Effects of body posture and tidal volume on inter- and intraregional ventilation distribution in healthy men

MIKAEL GRO¨ NKVIST,1 EDDIE BERGSTEN,1 AND PER M. GUSTAFSSON1,2
1Swedish Defense Research Agency, Department of Defense Medicine, S-580 13 Linköping; and 2Department of Paediatrics, Central Hospital, S-54185 Skövde, Sweden

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Grönkvist, Mikael, Eddie Bergsten, and Per M. Gustafsson. Effects of body posture and tidal volume on inter- and intraregional ventilation distribution in healthy men. J Appl Physiol 92: 634–642, 2002; 10.1152/japplphysiol.00161.2001.—The influences of body posture and tidal volume on inter- and intraregional ventilation inhomogeneity were assessed by normalized phase III slope (SnIII) analysis of multiple-breath washout recordings of SF6 and He in 11 healthy men. Washouts with target VT of 750, 1,000, and 1,250 ml were performed standing and supine. A linear-fit method was used to establish the contributions of convection-dependent (interregional) (cdi) and diffusion-convection interaction-dependent (intraregional) inhomogeneity (dcdi). Overall inhomogeneity was defined as the sum of cdi and dcdi. The difference in first-breath SnIII for SF6 vs. He, the (SF6 – He)SnIII, served as an index of intra-acinar inhomogeneity. Multiple-regression analysis revealed greater cdi supine vs. standing (P < 0.001) but no significant effects of posture on dcdi or overall inhomogeneity. Larger VT were associated with greater cdi (P < 0.001), particularly when supine, but reduced dcdi (P < 0.001), overall inhomogeneity (P < 0.001), and (SF6 – He)SnIII (P = 0.031). In conclusion, during resting breathing overall and intraregional ventilation inhomogeneities remain unchanged when the supine posture is assumed and improve with larger VT, but supine posture and larger breaths result in greater interregional inhomogeneities.

He; SF6; normalized phase III slope; ventilation inhomogeneity

MULTIPLE-BREATH WASHOUT (MBW) of inert tracer gases has been used for several decades to assess nonuniformity of ventilation distribution. Overall ventilation inhomogeneity can be determined by analysis of clearance curves of tracer gases, but such analyses may have limitations that prohibit the recognition of small changes in uniformity of ventilation distribution (28), and they do not give any information as to the site of ventilation inhomogeneity. The theories and lung models presented by Paiva and Engel (31) have made it possible to perform more detailed assessments of the degree and mechanisms of ventilation nonuniformities. By analysis of the progression of the concentration-normalized phase III slope of an inert tracer gas during a MBW, so-called normalized phase III slope (SnIII) analysis, the magnitude of convection-dependent (interregional) (cdi) and diffusion-convection interaction-dependent (intraregional) ventilation inhomogeneities (dcdi) can be determined (31). Indeed, when using such analysis on data from N2 MBW, it has been possible to demonstrate that the different pathological processes of chronic obstructive pulmonary disease and bronchial asthma both involve airways within or close to the gas-exchange units (40, 41). Washout studies using two inert tracer gases with widely differing diffusivity, such as SF6 and He, can provide further information on the distribution of ventilation within the most peripheral air spaces (intra-acinar inhomogeneity) (31).

Gravity is known to influence the distribution of ventilation between separate lung regions (5), but studies in weightlessness and on earth using vital capacity (VC) single-breath washouts (SBW) of SF6 and He have indicated that there may also be an effect of gravity on interregional gas mixing (37). Using the SF6 and He VC SBW test in a human centrifuge with up to a threefold increase of gravity, our laboratory was, however, unable to demonstrate any changes in ventilation distribution within the most distal airway regions (22). Our group also assessed the effects of posture on gas mixing within the lung periphery by use of the SF6 and He VC SBW test (21). That study showed no influence of posture on intra-acinar inhomogeneity when VC breaths were taken, but inhomogeneity between well-separated lung regions increased substantially, and there was also a modest increase in cdi within or between peripheral lung units when supine.

VC studies may generate findings of great theoretical interest, but the results of such test are obtained under considerably different conditions than during resting breathing, mainly because the preinspiratory lung volume (PILV) is much smaller and breath size is much greater (15). It has been shown that variations in PILV and tidal volume (VT) both affect the phase III slopes of inert tracer gases (9, 10, 32, 33), and standardization of body posture and VT during MBW tests may therefore be of great importance when these tests are used to disclose and quantify peripheral airway pathology. From those studies, it appears that the ratio of VT to functional residual capacity (FRC) (VT/FRC) is a strong determinant of intraregional inhomogeneity.

Address for reprint requests and other correspondence: M. Grönkvist, Swedish Defense Research Agency, PO Box 13 400, S-580 13 Linköping, Sweden (E-mail: mikgro@foi.se).

