $slope_{CO2/Ar}$ (P=0.08) at elevated G levels were observed.

Phase IV

The CV/VC ratios for both Ar and CO_2/Ar demonstrated a significant increase to approximately 160% of the control value at 3 G (Paper IV, Table 1). The most striking hypergravity-induced change in phase IV amplitude for both Ar and CO_2/Ar was an approximate doubling from 1 to 2 G, with little or no additional change at 3 G (Paper IV, Fig. 3b).

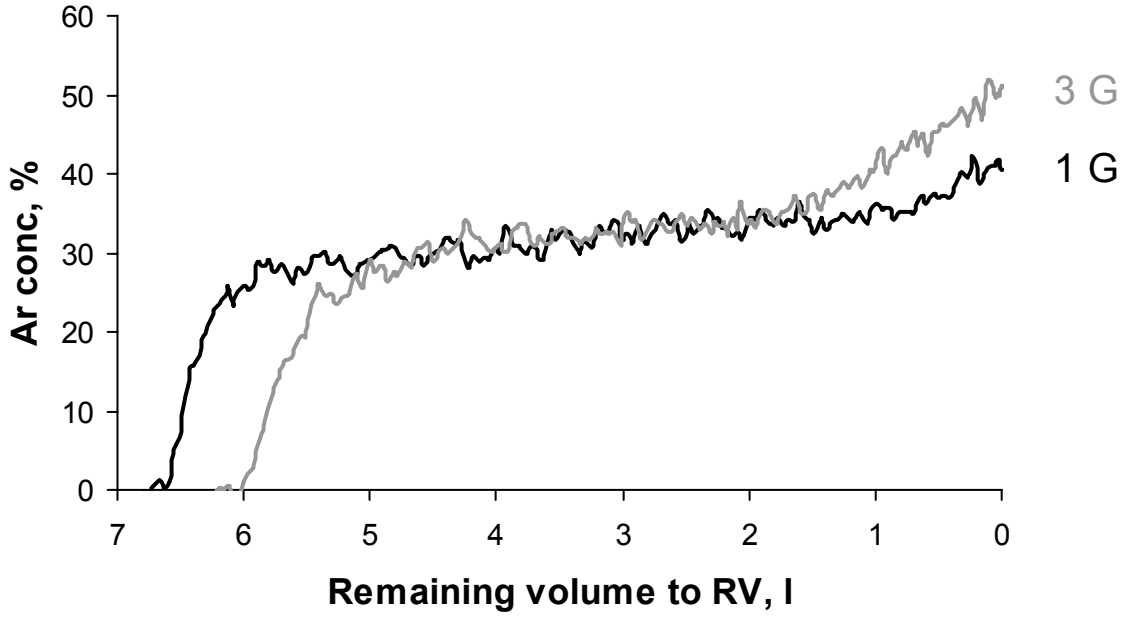

Fig. 7. Representative recording at normal (1 G) and 3 times normal gravity (3 G) of expired concentrations of the insoluble gas argon (Ar) as a function of the expired volume in connection with a vital capacity (VC) expiration at a rate of 0.5 l/s. This expiration was preceded by a) rebreathing of a 5% Ar mixture to obtain equilibrium Ar levels; b) an expiration to residual volume (RV); and c) an inspiration of one VC of atmospheric air. The recordings have been normalized to an initial equilibrium Ar concentration of 100% and a corresponding concentration in atmospheric air of 0%. Note the differences in the VC and phase IV amplitude between the G-levels.

DISCUSSION

LUNG FUNCTION IN PRONE AND SUPINE HUMANS

"The heart is an important component of the lung's container"

The above is a citation of a statement made by Hoffman in 1985 (51). Several investigations suggest that the different positions of the heart relative to the lungs in the prone and supine posture may account for the protective effect of prone positioning. When Hoffman and Ritman (52) performed a CT scan on dogs (who live in a prone posture) and sloths (living partly supine), they observed a vertical gradient in lung expansion with supine, but not with prone posture. The configurations of the rib cage and diaphragm were essentially the same for both postures in the sloth; whereas these configurations differed markedly between postures in the dog, although the two species had similar alterations in lung expansion gradient. These investigators concluded that the change in the intrathoracic position of the heart in the dog and sloth alters the pulmonary geometry, thus giving rise to the observed difference in the gradient of regional lung expansion between these postures. Further support for their conclusion is provided by the fact that the sloth has a smaller heart/lung volume ratio, which may explain its 30% smaller supine lung expansion gradient compared to the dog (52).

