The prone position results in smaller ventilation defects during bronchoconstriction in asthma

R. Scott Harris, Tilo Winkler, Guido Musch, Marcos F. Vidal Melo, Tobias Schroeder, Nora Tgavalekos, and José G. Venegas

Department of Medicine, Pulmonary and Critical Care Unit, and Anesthesia and Critical Care, Massachusetts General Hospital and Harvard Medical School, and Department of Biomedical Engineering, Boston University, Boston, Massachusetts

Submitted 19 October 2008; accepted in final form 11 May 2009

Harris RS, Winkler T, Musch G, Vidal Melo MF, Schroeder T, Tgavalekos N, Venegas JG. The prone position results in smaller ventilation defects during bronchoconstriction in asthma. J Appl Physiol 107: 266–274, 2009. First published May 14, 2009; doi:10.1152/japplphysiol.91386.2008.—The effect of body posture on regional ventilation during bronchoconstriction is unknown. In five subjects with asthma, we measured spirometry, low-frequency (0.15–0.40 Hz) lung elastance, and resistance and regional ventilation by intravenous 13N-nitrogen isotopes positron emission tomography before and after nebulized methacholine. The subjects were imaged prone on 1 day and supine on another, but on both days the methacholine was delivered while prone. From the residual 13N-nitrogen after washout, ventilation defective areas were defined, and their location, volume, ventilation, and fractional gas content relative to the rest of the lung were calculated. Independent of posture, all subjects developed ventilation defective areas. Although ventilation within these areas was similarly reduced in both postures, their volume was smaller in prone than supine (25 vs. 41%, P < 0.05). The geometric center of the ventilation defective areas was gravitationally dependent relative to that of the lung in both postures. Mean lung fractional gas content was greater in the prone position before methacholine and did not increase as much as in the supine position after methacholine. In the prone position at baseline, areas that became ventilation defects had lower gas content than the rest of the lung. In both positions at baseline, there was a gradient of gas content in the vertical direction. In asthma, the size and location of ventilation defects is affected by body position and likely affected by small differences in lung expansion during bronchoconstriction.

METHODS

Subject characteristics. Five subjects with mild asthma (Table 1) and normal baseline spirometry (Table 2) were studied with protocols and procedures approved by the Human Research Committee of the Massachusetts General Hospital. The subjects were recruited by advertisements posted in the hospital and through general e-mail announcements within the Partners Healthcare System. Subjects were considered eligible if they had been diagnosed with asthma and were over age 18 yr, had not been smoking for the 3 mo before screening, had less than a 10 pack·yr history of smoking in the past, and had not had an upper respiratory infection in the last month before screening. Subjects were questioned to determine whether their asthma met the National Institutes of Health definition for mild to moderate asthma. Subjects were excluded if they were a member of the study staff, had other lung diseases or heart disease, were pregnant, were unresponsive to albuterol, had an absolute contraindication for methacholine (MCh) challenge testing [forced expiratory volume in 1 s (FEV1) < 50% predicted or <1 liter, heart attack or stroke in the last 3 mo, uncontrolled hypertension, or known aortic aneurysm], had been exposed to more than half of the expected radiation dose for the protocol in the past year [375 mrem (milli-Röntgen equivalent in man)], or had taken oral steroids in the past year for their asthma.

Study protocol. The study protocol (Fig. 1) included imaging sessions on two different days, separated by at least 1 wk. If the subject had not had a standard MCh challenge test within the past year, one was conducted in the seated position at least 1 wk before the first session, and the provocative concentration (Provocholine, Methapharm, Coral Springs, FL) that caused a 20% fall in FEV1

