

Cardiogenic mixing increases aerosol deposition in the human lung in the absence of gravity



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ABSTRACT

Rationale: Exposure to extraterrestrial dusts is an almost inevitable consequence of any proposed planetary exploration. Previous studies in humans showed reduced deposition in low-gravity compared with normal gravity (1 G). However, the reduced sedimentation means that fewer particles deposit in the airways, increasing the number of particles transported to the lung periphery where they eventually deposit albeit at a smaller rate than in 1 G. In this study, we determined the role that gravity and other mechanisms such as cardiogenic mixing play in peripheral lung deposition during breath holds.

Methods: Eight healthy subjects inhaled boluses of 0.5 μm -diameter particles to penetration volumes (V_p) of 300 and 1200 ml that were followed by breath holds of up to 10 s. Tests were performed in 1 G and during short periods of microgravity (μG) aboard the NASA Microgravity Research Aircraft. Aerosol deposition and dispersion were calculated from these data.

Results: Results show that, for both V_p , deposition in 1 G was significantly higher than in μG . In contrast, while dispersion was significantly higher in 1 G compared to μG at $V_p=1200$ ml, there was no significant gravitational effect on dispersion at $V_p=300$ ml. Finally, for each G level and V_p , deposition and dispersion significantly increased with increasing breath-hold time.

Conclusion: The most important finding of this study is that, even in the absence of gravity, aerosol deposition in the lung periphery increased with increasing residence time. Because the particles used in this study were too large to be significantly affected by Brownian diffusion, the increase in deposition is likely due to cardiogenic motion effects.

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1. Introduction

The inhalation and deposition of small particles in the lungs is a health concern here on earth, but also for future space explorers. Dust on the surface of the Moon is thought to be toxic due to the fracturing processes involved in its formation, the chemical composition of the dust, and the radiation environment of the lunar surface [1]. Lunar dust

contains a significant size fraction below 1 μm in size [2], which is readily inhaled into the lung. During the Apollo explorations, lunar dust was pervasive, being readily transported into the habitats where astronauts were exposed to it.

Previous studies in humans showed reduced deposition of inhaled particles in the size range 0.5–3 μm in low gravity compared with normal gravity (1 G) [3–6]. While deposition is lowered by low gravity, the reduced sedimentation also means that fewer particles deposit in the airways, increasing the number of particles that remain in suspension and that are able to be transported to the lung periphery where they might eventually deposit. Because gravitational sedimentation will be reduced or absent in

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future space explorations to other planetary bodies or near-earth objects, it is important to assess the mechanisms by which particles that do penetrate to the lung periphery eventually deposit. A potential mechanism that may affect deposition is the effect of the motion of the heart as it impinges on the lung inside the thoracic cavity [7].

In this study, we performed a series of bolus inhalations of 0.5 μm -diameter particles that were followed by breath holds of up to 10 s providing a period during which cardiogenic motion had the potential to alter deposition. Tests were performed in eight healthy subjects on the ground (1 G) and during short periods of microgravity (μG) aboard the NASA Microgravity Research Aircraft in an attempt to better quantify the contribution of different mechanisms on aerosol deposition in the lung periphery.

2. Methods

2.1. Equipment

Aerosol bolus data were collected with the same equipment (Fig. 1) that we used in previous studies [5,6,8,9]. Briefly, the system allowed the injection of an aerosol bolus with a half-width of ~ 70 ml at a given point in the inhalation by switching computer-controlled pneumatic valves. The measurement of the aerosol concentration and the flow rate were provided by a photometer (model 993000, PARI, GmbH) [10] and a pneumotachograph (Fleisch #1, OEM medical), respectively. The photometer, the pneumotachograph and the valves were heated to body temperature to prevent water condensation. A diffusion dryer was located between the photometer and the mouthpiece to remove the water vapor from the exhaled air to avoid condensation on the lenses of the photometer.

A laptop computer equipped with a 12-bit multifunction I/O card (National Instrument, DAQPad 6020E) was used for

data acquisition. Signals from the photometer and the pneumotachograph were sampled at 100 Hz. We used the same custom software as in our previous study [9,11] for the data acquisition.