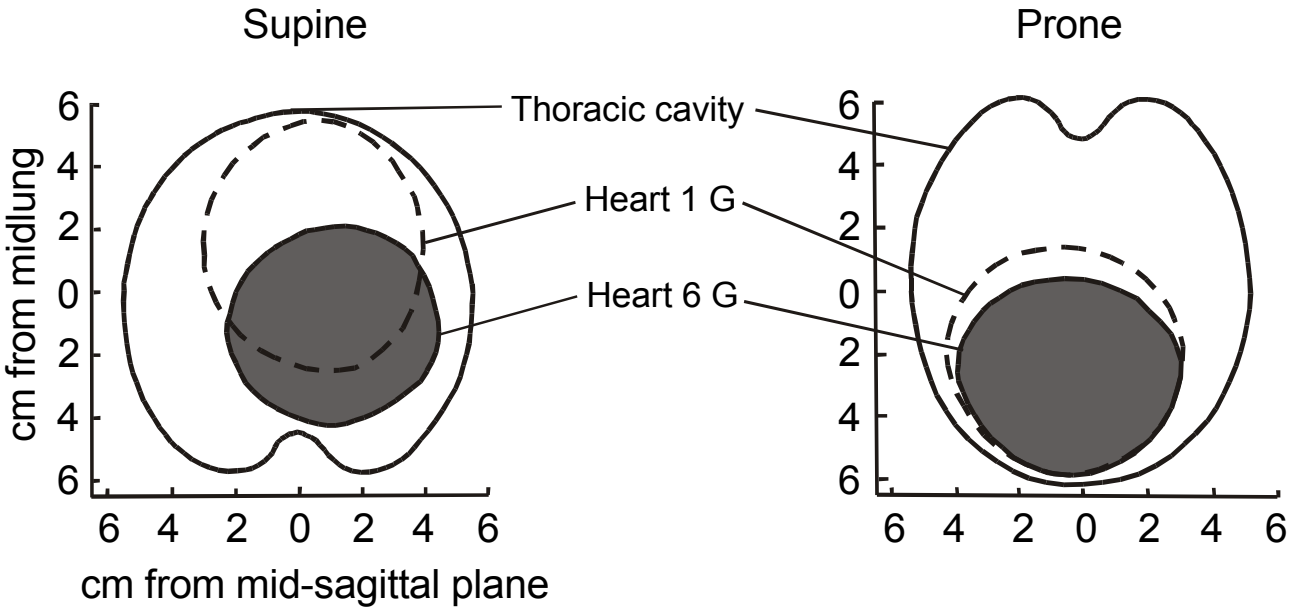

Fig. 8. Schematic representation of the displacement of the heart in the thoracic cage of dogs exposed to 1 and 6 G in prone and supine postures (as determined from biplane roentgenograms). Redrawn from Rutishauser et al. (106).

In addition, Wood and co-workers (105, 106) studied the topographic relationship of the heart to the lungs in dogs exposed to 1 and 6-7 G in the prone and supine postures employing biplane roentgenograms (Fig. 8). Since the dorso-ventral dimension of the thorax of the dogs

used was approximately 20 cm, or almost the same as in adult humans, the results obtained are probably of relevance for human beings as well. Severe dorsal displacement of the heart and consequent overdistension of non-dependent alveoli by hypergravity with supine posture was observed; whereas the position of the heart with prone posture was stable (105, 106). In the supine posture the center of the heart was located at 66% of the lung height at 1 G and at 38% at 6-7 G. The corresponding displacement with prone posture was from 33% to 29%.

Thus, under conditions of hypergravity, cardiac displacement in dogs with supine posture must have led to more extensive compression of lung tissue in the dorsal regions and more arteriovenous shunting than has been described previously (116). Even though the ventral-dorsal dimension of the dogs employed in these studies (105, 106, 123) was similar to that of adult humans, the human heart is much larger than that of the dog heart in relation to the ventral-dorsal dimensions and therefore the human heart is expected to be displaced to a lesser extent by hypergravity than shown for dogs in Fig. 8.

Furthermore, Albert & Hubmayr (1) measured the relative volumes of lung tissue located directly under the heart in the supine and prone positions in seven patients free from parenchymal lung disease. A large fraction of the lung was found to be located under the heart with supine posture; but in contrast almost none of this organ was located under the heart when prone, when the heart rests directly on the sternum and not, as in the supine posture, on pulmonary tissue located between the heart and the dorsal thoracic wall. These investigators therefore proposed a mechanism by which the improved gas exchange associated with prone posture may be the result of less pronounced compression of the lung by the heart.

Acute lung insufficiency induced by hypergravity in comparison to ARDS

Patients with ARDS exhibit severe arterial deoxygenation, but show pronounced and rapid improvement of this oxygenation when shifted from a supine (face-up) to a prone (face-down) posture (78). Despite a number of reports appearing during the past few decades, there is at present no consensus concerning the reason for this positive effect of prone positioning (79). In connection with ARDS, several factors contribute to the marked impairment of oxygen transfer from the inspired gas to the arterial blood, *e.g.* a) fluid accumulation in the alveolar space; b) edema in interstitial lung tissue; c) injuries to both the lung endothelium and epithelium (13); and d) compression of pulmonary tissue, both by the heavy, fluid-filled lung itself and by the enlarged heart (1, 38).

In an effort to characterize lung function in patients with ARDS, Gattinoni and colleagues (38, 87) introduced the concept of the ‘sponge model’, in which along a vertical gradient, the gas content decreases and the hydrostatic pressure at each level increases more rapidly than in normal subjects. The lung tends to collapse under its own weight, creating severe disturbances in ventilation and perfusion.

However, this model cannot explain the characteristics of the lungs in ARDS patients entirely. The sponge model predicts maximal loss of aeration in dependent regions of the lung as a consequence of an increase in the superimposed pressure. However, Puybasset et al. (96) demonstrated that this maximal loss occurs in regions of the lung in vicinity of the

diaphragm. This caudal lung tissue is probably compressed by the increased heart weight (69) and increased abdominal pressure (37), leading to lung atelectasis. Nor can the sponge model explain why there are postural differences in the closure of small airways (29) or why there is no substantial pleural pressure gradient with prone posture, although there is in the supine posture (71).

Upon examining supine ARDS patients with computed tomography, Malbouisson et al. (69) observed a marked increase in cardiac mass compared to healthy supine subjects, as well as an associated increase in the pressure exerted by the heart on the right and left lower lobes of the lung (even though they did not take into consideration possible weight-bearing functions of tissues that could have been stretched between the heart and the anterior chest wall). These researchers also estimated the fraction of the total gas content in the lung which was located in pulmonary tissue beneath the heart and found this fraction to be lower in the patients than in healthy subjects. Their conclusion was that in patients with ARDS the cardiac mass is increased, resulting in increased pleural pressure in the dependent regions of the lung, and consequent alveolar collapse (69). Even in patients with cardiomegaly, ventilation of the left lower lobe of the lung is impaired in supine, but not in prone patients, most probably due to more severe compression of the underlying lung tissue caused by the increased cardiac weight in the supine posture (120).