10% compared with prone (20), we theorized that, in bronchoconstricted asthmatic subjects, the formation of Vdefs, under the same level of bronchoconstrictive stimulus, should cover a larger volume of the lung in the supine position compared with that in prone.
(PC_{20}) was determined. Asthma medications were stopped before MCh challenge testing and imaging, according to MCh challenge guidelines (6). Subjects with a PC_{20} dose > 8 mg/ml were excluded from the study. On each study day, the subject also had pulmonary function tests in the upright position before any study procedures to verify that the subject was not bronchoconstricted. Subjects were studied in the prone position during the first session and supine on the second, but the inhalation of MCh was always done prone. The subject was positioned to include the largest lung volume within the 10-cm-long field of view of the PET scanner. The imaged lung was estimated to include 75 ± 7% of the whole lung. Lung volume was monitored continuously by impedance plethysmography (SomnoStar PT, SensorMedics, Yorba Linda, CA), and the signal was continuously displayed to the subject on a computer screen. Oscillatory mechanics were measured as previously described (29–31), and the low-frequency (0.15 Hz) resistance and elastance derived. After acquiring the 10-min transmission scan and baseline oscillatory mechanics measurements, the subject was instructed to take two deep breaths. During the exhalation phase of the second breath, the subject was instructed to stop breathing at lung volume equal to the mean lung volume previously estimated from the impedance plethysmographic signal during steady-state breathing. At the start of apnea, a bolus of 13NN-saline (~30 ml) was injected intravenously (5 ml/s), and dynamic acquisition of emission scans was initiated. After 30–40 s of apnea, the subject was instructed to resume breathing while coached to match his or her previous rate and tidal volume, as displayed on the computer screen. Spirometry was performed in the same position as the preceding emission scan using a hand-held portable spirometer (Satellite Spirometer, Jones Medical Instrument, Oak Brook, IL). While the subject was prone with the head turned to the side and arms outside the scanner resting on armrests, five breaths of MCh were administered to the subject at his or her previously determined PC_{20} dose via a DeVilbiss nebulizer and Rosenthal dosimeter (model 646, DeVilbiss Healthcare, Somerset, PA). An identical imaging sequence to that acquired in baseline conditions was repeated starting 5 min after administration of the MCh. On the second day, the subject was positioned supine in the PET scanner between the peak and end of plateau phase of MCh action (4).

**PET imaging.** A PET scanner PC-4096 (Scanditronix AB, Uppsala, Sweden) was used to image 15 contiguous 6.5-mm-thick slices of the thorax. Transmission scans were recorded using a rotating pin source of 68Ge/68Ga. These scans were used to correct the emission scans for energy attenuation caused by body tissues and supporting structures and to demarcate the lung field. To measure regional V, dynamic emission scans were acquired following a bolus injection of 13NN in saline solution at the beginning of a 30-s apnea (18, 25, 32). The scanner was programmed to count coincidence data over set periods of time (frames) as follows: 8 frames of 2.5 s, 16 frames of 5 s, and 4 frames of 30 s each, for a total of 28 frames lasting 3 h 40 min. Because of its low solubility in tissues (partition coefficient of water to air = 0.015 at 37°C), upon arrival into the pulmonary capillaries, virtually all 13NN diffuses into the alveolar air space at first pass, where it accumulates for the remainder of apnea. At that point, the subject begins to breathe, and the regional ventilation per unit of lung gas volume of perfused alveolar units [specific alveolar ventilation (sVA)] was assessed from the 13NN washout rate measured over the following 3 min of breathing, as the tracer was eliminated from a nonatelectatic lung almost exclusively by ventilation (35).

Emission scans were reconstructed by conventional back-projection algorithm and corrected for tissue attenuation and tracer radioactive decay. The lung fields were defined by thresholding the transmission scans and manually removing regions corresponding to main bronchi and large pulmonary vessels. The emission scans were low-pass filtered with edge effect correction to yield an in-plane resolution of 13 mm. Moving average filtering was conducted between contiguous slices in the axial direction to yield equal effective imaging resolution in all axes (13 * 13 * 13 mm).