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The present study was designed primarily to assess how a change in body posture from standing to supine and small changes in VT influence inter- and intraregional ventilation inhomogeneity as measured by $S_{III}$ analysis of MBW data. Because the gravity-dependent intrapleural pressure gradient is approximately halved supine vs. standing (1, 26), we expected to find decreased interregional ventilation inhomogeneity in the supine posture. On the other hand, the VT/FRC is increased when the supine posture is assumed, and alterations of VT/FRC are also expected to influence ventilation inhomogeneity (9, 10, 32, 33).

Eleven healthy male test subjects performed MBW of SF$_6$ and He standing and supine with three different VT within the physiological range. Parameters reflecting inter- and intraregional inhomogeneity were obtained by $S_{III}$ analysis of SF$_6$ and He data from MBW, and multiple-regression analysis was used to determine the influence of body posture and VT/FRC. We also report how changes in inter- and intraregional inhomogeneity as defined by the $S_{III}$ parameters are reflected in conventional markers of ventilation mal-distribution.

MATERIALS AND METHODS

Test Subjects

Eleven healthy, nonsmoking men participated in this study. Their mean age was 30 yr (range 17–51), their mean height was 182 cm (range 168–190), and their mean body weight was 81 kg (range 68–97), and they were all healthy nonsmokers. The study was approved by the Ethics Committee for Human Research at the University Hospital, Linköping, Sweden.

Equipment and Procedures

The MBW tests were performed in a randomized order in the standing and supine postures with three different target VT (750, 1,000, and 1,250 ml) in each body posture. Three MBW tests were performed in each test situation, resulting in a total of 18 washouts in each subject. The test subjects controlled their VT by using visual feedback of the inspired volumes, which were presented graphically on-line on a computer screen. They were instructed to keep inspiratory flow at ~0.5 l/s and asked to relax during expirations. The participants rested for 3 min between each washout and stood upright between supine tests. A nose clip was used during all tests.

Equipment. The washin (4% SF$_6$, 4% He, 21% O$_2$, balance N$_2$) and washout (21% O$_2$, balance N$_2$; i.e., air) gas mixtures were kept in two separate gas cylinders provided to the test subject through a Y-shaped two-way nonrebreathing valve (model 2630; Hans Rudolph, Kansas City, MO) via a demand valve (OTWO-systems, Toronto, ON, Canada), applied to the inspiratory part of the two-way valve. The dead space of the breathing system was ~70 ml. By manually controlled solenoids positioned between the gas cylinders and the demand valve, either gas was provided. Inspiratory and expiratory flows were measured by a heated Fleisch no. 2 pneumotachometer (PTM) attached to the two-way nonrebreathing valve. Dry gas concentrations (SF$_6$, He, O$_2$, CO$_2$, N$_2$) were measured at the mouth by a respiratory mass spectrometer (AMIS 2000, Innovision A/S, Odense, Denmark). The PTM was calibrated with separate calibration constants for inspiratory and expiratory flow rates by use of a 3,000-ml precision syringe (Hans Rudolph) at a flow rate of ~0.5 l/s. Recorded inspiratory and expiratory flows and volumes were converted to BTPS conditions. The technique described by Brunner et al. (4) was used to align the gas concentrations and flow signals. The sample flow rate of the mass spectrometer was 20 ml/min, and the gas concentration signals were updated at a rate of 33.3 Hz. The tip of the mass spectrometer capillary was positioned between the mouthpiece and the PTM in the center of the air stream. The mass spectrometer measured the concentrations of all respiratory gases used (SF$_6$, He, N$_2$, O$_2$, and CO$_2$) as dry gas concentrations. All signals were recorded at 100 Hz by a computer through a 16-channel analog-to-digital conversion board (DAS-1602, Keithley Metrabyte, Taunton, MA) by using custom-made software based on a commercially available data-acquisition software pack (TestPoint, Capital Equipment, Billerica, MA). The software corrected the flow signal sample by sample for changes in dynamic viscosity caused by the variations in gas composition. The correct function of the recording system was validated before and after completing the recordings in each test subject. The validation consisted of a simulated FRC measurement by a MBW of the tracer gases (SF$_6$, He) using the 3,000-ml precision syringe. The accuracy of the measured syringe volumes was within 3% of the geometric volume, and the precision was also within 3%.

Procedures. The MBW procedure started by tidal breathing of the washin gas and continued until equilibration of the inspiratory and expiratory tracer gas concentrations was achieved. Three VC breaths were then performed to ensure that all lung spaces had the same tracer gas concentrations and to standardize volume history. After these large breaths, the test subjects were instructed to breathe with the target VT (750, 1,000, or 1,250 ml). Data from the washin phase were not stored, and no analyses of data from this phase were undertaken. When breathing was regular, the washout was started by switching the solenoids during an expiration to provide air during the subsequent inspirations. The washout continued until the end-tidal SF$_6$ and He concentrations were below 0.1%, i.e., 1/40th of the starting concentration. The washout data was stored for off-line analysis.

Breathing Pattern Variables, FRC, and Lung Volume Turnover

The expiratory VT was calculated by integration of the expiratory flow. Respiratory rate (RR) for each washout was calculated from the mean RR of the individual first 20 breaths of the washout. Mean inspiratory and expiratory flows from the first breath of washout were noted.