Data were collected in normal gravity (1 G) on the ground and in microgravity (μG) aboard the NASA Microgravity Research Aircraft. A typical flight consisted of a climb to an altitude of $\sim 10,000$ m with the cabin pressurized to ~ 600 Torr. A “roller coaster” flight profile was then performed. The aircraft was pitched up at $\sim 1.6 G_z$ to a 45° nose-high attitude. Then the nose was lowered to abolish wing lift, and thrust was reduced to balance drag. A ballistic μG flight profile resulted and was maintained until the aircraft nose was 45° below the horizon. In this manner, μG ($0 \pm 0.03 G_z$) was maintained for ~ 27 s. A pullout averaging $\sim 1.6 G_z$ was maintained for ~ 40 s causing the nose to pitch up to a 45° nose-high attitude and allowed the cycle to be repeated.

2.2. Aerosol generation

The bolus tube was filled with aerosol containing monodisperse polystyrene latex particles (Duke Scientific). The particles were supplied in suspension (water) and the concentrate was diluted and dispensed via 2 Acorn II nebulizers (Marquest Medical Products, Inc). Before entering the bolus tube, the aerosol flowed through a heated hose and a diffusion dryer to remove water droplets so that the resulting aerosol was made of dry latex particles of uniform size.

The size of the particle used in this study was, as provided by the manufacturer, 0.505 ± 0.010 (SD) μm . For convenience, the particles are referred to as 0.5 μm -diameter particles. Aerosol concentration was $\sim 10^4$ particles/ml of gas. Previous size analysis [6] has shown that the number of doublets in the aerosol was $< 4.5\%$ for this particle size.

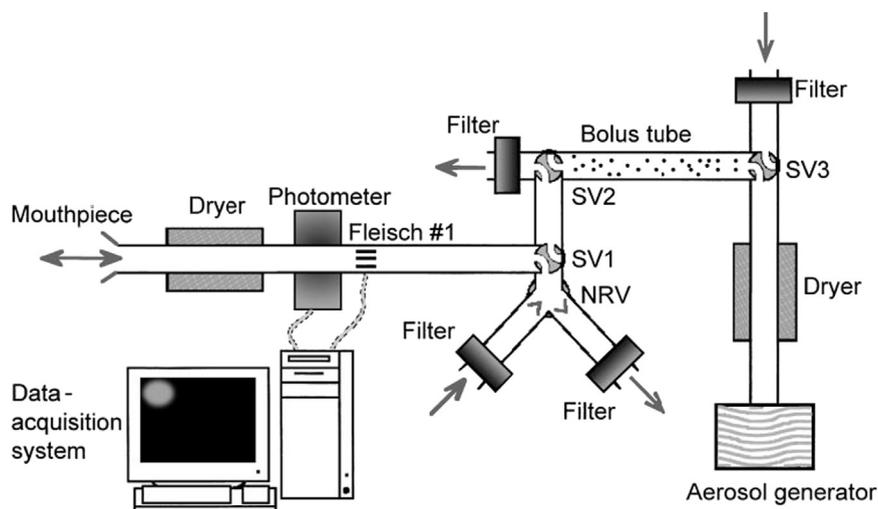


Fig. 1. Schematic representation of experimental setup. One configuration of the sliding valve (SV) SV1 allowed subject to breathe air from the room through a 2-way nonrebreathing valve (NRV) equipped with filters. The other configuration of SV1 allowed the subject to inspire an aerosol bolus located between SV2 and SV3. Measurements of aerosol concentration and flow rate are provided by a photometer and a pneumotachograph (Fleisch #1), respectively. A diffusion dryer is located between the photometer and the mouthpiece to remove water vapor from exhaled air.

2.3. Subjects and protocol

Eight healthy subjects participated in the study. Their relevant anthropometric data are listed in Table 1. After a few normal breaths, the seated subject exhaled to residual volume (RV) to ensure a known lung volume starting point. The test breath consisted of an inspiration from RV to 1 l above functional residual capacity (FRC, measured seated in 1 G) at a flow rate of ~ 0.45 l/s, a breath hold of 0, 5 or 10 s, and an expiration to RV, also at a flow rate of ~ 0.45 l/s. A flowmeter provided visual feedback to the subject who was well-trained in the maneuver. During the inspiration, an aerosol bolus of ~ 70 ml was introduced at two different target penetration volumes ($V_p=300$ and 1200 ml). The penetration volume was defined as the volume of air inhaled from the nose of the aerosol bolus to the end of the inhalation. Thus, at $V_p=300$ ml, the particle bolus was located near the acinar entrance at end inspiration, while at $V_p=1200$ ml, the bolus was well inside the acinus.

The protocol was repeated three times for each penetration volume and breath-hold time at each gravity level. The protocol was approved by the Human Research Protection Program at the University of California, San Diego and by the Committee for the Protection of Human Subjects at the NASA Johnson Space Center, Houston, TX. Subjects signed a statement of informed consent.