**Data analysis.** Images to display the topographic distribution of tracer retention before and during bronchoconstriction were generated by PET imaging, and spirometry, the subject was turned to the prone position for inhalation of five breaths of MCh at PC_{20} before returning to the supine position. Laser alignment markers from the PET scanner were used to ensure that the same cross section of thorax was imaged at baseline and after bronchoconstriction. Postbronchoconstriction measurements were acquired 5 min later (Fig. 1) and were finished within 20 min to ensure being done between the peak and end of plateau phase of MCh action (4).
to show the tracer activity remaining in each voxel at the end of the 3-min washout period. Using the tracer retention image taken during bronchoconstriction, a Vdef ROI was defined by selecting a set of voxels containing >20% of the highest tracer concentration on that scan and then manually refining it to only include a contiguous region incorporating a subset of neighboring voxels with elevated residual tracer. The threshold value was a compromise between obtaining a region large enough to reduce the effect of noise and small enough to include only areas of significant tracer retention. Little change in the size of the Vdef regions was seen, with values for thresholding near 20%. Once the Vdef ROI was defined, all voxels outside of this region, but within the lung mask, were considered to be better ventilated areas outside of Vdefs (out). The fraction of Vdef volume was calculated by dividing the number of voxels within the Vdef ROI by the total number of voxels in the imaged lung. Plots comparing upright vs. supine spirometry and baseline spirometry (upright or recumbent) vs. fraction of Vdef volume values were constructed with DeltaGraph 5.6 (Red Rock Software, Salt Lake City, UT), and Pearson correlation coefficients were calculated.

The $sV_{A}$ (alveolar ventilation per unit volume) within Vdefs was calculated from the washout kinetics of the average ROI $^{15}$N concentration and expressed as a fraction of the $sV_{A}$ of the rest of the imaged lung ($V_{Vdefs/out}$). The heterogeneity of the voxel-by-voxel $sV_{A}$ distribution for the imaged lung was characterized by the mean-normalized variance of the tracer washout rate [cov2V_{sV_{A}} = (SD/mean)^2]. Regional fractional gas content ($F_{gas}$), defined as the volume fraction of a lung region filled with gas, was calculated from the transmission scans (10). Because the transmission scan is acquired during tidal breathing, $F_{gas}$ is a regional equivalent of the average expansion of the lung. $F_{gas}$ for the entire imaged lung, the vertical gradient in $F_{gas}$, and the relative $F_{gas}$ of Vdef regions in relation to that of the rest of the lung ($F_{gas/Vdefs/out}$) were also calculated. The average location of all Vdef regions within a lung was calculated as the distance between the geometric center of the imaged lung field ($G_{C_{Lung}}$) and that of the Vdefs ($G_{C_{Vdefs}}$) in the left-to-right, dorsoventral, and caudo-cranial directions (Fig. 2). The deviations between the $G_{C_{Lung}}$ and $G_{C_{Vdefs}}$ were normalized by the corresponding width.
Because of the limited sample size of the study, the nonparametric Wilcoxon matched-pairs test was used to assess significance comparing before and after MCh at a level of \( P < 0.05 \), and analysis was performed using STATISTICA (StatSoft, Tulsa, OK). Data are expressed as means ± SD. Linear regression was performed on plot of \( F_{\text{gas}} \) vs. height using MATLAB (The Mathworks, Natick, MA).

### RESULTS

Consistent with our laboratory’s previous reports (10, 34), MCh-induced bronchoconstriction generated large and contiguous regions of tracer retention in all subjects. The decrease in FEV\(_1\) and forced vital capacity (FVC), and the increase in low-frequency resistance and low-frequency elastance and in the heterogeneity of ventilation (cov\( V_{\dot{V}} \)) caused by inhalation of MCh tended to be slightly greater in the supine than in the prone position, but these differences did not reach statistical significance (Table 3). The reduction in FEV\(_1\)/FVC during bronchoconstriction was greater in the supine position.