FRC was determined from the cumulative exhaled marker gas concentration divided by the initial end-tidal gas concentration minus the end-tidal concentration at completion of the washout. The number of lung volume turnovers (TO) for each breath during the washout was calculated as the cumulative expired volume (CEV) at that point divided by the FRC.

$S_{III}$ and $S_{III}$ Determinations

For each breath during the washout, the SF$_6$ and He concentrations were plotted as a function of expired volume. The slope of the alveolar phase (slope phase III; $S_{III}$) was calculated for each breath and gas by a least square fit in the interval of 60–90% of the expired volume. When cardiogenic oscillations produced distortions of the $S_{III}$ calculations, a manual best fit over the interval was done. The $S_{III}$ was then normalized by the mean tracer gas concentration over the
phase III interval of interest, to account for lung dilution, giving the concentration-normalized phase III slope (S_{III}) for SF_{6} and He, respectively. The difference between the SF_{6} and He concentrations (SF_{6} - He) was calculated sample by sample between 65 and 95% of the expired volume and plotted as a function of expired volume and concentration, giving the S_{III} for SF_{6} - He, which is referred to as the (SF_{6} - He)S_{III}. The first-breath S_{III} values from the three recordings in each test condition in each subject were averaged for SF_{6}, He, and SF_{6} - He, respectively, and used for further statistical evaluation and presentation.

Calculation of Inter- and Intraregional Inhomogeneity

Inter- and intraregional ventilation inhomogeneity were assessed by use of a previously presented linear-fit technique (41, 42). The S_{III} values for each washout were plotted as functions of TO. A linear-fit procedure utilizing these plots was undertaken to delineate the two underlying mechanisms of ventilation distribution contributing to total inhomogeneity. This in turn is based on previous lung modeling and experimental studies (12, 31, 39) of cd1 and dcdi (9, 17, 20, 34, 36). The cd1 and dcdi are calculated as the S_{III}(cd1) and the S_{III}(dcdi) for the first washout breath, and together they form the first-breath S_{III}(total). Further background to this theory is given in the Discussion. The increase in S_{III} per unit TO was calculated by linear regression between 1.5 and 6.0 TO, and it was termed ΔS_{cd1} in the present study. We then utilized the method described by Verbanck et al. (41, 42) and calculated the first-breath S_{III}(cd1) value by multiplying the ΔS_{cd1} with the first-breath TO value. The first-breath S_{III}(dcdi) value was determined by subtracting the calculated first-breath S_{III}(cd1) value from the first-breath S_{III} measured. The directly measured first-breath S_{III} for SF_{6} and He [first-breath S_{III}(total)], which are markers of overall inhomogeneity, and the directly measured first-breath (SF_{6} - He)S_{III}, an indicator of intra-acinar inhomogeneity, were both used without any further modifications.

Indexes of Overall Ventilation Inhomogeneity

(Conventional Markers)

Because the markers calculated from SF_{6} and He washouts were affected equally by changes in PILV and VT, only the results obtained with SF_{6} are reported. The lung clearance index (LCI) was calculated as the CEV needed to lower the end-tidal tracer gas concentration to 1/40th of the starting concentration divided by the FRC, i.e., the number of lung volume TO (27). The CEV was corrected for the external dead space (70 ml) in each breath. The mixing ratio was calculated as the ratio between the actual and the ideal number of breaths needed to lower the end-tidal tracer gas concentration to 1/40th of the starting values (27). The ideal number of breaths was calculated from the ratio between the logarithm for the end-tidal SF_{6} at end-washout and the logarithm for the FRC-to-(FRC + alveolar VT) ratio. The alveolar VT was calculated from the average VT during the MBW minus the predicted airway dead space [ = body wt (kg)\times 2\text{ ml}]. For calculation of the slope index (36), the logarithm of the end-tidal SF_{6} concentration was plotted as a function of TO. Two slopes from this curve were calculated, from 10 to 50% (A) and from 50 to 100% (B) of the washout, respectively. The slope index was obtained from the ratio between the slopes (i.e., B/A). So-called moment ratios based on the clearance curve of the inert tracer gas were also used to describe overall ventilation inhomogeneity (27). The first and second moments give more weight to the latter part of the washout curve, which means that the higher these indexes are, the more skewed is the washout curve. This in turn indicates that a greater portion of the lungs is slowly ventilated.

Data Presentation and Statistical Analysis

The individual average values of the directly measured and the calculated parameters from the three recordings in each test situation were used for analysis and presentation. VT, RR, first-breath inspiratory and expiratory flow, FRC, VT/FRC, S_{III} parameters, and the conventional indexes of overall inhomogeneity were tabulated for the six test situations. Two-way ANOVA was used to study the effects of body posture and target VT and a possible interaction effect of these variables on VT, RR, tidal inspiratory and expiratory flow, FRC, and VT/FRC. We used a multiple-regression model with the log-transformed first-breath values of S_{III}(total) and S_{III}(dcdi) as dependent variables and posture, VT/FRC, test subjects, and gas species as independent variables because this model showed the best fit with raw data. No log-transformations were, however, made of the first-breath S_{III}(cd1) values or the first-breath (SF_{6} - He)S_{III} values before a similar multiple-regression analysis was performed with posture, VT/FRC, and test subjects as independent variables. Multiple regression was also used to establish the effects of body posture and VT/FRC on the conventional markers of ventilation inhomogeneity. The obtained regression coefficient (β) and the P values from the regression analyses are given when statistically significant P values were obtained (P < 0.05). The R^2 values reported are adjusted for the degrees of freedom in the calculations. The statistical analyses were performed by use of the Statistica 5.5 (StatSoft, Tulsa, OK).