In critically ill patients it may be difficult to determine the relative contributions of factors a) - d) listed above to the impairment of oxygenation in the lungs and to the improvement which occurs in the prone posture. The rapid time-course of this improvement (36) speaks in favour of decreased lung deformation as an important mechanism. However, these findings provide only indirect evidence for a gravitational effect acting via deformation of pulmonary tissue.

We reasoned that when exposed to short periods of hypergravity, healthy subjects would become a partial analogue to ARDS in the sense that they would experience pronounced gravity-induced deformation of the lungs without interstitial or alveolar edema, or injuries to the alveolo-capillary membrane (40). The similarities between the deteriorated lung function in patients with ARDS and hypergravity-induced acute lung insufficiency include the fact that in both cases the density of the pulmonary tissue is markedly increased, as are the hydrostatic pressure gradients within the lung. Furthermore, the weight of the heart and its pressure on underlying lung tissue are increased in both situations. Healthy subjects exposed to hypergravity experience impaired lung function and consequent arterial deoxygenation (9). Here arterial desaturation in healthy subjects exposed to 5 G was found to be less severe in the prone than in the supine posture (Paper I), lending further support to the proposal that factors other than direct effects of interstitial and alveolar fluid are involved in the improvement of ARDS patients when placed in the prone posture.

In the present experiments, hypergravity impaired pulmonary gas exchange to an extent similar in magnitude to that seen in patients with acute lung insufficiency. Three independent measures demonstrated that under hypergravity arterial oxygenation was more efficiently preserved in the prone than in the supine posture (Paper I). Conventionally, the ratio P_{aO_2}/F_{IO_2} is used to indicate the degree of lung insufficiency (13), with values ≤300 mm Hg (40 kPa) per unit F_{IO_2} indicating acute lung injury and values of ≤200 mm Hg (27kPa) constituting one of the criteria for ARDS. Here, the P_{aO_2}/ F_{IO_2} ratio was 222 mm Hg (30 kPa)

per unit F_{IO_2} in the supine posture under hypergravity. In other words, healthy subjects exposed to 5 G supine show a lung insufficiency on the same order of magnitude as that of ALI and ARDS patients.

We have previously exposed healthy subjects in supine and prone postures to as much as 3 G in the human centrifuge resulting in moderate arterial desaturation, but without observing any dramatic differences in arterial oxygenation between postures (102) (Fig. 9). The weight of the pulmonary tissue of ARDS patients is elevated approximately 2-3 fold (38) which influences the hydrostatic pressure gradient and results in lung tissue compression. However, it appears that healthy subjects must be exposed to a gravitational force of at least 4 G and perhaps 5 G before major differences in gas exchange with prone and supine posture occur. This probably reflects the fact that hypergravity induces a similar increase in the hydrostatic pressure gradient, but without the alveolar and interstitial lung edema which impairs pulmonary function, even in regions not subjected to compression or ventilation-perfusion mismatch, in patients with ARDS.

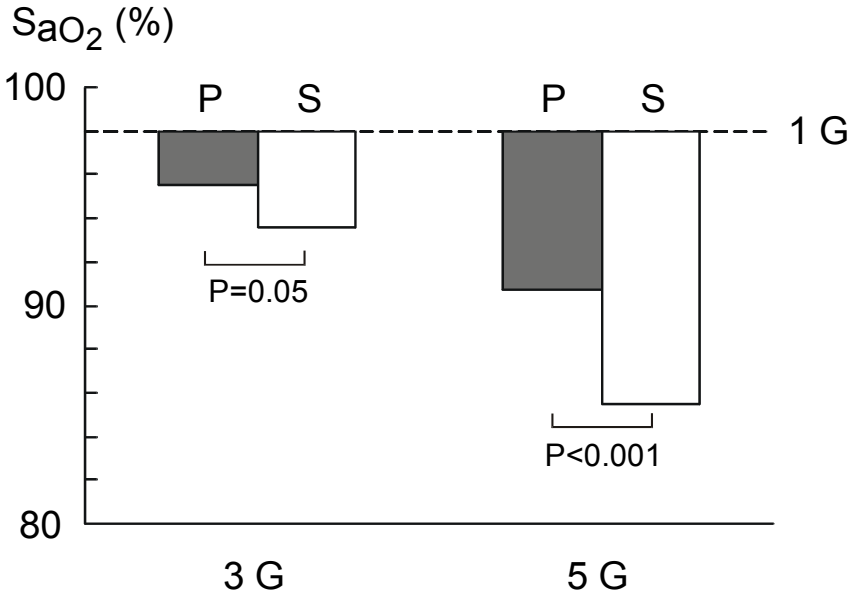

Fig. 9. Arterial oxygen saturation (S_{aO_2}) after ~6 min exposure to three and five times normal gravity (3 and 5 G, respectively) in prone (P) and supine (S) postures. The experiments at 3 and 5 G were not performed by the same subjects.

There are several possible mechanisms by which hypergravity might cause arterial desaturation, *e.g.* alveolar hypoventilation and/or impaired alveolo-arterial gas exchange (due to increased heterogeneities in ventilation and perfusion and/or decreased diffusing capacity). Accordingly, there are also different possible explanations for the more efficient gas exchange observed with prone posture under hypergravity. However, we found no evidence for alveolar hypoventilation or pulmonary edema, but rather a dramatically broadened difference in alveolo-arterial PO_2, pointing unequivocally to an impairment in alveolo-capillary gas exchange as the mechanism involved.