2.4. Data analysis

For each bolus test, we calculated the aerosol deposition (DE) and the aerosol bolus dispersion (H). Calculations were performed in a similar manner as in our previous studies [4–6,8,9,11]. Briefly, aerosol deposition was calculated using the following equation:

$$DE = 1 - \frac{N_{ex}}{N_{in}} \quad (1)$$

where N_{in} and N_{ex} are the number of particles in the inspired and expired bolus, respectively. N_{in} and N_{ex} were calculated from the integration of the aerosol concentration multiplied by the instantaneous flow rate. The integration was only done when the concentration exceeded 5% of the maximal expired concentration in order to reduce error due to the noise of the signal [5].

On a graph of aerosol concentration as a function of the respired volume, we computed the bolus half-width defined as the difference in volume (in ml) between the two points of one-half the maximum concentration of the

bolus. The change in half-width H reflects the aerosol dispersion, a standard measure of the degree of mixing between the inhaled bolus and the resident air in the lungs, and was obtained by the following equation

$$H = (H_{ex}^2 - H_{in}^2)^{0.5} \quad (2)$$

where H_{in} and H_{ex} are the half-width of the inspired and expired boluses, respectively.

2.5. Statistical analysis

The same type of statistical analysis as in our previous studies [9,11] was used. Briefly, for each experimental condition (penetration volume, breath-hold time and gravity level) and for each subject, one single value for DE and H was determined as described below and used in the statistical analysis. For each target penetration volume, there was some variability in the measured V_p . Therefore, DE and H were determined at each target V_p by linear regression of the repeated measurements as a function of measured V_p . Linear regressions were performed separately for each subject and each experimental condition. By doing so, we eliminated the confounding effect of variations in penetration volume on DE and H .

For each penetration volume, a two-way analysis of variance (ANOVA) for correlated samples was then performed to test for differences in deposition and dispersion between breath-hold times and gravity levels. Post-hoc testing by Bonferroni adjustment was performed for tests showing significant F ratios. Significant differences were accepted at the $p < 0.05$ level.

3. Results

For each penetration volume and gravity level, deposition increased with increasing breath-hold time (Fig. 2A and B). At $V_p=300$ ml, deposition increased from $19 \pm 7\%$ (mean \pm SD) for $t_{BH}=0$ to $31 \pm 10\%$ for $t_{BH}=10$ s in μ G and from $24 \pm 9\%$ for $t_{BH}=0$ to $54 \pm 12\%$ for $t_{BH}=10$ s in 1 G. At $V_p=1200$ ml, deposition increased from $35 \pm 5\%$ for $t_{BH}=0$ to $50 \pm 10\%$ for $t_{BH}=10$ s in μ G and from $67 \pm 19\%$ for $t_{BH}=0$ to $83 \pm 9\%$ for $t_{BH}=10$ s in 1 G. Deposition was significantly affected by gravity at all t_{BH} and V_p tested ($p < 0.05$) except for tests with no breath holds at $V_p=300$ ml.

Sharp differences from the results for deposition were observed in the effect of gravity on aerosol dispersion between penetration volumes and gravity levels (Fig. 2C and D). While there was no significant gravitational effect on dispersion at $V_p=300$ ml, dispersion was significantly higher in normal gravity compared to μ G for all breath-hold times at $V_p=1200$ ml. At $V_p=300$ ml, dispersion increased from 250 ± 56 ml for $t_{BH}=0$ to 368 ± 86 ml for $t_{BH}=10$ s in μ G and from 247 ± 53 ml for $t_{BH}=0$ to 366 ± 69 ml for $t_{BH}=10$ s in 1 G, increases that were not different between gravity levels. In contrast, at $V_p=1200$ ml, dispersion was higher at all t_{BH} in 1 G than in μ G. Dispersion increased from 424 ± 97 ml for $t_{BH}=0$ to 594 ± 95 ml for $t_{BH}=10$ s in μ G and from 617 ± 103 ml for $t_{BH}=0$ to 863 ± 199 ml for $t_{BH}=10$ s in 1 G. An approximately linear increase in dispersion with increasing breath-hold time was observed at all V_p s and G levels except at $V_p=1200$ ml in 1 G.

Table 1

Anthropometric data.