RESULTS

VT, RR, Tidal Flow, FRC, and VT/FRC

VT were on average close to the target VT with little scatter (Table 1). They were significantly greater supine vs. standing, but this difference was at maximum 29 ml on average only. The RR decreased significantly with larger VT, which was expected, because the test subjects were instructed not to voluntarily control their RR. In the standing posture the mean ± SE first-breath inspiratory flows were 0.43 ± 0.02, 0.49 ± 0.03, and 0.50 ± 0.03 l/s for target VT of 750, 1,000, and 1,250 ml, respectively. Inspiratory flows were significantly greater at a target VT of 1,250 ml vs. 750 ml (P < 0.05). The first-breath expiratory flows were 0.30 ± 0.03, 0.33 ± 0.03, and 0.37 ± 0.03 l/s for target VT of 750, 1,000, and 1,250 ml, respectively. Expiratory flows were significantly greater at a target VT of 1,250 ml vs. 750 ml (P < 0.001) and vs. 1,000 ml (P < 0.05). The first-breath inspiratory and expiratory flows recorded in the supine posture (data not presented) were almost identical to those recorded when standing. FRC decreased significantly by 24% on average when body posture was changed from standing (average 3.96 liters) to supine (average 2.99 liters) (Table 1; P < 0.001). A statistically significant but physiologically insignificant increase of FRC was seen with increased VT in the standing posture (+6%). As expected, the VT/FRC varied significantly with changes in VT and body posture.
Table 1. Breathing pattern parameters, FRC, and VT/FRC in relation to body posture and target VT

<table>
<thead>
<tr>
<th>Target VT</th>
<th>RR, min⁻¹</th>
<th>FRC, ml</th>
<th>VT/FRC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standing</td>
<td>Supine</td>
<td>Standing</td>
</tr>
<tr>
<td>750 ml</td>
<td>12.6 ± 0.8</td>
<td>12.4 ± 0.8</td>
<td>3,850 ± 270</td>
</tr>
<tr>
<td>1,000 ml</td>
<td>10.7 ± 0.7</td>
<td>9.4 ± 0.6</td>
<td>3,942 ± 281</td>
</tr>
<tr>
<td>1,250 ml</td>
<td>9.3 ± 0.6</td>
<td>8.8 ± 0.6</td>
<td>4,073 ± 282</td>
</tr>
</tbody>
</table>

ANOVA effects

<table>
<thead>
<tr>
<th>Posture</th>
<th>Target VT</th>
<th>Posture vs. Target VT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>P &lt; 0.05</td>
<td>P = ns</td>
<td>P = ns</td>
</tr>
</tbody>
</table>

Values are means ± SE. FRC, functional residual capacity; VT, tidal volume; ns, not significant; VT/FRC, VT-to-FRC ratio; RR, respiratory rate. P values from 2-way ANOVA are presented displaying the influence of body position, VT, and the interaction effect of these on the parameters measured.

SnIII vs. Breath Number

Figure 1 presents the group average measured SF₆ SnIII plotted vs. breath number standing and supine for different target VT. For all three target VT, the SnIII values obtained over the initial breaths were higher standing vs. supine. The initial SnIII values from the washouts were lower when larger VT were taken. After the 5th breath, the SnIII values increased more steeply with lung volume turnover in the supine than in the standing posture for all three target VT.

First-breath SnIII Results vs. Body Posture, VT/FRC, and Gas Species

Average results from all first-breath SnIII parameters in relation to body posture and target VT are given in Table 2. In Figs. 2–4, SnIII results are given in relation to VT/FRC for the two body postures. Body posture had a significant effect on the first-breath SnIII(cdi) (P < 0.001), indicating increased (interregional) cdi subjects went supine. The SnIII(dcdi) results were not significantly influenced by a change in body posture, indicating that intraregional inhomogeneities are not influenced by body posture. SnIII(total) was not significantly influenced by posture, but there was a tendency to impaired overall uniformity when supine (β = 0.096; P = 0.054), reflecting the contribution of increased SnIII(cdi). Body posture did not significantly influence (SF₆ – He)SnIII, although the average results obtained in the supine posture were numerically lower than those from the standing posture.