LUNG FUNCTION IN SITTING HUMANS

Lung diffusing capacity and tissue volume during exposure to hypergravity

Under normal gravity, changes in the DL_{CO}, pulmonary-capillary blood volume, lung tissue volume and central blood volume occur in a coherent fashion, for example, during transitions between supine and upright postures and between rest and exercise (31, 56, 107, 113). The underlying reason for this is that as consequence of the increased central blood volume and cardiac output in the supine compared to upright posture and during exercise compared to rest, the distribution of pulmonary-capillary blood volume in relationship to the alveolar volume in the human lung is more homogenous (19, 33).
Under conditions of hypergravity, the heterogeneities in the distributions of $\dot{V}$ and $\dot{Q}$ in the human lung are impaired and as a result the gas exchange is impaired (9, 40, 104). Therefore, our hypothesis was that the DL_{CO} would be reduced in seated subjects exposed to hypergravity. Such a hypergravity-induced decrease in the DL_{CO} might be expected to be accompanied by similar decreases in the volumes of pulmonary-capillary blood, lung tissue and central blood.

On the other hand, blood pooling in dependent parts of the body also increases under hypergravity, resulting in impaired venous return and impaired cardiac output (104). It has been reported that when seated subjects were exposed to hypergravity the decrease in central blood volume was more pronounced than the smaller increase in sequestration of blood in dependent parts of the body (55). Therefore it has been speculated that there must be additional sequestration of blood in splanchnic vessels and/or in the dependent parts of the pulmonary circulation. Such sequestration in the pulmonary circulation might be expected to be accompanied by an increase in the LTV (including the pulmonary-capillary blood volume), despite a decrease in the DL_{CO} and cardiac output.

The present results (Paper II) document a significant decrease in DL_{CO} and a simultaneous increase in LTV in seated subjects exposed to 3 G, in comparison to normal gravity. In support of this Arieli et al. (5), while employing a CO_2-rebreathing technique to assess LTV, observed a 58% increase in this parameter in seated subjects at 3 G compared to the 1-G control values. Our interpretation is that these findings are compatible with sequestration of blood in the dependent part of the pulmonary circulation, just as occurs in the systemic counterpart. The DL_{CO}, which under normoxic conditions, is primarily determined by its membrane component, was decreased under hypergravity despite an increased pulmonary-capillary blood volume. It appears most likely that this situation is a consequence of a more heterogenous distribution of alveolar volume with respect to pulmonary-capillary blood volume. The hypergravity-induced decrease in DL_{CO} would most probably be even more pronounced without the simultaneous increase in LTV. From a hemodynamic standpoint, sequestration of blood in the pulmonary circulation would be equally disadvantageous for venous return to the heart as is sequestration in the systemic circulation.

Distributions of ventilation and perfusion

We observed here a pronounced difference in the effects of hypergravity on seated subjects with respect to phase III phenomena (COS/SV and phase III slope) as compared to phase IV phenomena (phase IV amplitude and CV/VC) (Paper III, Table 1). There was a trend towards a gravitational effect on the phase III slope, and COS/SV was significantly altered by increased gravity. However, in relative terms, the gravity-induced changes in phase IV phenomena were considerably larger.

Prisk et al. (94) assessed the distribution of pulmonary perfusion from CO_2 expirograms in astronauts prior to and during a 9-day spaceflight, and found that under conditions of microgravity, the reduction in phase IV amplitude was relatively much greater than the change in COS, compared to 1-G control values. These investigators ascribed this difference to the fact that microgravity eliminates apico-basal differences in perfusion, rather than the smaller-scale mechanisms of heterogeneity *e.g.* differences in lung compliance within small regions of the lung which are not affected by gravity (94). At the same time, there were small-scale heterogeneities in $\dot{V}$ and $\dot{Q}$ which were affected by gravity, probably including small gradients in the dependent-to-non-dependent direction within a given region of the lung. We conclude that in seated subjects, hypergravity causes increases not only in large-scale heterogeneities of $\dot{V}$ and $\dot{Q}$ (as reflected by phase IV amplitude), but also in smaller-scale heterogeneities (as reflected by the COS/SV ratio). With the exception of small-scale distribution of $\dot{V}$, most of the impairments observed at 3 G were already apparent at 2 G.

COMPARISONS BETWEEN SEATED AND RECUMBENT SUBJECTS

We have found a striking similarity between the SBW values obtained for seated (Paper III) and prone (Paper V) subjects under hypergravity. These similarities are most pronounced for phase III slope (Paper V, Fig. 3A) and phase IV amplitude (Paper V, Fig. 4A) of the Ar expirograms, indicating that the distribution of ventilation, both on a small- and large-scale, is similar between seated and prone subjects in hypergravity. We speculate that these similarities are due to qualitatively similar interactions between the heart and the lung and between the diaphragm and the lung.

With both body postures, the heart is located adjacent to one of the inner walls of the thoracic cavity, in the seated posture against the diaphragm and in the prone posture against the anterior chest wall. Thus, the pulmonary tissues are not likely to be either extended or compressed to any significant extent by any gravity-induced displacement of the heart. Consequently, the distributions of ventilation and perfusion are determined primarily by gravity-induced gradients within the lung tissue itself. Although linear along the axis of gravity (42), such gradients also include non-linear threshold phenomena, such as airway closure at the point at which the pleural pressure exceeds alveolar pressure in the lungs, which occurs to an increasing extent as the expiration proceeds to lower lung volumes (42).