Subject no.	Sex	Age (Yr)	Height (cm)	Weight (kg)	FVC (%pred)	FEV ₁ /FVC (%pred)
1	F	36	164	56	117	96
2	F	33	163	67	105	100
3	M	54	191	99	131	102
4	M	46	185	116	104	106
6	M	34	188	110	91	93
7	M	37	185	100	114	77
8	F	39	175	82	89	107
9	F	26	167	61	89	109

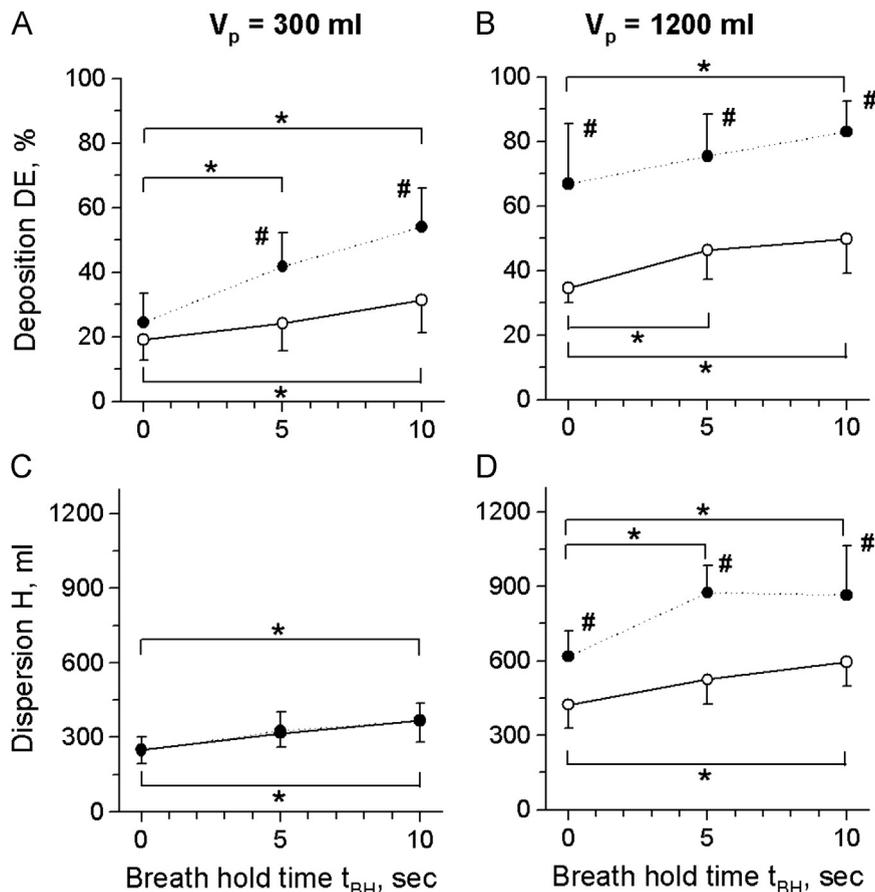


Fig. 2. Aerosol bolus deposition (DE, panels A and B) and dispersion (H, panels C and D). Data are means \pm SD, averaged over 8 subjects, and plotted as a function of breath hold time t_{BH} , ●, normal gravity (1 G), ○, microgravity (μ G). A,C: penetration volume $V_p=300$ ml. B,D: $V_p=1200$ ml. Note that there is no difference in dispersion at $V_p=300$ ml between gravity levels. *Significant differences between t_{BH} ; # significantly different from μ G ($p < 0.05$).

4. Discussion

The principal finding of this study is that even in the absence of gravitational sedimentation, aerosol deposition increases with increasing breath-hold time. This suggests that other factors, likely cardiogenic mixing, contribute to aerosol deposition in the human lung.

The deposition of inhaled particles is generally considered to be governed by the mechanisms of inertial impaction, gravitational sedimentation and Brownian diffusion. Inertial impaction causes most of the particles larger than $5 \mu\text{m}$ to deposit in the upper and large airways. Brownian diffusion affects smaller particles ($< 0.5 \mu\text{m}$), which deposit mainly in the alveolar region. Sedimentation is the gravitational settling of particles and mainly affects particles in the size range $0.5\text{--}5 \mu\text{m}$. Of these three mechanisms, sedimentation is a gravity-dependent process and is therefore changed in altered gravity (G) environments.

Our data showed that, as expected, deposition in 1 G was always significantly higher than in μ G except for tests performed at $V_p=300$ ml with no breath hold (Fig. 2A and B). The similar values for deposition in this latter case was likely the result of a short particle residence time in the airways that did not allow for particles to significantly

deposit by gravitational sedimentation, a time-dependent mechanism. Results obtained at $V_p=300$ ml were similar to those obtained in a previous study by our group [8]. In that previous study, a bolus containing $1.0 \mu\text{m}$ aerosol particles was inhaled to penetration volumes of 150 and 500 ml. The inspiration was followed by short periods of breath holds of up to 5 s and by an expiration to residual volume. As deposition by gravitational sedimentation is proportional to the settling velocity of the particles, the linear increase in deposition as a function of time we measured using $0.5 \mu\text{m}$ particles (Fig. 2A and B) suggests that gravitational sedimentation is the main deposition mechanism during a breath hold in 1 G.