Increased VT/FRC were associated with reduced first-breath SnIII(total) and SnIII(dcdi) (P < 0.001) as well as with lower (SF₆ – He)SnIII (P = 0.031; Table 2). The reduced SnIII(total) and SnIII(dcdi) results indicate improved intraregional uniformity, and the (SF₆ – He)SnIII finding indicates improved intra-acinar uniformity with increased VT/FRC. The resulting $R^2$ value for the latter parameter was, however, low, reflecting the large scatter of these data. The first-breath SnIII(cdi) increased significantly with higher VT/FRC (P < 0.001) when supine. Figure 2 shows that for similar VT/FRC SnIII(cdi) was greater supine vs. standing, and Fig. 3 shows that for similar VT/FRC SnIII(dcdi) was equivalent in the two postures.

The first-breath SnIII(total) and SnIII(dcdi) results were significantly greater for SF₆ than for He (P < 0.001), indicating greater inhomogeneity for the less diffusive tracer gas (SF₆).

Conventional Indexes of Ventilation Inhomogeneity

The multiple-regression analysis showed that posture and VT/FRC did not influence the LCI or the
moment ratios (Table 3). The mixing ratio was, however, significantly reduced in the transition to supine posture, indicating improved uniformity ($P < 0.001$), and larger $V_{T}/FRC$ were associated with significantly greater mixing ratios ($P < 0.001$), indicating impaired uniformity. The slope index tended to decrease in the transition to supine ($\beta = -0.015$; $P = 0.060$), which indicates impaired homogeneity and contrasts to the mixing ratio finding. Larger $V_{T}/FRC$ resulted in significant reductions of the slope index ($P < 0.001$), i.e., impaired uniformity, a finding similar to that with the mixing ratio. On the whole, the statistically significant changes of these markers of ventilation maldistribution were physiologically relatively small.

**DISCUSSION**

**Overview of the Results**

The present study demonstrates that intraregional ventilation inhomogeneity, the largest contributor to overall inhomogeneity during normal tidal breathing, remains unchanged when a subject assumes the supine posture. On the other hand, interregional inhomogeneity increases significantly when the subject goes supine. For a given preinspiratory lung volume (FRC), larger $V_{T}$ result in less intraregional and intra-acinar inhomogeneity in both postures but greater interregional inhomogeneity when supine. Only one of the five conventional markers of overall ventilation inhomogeneity investigated (mixing ratio) was influenced by alterations of body posture, and only two indexes (mixing ratio and slope index) indicated impaired uniformity of ventilation distribution with increased $V_{T}$.

**Theory**

Ventilation distribution is to a large extent determined by the inherent structure of the normal lung in interaction with the pattern of breathing (31). The

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**Table 2. First-breath $S_{nIII}$ results in relation to target $V_{T}$ in standing and supine postures**

<table>
<thead>
<tr>
<th>Target $V_{T}$</th>
<th>1st Breath $S_{nIII}(total)$</th>
<th>1st Breath $S_{nIII}(cdi)$</th>
<th>1st Breath $S_{nIII}(cdi)$</th>
<th>1st Breath $(SF_{6} - He)/S_{nIII}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>750, ml</td>
<td>$SF_{6}$ 70 ± 8 62 ± 9</td>
<td>$SF_{6}$ 68 ± 8 60 ± 9</td>
<td>$SF_{6}$ 1.7 ± 0.3 2.2 ± 0.4</td>
<td>40 ± 12 22 ± 12</td>
</tr>
<tr>
<td>1,000, ml</td>
<td>$He$ 54 ± 7 45 ± 5</td>
<td>$He$ 52 ± 7 43 ± 5</td>
<td>$He$ 1.9 ± 0.3 2.4 ± 0.4</td>
<td>55 ± 3 25 ± 12</td>
</tr>
<tr>
<td>1,250, ml</td>
<td>$SF_{6}$ 54 ± 6 37 ± 5</td>
<td>$SF_{6}$ 53 ± 6 34 ± 5</td>
<td>$SF_{6}$ 1.4 ± 0.4 3.4 ± 0.7</td>
<td>33 ± 11 17 ± 8</td>
</tr>
</tbody>
</table>

Multiple-Regression results

- **Posture**
  - $P = ns$
  - $V_{T}/FRC$
    - $\beta = -4.19; P < 0.001$
    - $\beta = -4.89; P < 0.001$
  - **Gas**
    - $\beta = 0.34; P < 0.001$
    - $\beta = 0.38; P < 0.001$
  - **Adjusted $R^{2}$**
    - 0.81
    - 0.82
    - 0.76
    - 0.23