In the supine posture under conditions of hypergravity, however, the heart, with its much greater density than the surrounding pulmonary tissues, is displaced downwards. This

phenomenon is likely to contribute to the development of more negative pleural pressures in lung tissues above the heart, even at low lung volume when supine, so that airway closure is not likely to occur to the same extent as with prone and upright postures. There is probably also a difference in interaction between the lung and diaphragm in the supine posture compared to seated and prone postures. With supine posture, the dorso-caudal regions of the lung are mechanically distorted by a cephalad positional shift of the dorsal portions of the diaphragm (76); whereas in prone and seated postures a caudal positional shift of the diaphragm occurs instead (40, 76). The pulmonary tissue that is compressed by the diaphragm and the heart in connection with supine-hypergravity is unlikely to be involved fully, if at all, in the VC maneuver.

CARDIOVASCULAR RESPONSES TO HYPERGRAVITY

Sitting posture

During exposure to hypergravity, the venous return from vascular beds below the heart is decreased due to an increase in the hydrostatic pressure gradient (24). The direct consequences of this inadequate venous return are rapid decreases in the cardiac output and arterial blood pressure (24). Our finding that hypergravity decreases cardiac output in seated subjects are in agreement with previous studies (5, 17, 104). The mechanism underlying the reduction of SV caused by hypergravity involves a decrease in the effective circulating volume of blood, both in the systemic (104) and pulmonary circulations (Paper III).

Interestingly, there are ways to improve this venous return and thereby prevent rapid decreases in cardiac output and arterial blood pressure. Arieli et al. (5) compared the effects at 1-, 2-, and 3-G on the systemic circulation of seated subjects immersed in water to the level of the heart to the effects without such immersion. As expected, the cardiac output was decreased by hypergravity without immersion but was elevated under normogravity and unaffected by hypergravity with immersion (5). Futhermore, Linnarsson and Rosenhamer (67) demonstrated that the arterial hypotension developed gradually in seated, resting subjects exposed to 3 G. The arterial hypotension was instantaneously eliminated when the subjects began to perform dynamic leg exercise, which markedly improves venous return through the action of the muscle pump (34, 65).

Tachycardia is a common feature when seated subjects are exposed to hypergravity (Paper I) (5, 67) and is of baroreflex origin, *i.e.* due to reduced arterial blood pressure at the level of the carotid baroreceptors (67). This tachycardia contributes further to the reduction in SV that occurs in response to hypergravity (104).

Prone and supine postures

It is generally agreed that from a hemodynamic point of view it is advantageous to be recumbent rather than seated when exposed to hypergravity, *e.g.* during the take-off of a spacecraft, because of the smaller hydrostatic pressure gradient between the heart and the

head in recumbent posture (115). Human tolerance to hypergravity with supine posture is more than three times greater than our tolerance when seated (24).

However, in the recumbent subjects exposed to hypergravity here, cardiovascular function was also severely affected, as reflected in the dramatic reduction in cardiac output. The cardiac output was higher in the prone than in the supine posture at 5 G, probably accompanied by recruitment of a larger number of pulmonary capillaries and, as a consequence, a more homogenous distribution of perfusion with prone posture. As also seen with seated subjects, HR increased and SV decreased upon exposure to hypergravity. Interestingly, the HR was always higher with prone than supine posture, independent of the level of gravitational force. One possible mechanism involved here could be tachycardia resulting from stimulation of cardiopulmonary mechanoreceptors. The occurrence of such a reflex has been suggested by Bainbridge (7) on the basis of studies on acute atrial distension in an animal model. Recent studies have revived the idea that the Bainbridge reflex is also functionally important in humans (8, 85). Considered altogether, the present findings, data concerning transmural atrial pressures in prone and supine dogs (123) and this recent study suggesting the presence of a functional Bainbridge reflex in humans (8, 85) may explain the relative tachycardia associated with prone posture during exposure to hypergravity. However, these results do not readily explain this phenomenon at 1 G, where transmural right atrial pressures may be the same with prone and supine posture.

The rôle of changes in autonomic outflow to the heart due to stress (caused by hypoxemia and/or pain) is difficult to assess. Likely, there was no stress involved in the 1 G experiments. However, it is of interest to note that almost all of our subjects complained about it being more difficult to breathe in the supine posture at 5 G, because of substernal pain. To our knowledge, this phenomenon has not been described previously in the literature.

One major difference between our experimental set-up and those used in most previous studies is that our supine subjects had their legs at the same level as the rest of their body, and not in “launch position”, *i.e.* in the supine posture with their legs elevated and the hips and knees flexed at right angles. Our subjects also endured a relatively long period of exposure of to hypergravity, which may have affected their level of pain.

In the few earlier investigations of cardiac output in recumbent humans exposed to hypergravity, the subjects have been placed almost exclusively in the “launch position” (66, 70). When Lindberg and coworkers (66, 70) exposed subjects in this launch position to 3.5 and 5 G for periods as long as 10 minutes, they either observed no systematic change or a slight increase in cardiac output assessed with an indicator dilution technique compared to normal gravity. In the study by Nolan et al. (82) on supine subjects, two of the four volunteers experienced “grayout” at 5.8 G. In contrast, this phenomenon did not occur in subjects placed in the launch position (66, 70). Together, these findings indicate the importance of a hydrostatic blood column above the heart for the maintenance of venous return under conditions of hypergravity.