However, even in μ G where sedimentation is absent, there was a significant increase in deposition with increasing breath-hold time (Fig. 2A and B). This implies that mechanisms other than sedimentation (which is by definition zero in μ G) are responsible for the increase in deposition with increasing breath-hold time. As there is no inspiratory or expiratory flow in the airways during the breath-holds, impaction cannot have caused the observed increase in deposition. The likely potential contributor is cardiogenic mixing resulting from the physical motion of the heart that generates an oscillating motion

of air in the lungs [12–14]. Scheuch and Stahlhofen [7] investigated the effect of cardiogenic mixing on aerosol bolus behavior. They performed bolus inhalations of 1 μm -diameter particles on a subject at rest and after exercise when the heart rate was increased by more than a factor 2. They showed that the motion of the heart considerably influences both the aerosol dispersion and deposition and that the effect was more obvious at shallow penetration volumes. Our previous study [8] using 1 μm aerosols and breath holds up to 5 s showed a strong effect of gravity with increasing breath hold time on aerosol deposition in 1 G at both penetration volumes studied ($V_p=150$ and 500 ml). In μG , when gravity was absent, deposition was smaller than in 1 G and less affected by the presence of a breath hold. Nevertheless, the breath-hold data in μG suggested that cardiogenic mixing was important for aerosol deposition at least in the proximal airways [8]. In this study, we probed both the entrance of the acinar region ($V_p=300$ ml) and the lung periphery ($V_p=1200$ ml) and extended breath-hold times to 10 s. Our data suggest that cardiogenic mixing also affects aerosol deposition in the lung periphery. While heart rate is not affected by microgravity, stroke volume is significantly higher in μG compared to 1 G [15]; therefore we would expect cardiogenic mixing to be larger in μG than in 1 G. It should be noted that, in the lung periphery where airspaces are small, Brownian diffusion may be non-negligible even for 0.5 μm particles. The Brownian displacements of these particles average ~ 20 μm in 1 s [6]. Therefore, during a 10 s breath hold, particles can diffuse over a distance that is comparable to the diameter of an alveolus.

Mixing between the inhaled bolus and the resident air is usually assessed by aerosol bolus dispersion. The particles used in this study have minor diffusive properties and are therefore well-suited to probe convective gas transport. Most of the mixing occurs during inspiration and expiration, however the increase in dispersion in μG with increasing breath-hold time (Fig. 2C and 2D) suggest that other mechanisms than inhaled and exhaled flows contribute to the measured aerosol bolus dispersion. In μG , for $V_p=300$ and 1200 ml, dispersion increased by $\sim 50\%$ and $\sim 40\%$, respectively, between tests performed with $t_{BH}=0$ and $t_{BH}=10$ s. Cardiogenic mixing is likely one contributor to this increase in dispersion. This is supported by observations from a study in dog lungs on the effect of heart rate and stroke volume on gas mixing where it was shown that cardiogenic mixing increases the effective diffusion coefficient in the airways [16].

5. Relevance to space exploration

Exposure to extraterrestrial dusts is an almost inevitable consequence of any proposed planetary exploration and that exposure will certainly occur in reduced gravity conditions. The key finding of this study is that, for 0.5 μm -diameter particles, even in the complete absence of gravity, aerosol deposition in the lung periphery is increased with particle residence in the lungs, likely because of cardiogenic motion effects and also to a lesser extent because of Brownian diffusion. Therefore, existing models that consider only the prime mechanisms of deposition will underestimate aerosol

dose to the lungs in these reduced gravity environments. Better models will require the inclusion of the effect of cardiogenic mixing in order to provide good estimates of deposition of these potentially toxic dusts.

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Chantal Darquenne is a Professor of Medicine at the University of California, San Diego. She studies the deposition and dispersion of aerosols in the human lung in an attempt to gain greater insight into the mechanisms involved in particle transport in the lung. A major aspect of her research is to study aerosol inhalations in altered gravity in order to differentiate the gravitational effects on aerosol behavior from other mechanisms, like diffusion processes. She has participated in numerous parabolic flight campaigns both with NASA and ESA.