Values are means ± SE. $S_{nIII}$, normalized phase III slope; cdi, diffusion-convection interaction-dependent inhomogeneity; dci, convection-dependent inhomogeneity; $SF_{6} - He)/S_{nIII}$, sulfur hexafluoride-helium slope difference. $P$ values from a multiple-regression model are given displaying the influences of body posture, $V_{T}/FRC$, and gas species on the parameters measured. The adjusted $R^{2}$ from the regression model is also given. Please note that the $S_{nIII}$ results are given in the unit ($10^{-6}$), i.e. the mean and SE values given have been multiplied by 1,000.
uniformity of ventilation distribution in the human normal lung is also determined by external factors, such as the pleural pressure, the chest wall, the position of the heart, and the intrathoracic blood volume (19). The phase III slope of an inert marker gas results from the volume-averaged influence of all unequally and sequentially ventilated parallel airway regions that contribute to that portion of the exhaled gas volume (18). Approximately 10% of the phase III slope in adult men result from the concentrating effect of gas exchange on insoluble marker gases during exhalation (7). Modeling work and experimental studies by Paiva and Engel and colleagues (20, 30, 34) have revealed the nonuniformity of the geometry of airway branchings and sequentially ventilated parallel airway regions is responsible for most inhomogeneity of gas distribution during normal tidal breathing (12). Because of the asymmetrical structure of the distal airway regions, diffusion-convection interaction processes in the zone of the diffusion-convection front result in peripheral ventilation inhomogeneities that compose the cdi of the phase III slope (18, 30). The location of the diffusion-convection front is the transition between convection- and diffusion-dominated gas transport and is consequently a function of gas diffusivity (17, 31, 43). Unequal ventilation between joined regions proximal to the diffusion-convection front is not influenced by diffusive mixing in the time of a breath. This cdi component has been found to be the lesser contributor to total inhomogeneity during resting breathing (12). The diffusion-convection front for He, a highly diffusive gas, is proposed to occur at the entrance of the acinus during normal breathing (34). For SF6, a six times less diffusive gas, the front is proposed to occur two to three airway generations more distally, i.e., within the acinus (34). Inhomogeneities originating well mouthward of the entrance of the acinus (i.e., cdi) are assumed to be similar for SF6 and He. Consequently, the difference in overall gas mixing of the two tracer gases, i.e., the (SF6 – He) phase III slope, which is caused mainly by dcdi, is an indicator of intra-acinar ventilation inhomogeneity.

Previous reports suggest that gravity-dependent and gravity-independent mechanisms both contribute to the phase III slope, including 1) gravitational cdi, 2) nongravitational cdi, and 3) dcdi (31, 37). Gravitational cdi is that component of cdi that results from the gravity-dependent gradient of pulmonary inflation pressure (31). Nongravitational cdi represents nonuniform ventilation between lung units joined mouthward of the diffusion-convection front and is produced by differences in mechanical properties, which are not affected by altering gravitational force (29, 44).

Methodological Considerations

Several variables were included in the multiple-regression analyses, performed which may not be ideal with respect to the rather low numbers of test subjects (n = 11). Furthermore, the age range among participants was rather large. We could have used only one inert tracer gas in the analyses, thereby reducing the number of variables. When performing the analyses including only one gas species at a time, we obtained very similar results as when both were included. Because the regression analysis showed the same pattern of influences on both gas species when posture and VT were altered, we feel confident about the validity of the

### Table 3. Parameters of overall ventilation distribution in relation to body posture and target VT

<table>
<thead>
<tr>
<th>Target VT</th>
<th>LCI Mixing Ratio</th>
<th>Slope Index</th>
<th>μ1/μ0</th>
<th>μ2/μ0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standing</td>
<td>Supine</td>
<td>Standing</td>
<td>Supine</td>
</tr>
<tr>
<td>750, ml</td>
<td>7.10±0.17</td>
<td>6.95±0.16</td>
<td>1.33±0.04</td>
<td>1.27±0.03</td>
</tr>
<tr>
<td>1,000, ml</td>
<td>7.05±0.15</td>
<td>7.07±0.16</td>
<td>1.38±0.03</td>
<td>1.32±0.03</td>
</tr>
<tr>
<td>1,250, ml</td>
<td>7.05±0.17</td>
<td>7.23±0.18</td>
<td>1.39±0.03</td>
<td>1.38±0.04</td>
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<tr>
<td>Multiple-Regression results</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Posture</td>
<td>P = ns</td>
<td>β = −0.09; P &lt; 0.001</td>
<td>P = ns</td>
<td>P = ns</td>
</tr>
<tr>
<td>VT/FRC</td>
<td>P = ns</td>
<td>β = 0.51; P &lt; 0.001</td>
<td>P = ns</td>
<td>P = ns</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.72</td>
<td>0.71</td>
<td>0.76</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Values are means ± SE. P values from a linear multiple regression model are given displaying the influences of body posture and VT/FRC on the parameters measured. The adjusted R² from the regression model is also given. LCI, lung clearance index; μ1/μ0 and μ2/μ0, ratios between moment 0, 1, and 2, respectively, from the moment analysis. For explanation of the parameters see METHODS.
results. The rather large range in age between the test subjects could lead to an increase in variation of the results. If it is possible to demonstrate significant effects despite these differences in age, then it should be possible to find the same effects in a larger and more homogenous group of test subjects. Actually, large interindividual variations in Vt/FRC between the different test situations could even improve the basis for the multiple-regression analysis. Because of the normal control of breathing, altering one variable such as Vt will necessarily lead to changes in RR. We found that RR decreased from ~12 to 9 breaths/min when the target Vt was increased from 750 to 1,250 ml. The longer duration of the breath with increased Vt is expected to improve diffusive gas mixing in the lung periphery. On the other hand, the higher inspiratory flows with larger breaths are expected to move the diffusion-convection front more distally, resulting in an opposing increase in SnIII(cdi). Physiologically, the alterations in RR and tidal flows observed are, however, rather small and should not significantly influence the effects assumed to be the result of changes in Vt only.