Because of the relatively different positions of the heart in the thorax with prone and supine posture, the negative hydrostatic gradient for venous return in the supine posture is likely to have increased proportionally with increases in G, as would the corresponding positive gradient in the prone posture. The FRC was higher in prone hypergravity than in

supine and may also have helped establish more favourable conditions for diastolic filling. In summary, therefore, an improved preload with the prone compared to supine posture most likely accounts for the more effective preservation of cardiac output in the former posture under conditions of hypergravity.

The military value of finding ways to enable humans to adjust to hypergravity is emphasized by a number of crashes caused by G-induced loss of consciousness with high-performance fighter planes. The reduced arterial pressure in cerebral level determines the tolerance to elevated G-forces of seated humans (122). One way to improve arterial pressure is by assuming recumbent posture. Accordingly, there have been numerous investigations suggesting that pilots in fighter planes should be recumbent (122). However, for both physiological and psychological reasons prone posture is superior to supine or, as put by Earl Wood; "after all, *Superman flies in the prone position*" (122).

VENTILATORY RESPONSES TO HYPERGRAVITY

Rosenhamer's (104) study on seated subjects exposed to 1-3 G revealed that pulmonary ventilation was markedly increased under hypergravity, despite an unchanged P_{aO_2}, a *reduced* P_{aCO2}, and a modest alkalosis. Thus, it could be safely concluded that the accompanying hyperventilation is not due to stimulation of the arterial chemoreceptors. Furthermore, similar experiments performed by Boutellier et al. (17) showed that although ventilation was altered more by a change from 2 to 3 G than from 1 to 2 G, alveolar P_{aCO2} was not. Interestingly, this can be considered to be an extension of the physiological changes which occur during a positional shift from supine to upright posture at normogravity, the latter condition being also associated with an increase in ventilation and a decrease in alveolar CO_2 tension (18, 98). This demonstrates the existence of at least one other respiratory stimulus in addition to P_{aO_2}, P_{aCO_2}, and pH_a.

It has been proposed that this orthostatically-induced hyperventilation is a consequence of reduced cerebral perfusion (6, 14, 17, 98). This proposal is based on the fact that after a transition from the supine to an upright posture at normal gravity or from 1 G to hypergravity with sitting posture (54, 64), the carotid pressure is highly likely to be reduced, causing a reduction in cerebral blood flow and thereby an increase in P_{CO2} in the respiratory center (98). The involvement of cerebral blood flow in regulation of ventilation has been demonstrated clearly by Chapman et al. (25). Alternative speculations are that the hyperventilation observed under hypergravity is the result of a combination of mechano- and chemoreceptor inputs (68) and/or increased circulating levels of catecholamines (111).

In light of the data described above concerning upright exposure to hypergravity, it is of interest to note that pronounced hyperventilation also occurs in recumbent subjects upon exposure to hypergravity (5 G) (Paper I, Table I and II). In comparison to the corresponding values at 1 G, these recumbent subjects exhibit increased mean arterial blood pressure at the level of the heart and thus also at the carotid and cerebral levels. Therefore, baroreceptor unloading and/or cerebral hypoperfusion are not likely to account for the exaggerated ventilatory stimulus. In contrast to upright posture at 3 G, however, pronounced arterial hypoxemia (with a P_{aO_2} on the order of 6-7 kPa) was observed in recumbent subjects at 5 G.

Thus, in summary, hypergravity-induced hyperventilation in upright and recumbent postures may very well have different causes. At the same time, deformation of lung tissue, resulting in stimulation of pulmonary and thoracic mechanoreceptors occurs with both upright and recumbent exposure to hypergravity and must be considered as a possible stimulus for the hyperventilation (28), as well as for the subjective sensation of labored breathing (125).

LIMITATIONS OF THE METHODOLOGY FOR ASSESSING DL_{CO} AND THE DISTRIBUTIONS OF $\dot{V}$ AND $\dot{Q}$

The major advantage of the approach involving a combined REB-SBW maneuver (Papers II-V), is its ability to estimate the lung diffusing capacity, as well as the distributions of $\dot{V}$ and $\dot{Q}$ non-invasively and simultaneously in real time *during* exposure to each gravitational condition. This can contrasted with the high-resolution microsphere technique utilizing SPECT (90), in which markers for the distributions of regional $\dot{V}$ and $\dot{Q}$ are administered under hypergravity, but their distributions are determined later at normal gravity. Because of the hypergravity-induced displacement of lung parenchyma during the injection and return of the lung to its normal shape prior to the measurements (53), such data are difficult to interpret. On the other hand, the obvious limitation of the present REB-SBW approach is its inability to provide data concerning the topographical distribution of $\dot{V}$ and $\dot{Q}$, resulting instead in general indices of heterogeneity.

The rebreathing technique has several advantages over other non-invasive procedures, such as breath-holding method when determining DL_{CO}. In connection with rebreathing the heterogeneity of alveolar gas composition is diminished as a result of mixing between the alveolar compartments and dead space, as well as between different alveolar compartments (91). Furthermore, the variability in alveolar volume associated with different duration of breath-holding is avoided. Finally, the REB procedure requires less time for data collection and provides better reproducibility (91).