The design of the study could be criticized because we did not assess ventilation distribution using the same preinspiratory lung volume in the two body postures. It would have been possible to control preinspiratory lung volume voluntarily or mechanically, e.g., by applying different airway pressures or using externally controlled breathing valves. We felt, however, that such interventions might affect lung mechanics and ventilation distribution and were therefore not considered.

The SnIII(total), SnIII(ddci), and SnIII(cdi) were determined by using a linear-fit technique (41, 42). These parameters can also be calculated by using the two-exponential curve-fit method previously described by Tsang et al. (38). The latter method takes into account the measured SnIII values from all breaths in the washout, which could be an advantage. On the other hand, there is a risk for bias when using the exponential curve-fit method, e.g., because starting values for the calculations must be given. We have found the linear method to be robust, but it tends to produce lower SnIII(cdi) results than the exponential method does. In the present study, the SnIII(cdi) contribution to SnIII(total) was smaller than previously reported (12), particularly with the lowest target Vt.

**Interregional Ventilation Inhomogeneity: SnIII(cdi)**

Despite the known low contribution of cdi to overall inhomogeneity during normal breathing (12), we were able to demonstrate that cdi becomes significantly greater when the supine posture is assumed and that cdi increased further with larger Vt in the supine posture. The almost identical SnIII(cdi) results for SF6 and He confirm that the cdi values obtained actually resulted from increased inhomogeneities of ventilation distribution between airway regions well mouthward of the diffusion-convection fronts for the two gases. Because cdi constituted <10% of total inhomogeneity, this increase had no significant impact on overall inhomogeneity as measured by the first-breath SnIII(total).

When the supine posture is assumed, the FRC is reduced by ~25%. This is the result of, inter alia, the increased imposition of the diaphragm into the thoracic cavity (26), the weight of the heart on pulmonary structures (26), and the increased sequestration of blood volume within the gravity-dependent thorax (2). On the other hand, the gravity-dependent intrapleural pressure gradient is approximately halved in the supine posture (12, 13), resulting in a decrease of the craniocaudal regional lung volume gradient by 40% (1). The former changes are expected to result in lower regional preinspiratory volumes in the dorsal or dorso-basilar lung spaces as well as slower ventilation of these lung regions (6, 14, 24, 26). Furthermore, the reduced FRC when supine allows the heart to move further into the dorsal thorax, compressing the underlying regions further while causing overlying lung regions to be even more expanded (26). Such interregional differences in preinspiratory lung inflation and sequencing of ventilation will manifest themselves as increased cdi. The reduced pleural pressure gradient is assumed to counteract these effects to some degree. Crawford et al. (10) have previously also demonstrated that nonuniformity due to cdi becomes greater with larger Vt in humans. More recent studies performed in excised lung lobes from dogs did not, however, show an increase in cdi with larger Vt (16). The absence of greater cdi with larger Vt in the dog experiments may seem surprising but could be explained by the obvious differences in extralobar influences and/or the lung perfusion in vivo vs. ex vivo (16).

Studies using the VC SBW method to study ventilation nonuniformity have demonstrated that overall ventilation inhomogeneity is significantly greater supine vs. standing (8, 21, 37). In the study by Grönkvist et al. (21), the effects of a 10-s breath hold on SF6 and He distribution were evaluated in the standing and supine postures. A 10-s postinspiratory breath hold will allow continued diffusion to eliminate most if not all inhomogeneity within and among groups of acini (11, 32, 34). The results from the study by Grönkvist et al. suggested that at least two mechanisms are responsible for the increased inhomogeneity supine vs. standing when VC breaths are taken. The major mechanism is a substantial increase in interregional cdi, and another minor one is a less prominent increase in cdi within and/or between peripherally located lung units (intrapulmonary cdi) (21). Most of the phase III slope generated by the VC SBW test is known to be caused by nonuniformity of ventilation distribution occurring near residual volume and close to total lung capacity, whereas it is not sensitive to nonuniformities occurring around the FRC (15). The results of the VC SBW test thus contrast to those obtained by using the tidal breathing MBW test, which is particularly sensitive to the intraregional inhomogeneities that are the major contributors to overall inhomogeneity during normal
breathing (9, 12). The interregional differences in lung mechanics that occur upon assumption of the supine posture are thus expected to be expressed more distinctly with the VC SBW test than with the MBW test.

Intraregional Ventilation Inhomogeneities: \( \text{Sn}_{\text{III}}(\text{dcdi}) \) and \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \)

We could not demonstrate any significant effect from changes in body posture on ventilation inhomogeneities around or distal to the diffusion-convection fronts for the two gas species.