The possibility that the present findings from the REB procedure on healthy subjects exposed to hypergravity are artifacts resulting from increased heterogeneities in the distribution of ventilation must be considered. We have several reasons to believe that this is not the case. First, the lack of phase IV phenomena in the insoluble gas tracings recorded in connection with the prolonged expiration to RV following the REB maneuver (Paper II, Fig. 3) indicates that the alveolar gas content, indeed, was well-mixed towards the end of the rebreathing period under all experimental conditions employed. This is so because sequential emptying and airway closure becomes much more pronounced with increasing G force (40). If there had been heterogeneities in the insoluble gas composition between alveolar compartments following rebreathing, these would have been clearly have manifested as phase IV phenomena. This reasoning agrees well with the report by Glaister (39), who employed rebreathing in order to obtain homogenous distribution of radioactive Xe gas in seated subjects exposed to hypergravity. A second reason for dismissing the possibility of artifacts among our data is a modeling study performed by Burma and Saidel (23), which demonstrated that with little or no heterogeneity in ventilation and/or perfusion, rebreathing measurements tend to overestimate LTV; whereas with higher levels of ventilation-perfusion

heterogeneity, LTV tends to be underestimated. To the extent that the relatively simple model of Burma and Saidel (23) is correct, any possible errors here would involve an underestimation of the true increase in LTV under hypergravity.

Finally, Burma and Saidel (23) also predict that heterogeneity in ventilation-perfusion would lead to an underestimation of cardiac output by the rebreathing procedure. In comparison to LTV the estimate of cardiac output varies much less with heterogeneities (23). However, our rebreathing estimates at 1 and 3 G (6.3 and 5.2 l/min) were remarkably similar to those obtained by Rosenhamer (104) using dye dilution (6.7 and 5.1 l/min) under identical conditions.

CONCLUSIONS

Paper I: In this study, we found that when gas exchange is impaired by hypergravity, pulmonary function is more effectively preserved with prone than with supine posture. These results suggest that hypergravity-induced acute lung insufficiency is a potentially useful model for studies on the mechanisms underlying the more efficient gas exchange in the prone posture. This model has the advantage of using healthy subjects instead of patients, but does not include effects of the increased pulmonary fluid content in the lungs of patients with ARDS other than increased hydrostatic pressure gradients. Thus, the diffusion limitations resulting from tissue and alveolar edema are not present in our model.

Paper II: The findings obtained when a rebreathing procedure was applied in seated subjects exposed to hypergravity are compatible with sequestration of blood in the dependent part of the pulmonary circulation, just as occurs in the systemic counterpart. The lung diffusing capacity which, under normoxic circumstances, is determined primarily by its membrane component, was decreased despite an increased pulmonary-capillary blood volume. This phenomenon appears to be a consequence of a more heterogenous distribution of alveolar volume with respect to pulmonary-capillary blood volume.

Paper III: In seated humans both large-scale (as reflected by phase IV amplitude) and smaller-scale (as reflected by the amplitude of cardiogenic oscillations) heterogeneities of ventilation and perfusion are enhanced by hypergravity. The reliability of the present approach for estimating both the small- and large-scale distributions of the ventilation and perfusion in the lung is supported by a comparison with previous results from similar studies, although such data is limited.

Paper IV: We observed a lower lung diffusing capacity in supine than in prone resting humans exposed to hypergravity, which supports our previous detection of larger differences in alveolar-arterial P_{O_2} with supine posture under identical conditions. Reductions in pulmonary-capillary blood flow and the estimated alveolar volume can explain most of the decrease in lung diffusing capacity in the supine posture. We speculate that this difference in cardiopulmonary function between the two postures is of little consequence for healthy subjects at normal gravity, but does appear to make a difference when pulmonary gas exchange is impaired, *e.g.* in patients with acute lung insufficiency or upon exposure of healthy subjects to hypergravity.

Paper V: This study indicates that hypergravity induces more severe heterogeneities of ventilation and perfusion in the supine than in the prone posture. The results are consistent with more extensive airway closure and gas trapping with supine posture upon hypergravity, due to a greater pleural pressure gradient. We speculate that this phenomenon reflects differences in heart-lung interaction and in the position of the diaphragm between the postures: the positions of the heart and diaphragm are stable in prone hypergravity, in contrast to supine posture where the weight of the heart and a cephalad shift of the diaphragm result in compression of lung tissue. Since our experimental model involves severe, gravity-induced distortion of the lung but not the other characteristics of ARDS (*i.e.* edema in the pulmonary interstitial tissue and alveoli). Thus, the similarity between the

present findings and the favorable effects of prone posture on patients with ARDS support the hypothesis that attenuated compression of the lung is a key factor underlying the protective effect of prone positioning on patients with ARDS.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Påverkas lungan av tyngdkraften?

Jordens tyngdkraft påverkar alla organsystem hos landlevande djur på en rad olika sätt. Ryggradsdjur, som tidigare var anpassade till ett liv i vatten, har under miljoner år utvecklats för att fungera bättre vid ett fyrfota liv på land. Trots att landlevande ryggradsdjur har anpassats för ett liv på vår jord vid normal tyngdkraft (1 G) har människokroppen en förvånansvärd fysiologisk reservkapacitet och kan anpassa sig till såväl ökad tyngdkraft som tyngdlöshet.

Lungfunktionen är extremt känslig för förändringar i tyngdkraftens storlek och riktning. Detta beror på lungans elastiska struktur och stora densitetsskillnader mellan de luftfyllda lungblåsorna och det omgivande finmaskiga nätverket av blodkärl (se bild på omslaget). Ett exempel på detta är att patienter med akut försämring av lungfunktionen (lungsvikt) får en dramatisk förbättring av blodets syresättning om man vänder dem från rygg till mage (bukläge). Trots hög medicinsk relevans är de bakomliggande mekanismerna som förklarar denna effekt ofullständigt kända. Skillnaden i lungfunktion på grund av kroppsläget är självklart en effekt av hur tyngdkraften påverkar kroppen på olika sätt, beroende på om vi har magen, ryggen eller fötterna närmast jordens medelpunkt.