Both \( \text{Sn}_{\text{III}}(\text{dcdi}) \) and \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) were, however, significantly reduced with larger \( V_T/FRC \), i.e., with larger \( V_T \) for a given preinspiratory lung volume. We feel that the lack of statistically significant reduction in \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) in the supine posture should be regarded with some caution. Numerically the average values were halved, but they showed a larger scatter than the other \( \text{Sn}_{\text{III}} \) parameters.

Gravity has been shown to influence ventilation distribution between well-separated lung regions, i.e., interregional ventilation distribution, via the gravity-dependent intrapleural pressure gradient (3), but an effect of gravity on ventilation distribution within small regions has generally not been considered until the last decade. \( \text{SF}_6 \) and He VC SBW studies in space have shown a reduced \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) phase III slope in microgravity, indicating an effect of gravity on the distribution of ventilation between and/or within adjacent acinar regions (37). Our group did not, however, find any effect of two- or threefold increase of gravity on the \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) phase III slope (22). Evidence for a gravitational effect on gas mixing within small regions was nevertheless found in a MBW study performed on earth and in microgravity, demonstrating reduced \( \text{SF}_6 \), He, and \( \text{N}_2 \)/\( \text{Sn}_{\text{III}} \) as well as reduced \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) in weightlessness (35).

When body posture changes from standing to supine, the intrapleural pressure gradient is decreased, as is the PILV. Whereas the reduced intrapleural pressure gradient is expected to result in improved overall uniformity of ventilation distribution, reduced PILV has been demonstrated to impair overall ventilation uniformity (13, 25) as well as intraregional homogeneity (33). Those findings contrast, however, to the MBW results reported by Crawford et al. (9) obtained in the sitting position. They found that the normalized phase III slopes recorded at a PILV above FRC were greater than those recorded at a PILV equal to or below FRC during breathing with a \( V_T \) of 1 liter. The two latter studies both indicate, however, that increased \( V_T/FRC \) reduces intraregional inhomogeneity. The reduced first-breath \( \text{SF}_6 \) and He \( \text{Sn}_{\text{III}}(\text{dcdi}) \) and the reduced first-breath \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) with larger \( V_T \) in the present study are both in agreement with the results from those earlier studies.

We do not think that the slightly longer breathing cycle with larger \( V_T \) in the normal range can explain the reduced nonuniformities. Instead, we propose that increased \( V_T/FRC \) cause a greater proportion of ventilation to take place in lung regions with a relatively large preinspiratory expansion, e.g., the more ventral aspects of the lungs when supine. This results in less inhomogeneity within small regions in both postures but also in larger interregional inhomogeneities, particularly in the supine posture. As mentioned above, previous \( \text{SF}_6 \) and He VC SBW in the standing and supine postures demonstrated greater overall inhomogeneity supine vs. standing, but the \( (\text{SF}_6 - \text{He})/\text{Sn}_{\text{III}} \) phase III slope (intra-acinar inhomogeneity) did not differ between the postures (21, 37). In an \( \text{SF}_6 \) and He MBW study performed by Prisk et al. (35) on four subjects in microgravity and on Earth, comparisons were also made of \( \text{Sn}_{\text{III}} \) when standing and supine, and no significant changes in intraregional inhomogeneity related to body posture were noted in this study.

Conventional Markers of Ventilation Maldistribution

The ability of the conventional ventilation maldistribution markers to replicate the \( \text{Sn}_{\text{III}} \) changes in uniformity of ventilation with alterations in body posture and \( V_T \) varied markedly. The moment ratios and LCI failed to distinguish any changes. The slope index and the mixing ratio both demonstrated statistically significant impairments of ventilation uniformity with larger \( V_T \) that tended to be greatest in the supine posture, and these indexes paralleled the changes in cdi. In addition, the mixing ratio indicated a statistically significant improvement of ventilation uniformity supine vs. standing. Because the calculation of the mixing ratio is based on the predicted airway dead space for both postures (see METHODS) but the actual airway dead space is reduced when subjects are supine, it follows that the change in the mixing ratio recorded could be an artifact. Because the mixing ratio demonstrated the occurrence of impaired uniformity with larger \( V_T \), this index appears to be sensitive to changes in cdi. The slope index may also be a marker reflecting cdi, which could be expected because this index constitutes the comparison between the efficiency of washout from the most slowly and the best ventilated lung regions (27). On the whole, the changes observed with these markers were small and physiologically insignificant, and the results support the notion by Nye (28) that the conventional markers are rather insensitive to actual changes in uniformity of ventilation distribution. In addition, they convey little information about the mechanisms of altered ventilation distribution.

In conclusion, assuming the supine posture does not significantly alter intraregional inhomogeneity of ventilation distribution but results in increased interregional, convection-dependent, inhomogeneity during normal breathing. Because of the small contribution of interregional to overall inhomogeneity during resting breathing, there is, however, no significant impairment of total inhomogeneity when supine. Relatively small increases in breath size result in improved total and interregional ventilation uniformity both standing and supine but also produce greater interregional ventilation inhomogeneities in the supine posture. \( \text{Sn}_{\text{III}} \)
derived parameters are more sensitive than conventional markers of ventilation maldistribution.

REFERENCES

7. Cormier Y and Be