Lungans funktion: gasutbyte

Lungans huvudsakliga och livsviktiga funktion är att transportera gaser mellan luften i lungblåsorna och blodet; syre från lungblåsorna till blodet och koldioxid från kroppens vävnader åt andra hållet. En förutsättning för att gasutbytet sker på ett optimalt sätt är att luften vi andas in möter blod som strömmar i lungkärlen, endast skilda åt av ett mycket tunt membran. Tyngdkraften gör att både blod och luft strömmar till lungans nedre delar hos en människa i upprätt kroppsställning.

Vi vill försöka förstå hur lungans gasutbyte påverkas av förändringar av kroppsläge och av tyngdkraftens storlek. Eftersom tyngdkraften alltid är närvarande på jorden försvårar det om man vill veta om det existerar andra faktorer som påverkar lungfunktionen. Vi har därför använt oss av tre olika försöksbetingelser; långvarig tyngdlöshet under rymdflygning med astronauter som försökspersoner, kortvarig (23 sek) tyngdlöshet under parabolflygningar och ökad tyngdkraft i humancentrifugen vid Karolinska Institutet, Stockholm. Det är experiment från humancentrifugen som ingår i min avhandling och som jag ska redogöra för här.

Man vet från tidigare studier att friska försökspersoner som utsätts för en ökad tyngdkraft i en humancentrifug får en markant försämrad syresättning av blodet som tecken på en akut, men snabbt övergående, lungsvikt. Bakgrunden till våra experiment var idén att undersöka om friska försökspersoner, i likhet med patienter med akut lungsvikt, får bättre lungfunktion i bukläge än i ryggläge när de stressas med höga G-krafter i centrifugen.

Är lungfunktionen bättre på mage än på rygg vid G-inducerad lungsvikt?

I vår **första** studie så undersökte vi friska försökspersoner som låg på mage och rygg och exponerades för normal tyngdkraft samt upp till 5 gånger normal tyngdkraft (5 G) i humancentrifugen vid Karolinska Institutet. Vi tog blodprover 'i farten' dvs. med fjärrstyrda sprutor medan centrifugen roterade. Resultaten var i enighet med vår hypotes, dvs. blodets syremättnad sjönk i båda kroppslägena vid ökad tyngdkraft men mer påtagligt på rygg än på mage. Vidare upptäckte vi att detta inte beror på att för lite luft når lungblåsorna utan att det är en sämre syretransport från lungblåsorna till lungans blodkärl i ryggläge än i bukläge.

Hur påverkas lungfunktionen hos sittande människor av ökad tyngdkraft?

Det finns många praktiska problem med att utföra experiment och mätningar under det att en försöksperson snurrar runt i centrifugen. I vår **andra** studie ville vi vidareutveckla en metod som används vid normal tyngdkraft för att fortsätta studera orsakerna bakom skillnaden i lungfunktion mellan mage och rygg vid ökad tyngdkraft. Vi använde en metod där man genom att andas lösliga och olösliga gaser kan mäta lungans kapacitet för gasutbyte, lungans syreupptag och vävnadsvolym, olika lungvolymer, volymen blod som hjärtat pumpar per minut samt hur flödet av blod och luft fördelar sig i lungorna.

Vi valde att först använda denna nya metod på sittande försökspersoner eftersom det finns flera tidigare studier utförda med liknande metoder att jämföra med. Resultaten bekräftade att sittande människor får en försämrad kapacitet för gasutbyte i lungorna när de exponeras för ökad tyngdkraft (3 G). Vidare verkar det som om man får en ansamling av blod i nedre delar av lungan, på samma sätt som det tidigare är känt att man får motsvarande blodansamling i nedre kroppsdelar vid ökad tyngdkraft. Fördelningen av luft- och blodflödet blev mer ojämn mellan olika lungdelar vid ökad tyngdkraft och detta var tydligare för lungdelar som befinner sig längre ifrån varandra än de som ligger nära varandra.

Varför är en G-inducerad lungsvikt lindrigare i bukläge?

I vår **tredje** studie ville vi använda samma metod för att studera lungfunktionen hos liggande människor. Resultaten visar att lungans kapacitet för gasutbyte var markant nedsatt vid 5 G och påtagligt mer försämrad i ryggläge än i bukläge. Detta beror på att luft- och blodflödet i lungorna är mer fördelaktigt fördelade på mage än på rygg. Vi upptäckte en intressant likhet mellan lungfunktionen hos människor när de sitter och när de ligger på mage. Denna likhet beror troligen på att hjärtat vilar mot mellangärdet/diafragma i sittande och mot främre delen av bröstkorgen på mage till skillnad från i ryggläge då hjärtat kommer att pressa ihop underliggande lungvävnad och därmed försämrar dess funktion. En annan likhet är att diafragma förflyttas nedåt i bukläge och i sittande och på så sätt ökar lungvolymen, medan diafragma pressas uppåt av bukorganen i ryggläge.

Lungorna är anpassade till ett fyrfota liv

Våra experiment visar att när man utsätter friska människor för ökad tyngdkraft försämras lungans gasutbyte mindre när man ligger på mage jämfört med rygg. Hos friska människor vid normal tyngdkraft verkar denna skillnad mellan kroppslägen inte spela någon roll men

vid nedsatt lungfunktion, exempelvis patienter med akut lungsvikt eller om man utsätts för ökad tyngdkraft, finns det anledning att föredra bukläge. Vi har vidare funnit flera likheter mellan lungfunktionen hos människor liggande på mage jämfört med i sittande.

Resultaten från våra vetenskapliga experiment visar att människans lungfunktion fortfarande är anpassad till ett fyrfota liv.

APPENDIX (PAPERS I-V)