In both body positions, Vdef regions were generally, but not always, located in relatively dependent regions of the lung (Fig. 3). The ventral deviations of the GCVdef had opposite sign, but similar absolute value in the two positions (Table 3). In other words, Vdefs deviated from the GCVlung in the gravitational direction by about the same amount in both positions, (i.e., in the supine position they deviated dorsally, and in the prone position ventrally). The average degree of hypoventilation within the Vdefs relative to the rest of the lung after MCh was similar in the two positions (\( V_{\text{Vdef}/out} \sim 0.55 \)), but the volume of the lung covered by Vdefs was significantly greater in supine compared with prone (\( P < 0.05 \)) and was elevated after MCh in both positions, but the increase was lower in the prone than in the supine position (0.04 ± 0.02 vs. 0.1 ± 0.02, \( P < 0.05 \), Fig. 4, top), as was the percent increase in imaged lung volume (7.0 ± 7.9 and 16 ± 6.1%, \( P < 0.05 \)). As a result, average lung \( F_{\text{gas}} \) after MCh was higher in the supine position. Collectively, these results demonstrate that the prone position was associated with smaller Vdefs, a higher baseline global lung volume, and a lower increase in global lung volume after MCh than the supine position, even though MCh was always inhaled prone.

There was excellent correlation between upright FEV\(_1\) or FVC and recumbent values (\( r = 0.97, P < 0.002; r = 0.88, P = 0.002 \), respectively, Fig. 5), but poor correlation between upright FEV\(_1\) or FVC and the size of Vdefs during bronchoconstriction (\( r = 0.29, P = 0.42; r = 0.16, P = 0.67 \), respectively). Plotted recumbent values were consistently less (below identity line) than upright for FEV\(_1\) (mean 640 ± 240 ml) and FVC (mean 1,050 ± 430 ml, Fig. 5). The change in FEV\(_1\) or FVC was not correlated with the change in Vdef volume (\( r = 0.43, P = 0.25 \) and \( r = 0.20, P = 0.60 \), respectively). The vertical gradient of \( F_{\text{gas}} \) was in the gravitational direction for both positions before MCh (0.0083 ± 0.0014/cm prone and 0.0044 ± 0.0015/cm supine), with gas content increasing in the dependent-to-nondependent direction (Fig. 6). After MCh, the vertical gradient did not change significantly in the prone position (0.0066 ± 0.0010/cm), but did so in the supine position.

### Table 3. Results

<table>
<thead>
<tr>
<th>Posture During Imaging</th>
<th>Supine</th>
<th>Prone</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV(_1), % change</td>
<td>-32±18</td>
<td>-27±13</td>
</tr>
<tr>
<td>FVC, % change</td>
<td>-21±19</td>
<td>-17±18</td>
</tr>
<tr>
<td>FEV(_1)/FVC, % change</td>
<td>-14±4.4</td>
<td>-4.6±11*</td>
</tr>
<tr>
<td>R(_{low}), % change</td>
<td>243±192</td>
<td>193±83</td>
</tr>
<tr>
<td>E(_{low}), % change</td>
<td>84±67</td>
<td>62±42</td>
</tr>
<tr>
<td>covV, % change</td>
<td>70±116</td>
<td>59±42</td>
</tr>
<tr>
<td>Ventral deviation of Vdef</td>
<td>-0.12±0.07</td>
<td>0.14±0.10*</td>
</tr>
<tr>
<td>Rightward deviation of Vdef</td>
<td>-0.02±0.10</td>
<td>0.15±0.18</td>
</tr>
<tr>
<td>Basal deviation of Vdef</td>
<td>0.24±1.19</td>
<td>0.08±2.72</td>
</tr>
<tr>
<td>V(_{\text{Vdef}/out}) (Control)</td>
<td>1.15±0.24</td>
<td>0.96±0.18*</td>
</tr>
<tr>
<td>V(_{\text{Vdef}/out}) (MCh)</td>
<td>0.56±0.17</td>
<td>0.55±0.11</td>
</tr>
<tr>
<td>Vertical gradient ( F_{\text{gas}} ), % change</td>
<td>-110±13</td>
<td>-18±19*</td>
</tr>
<tr>
<td>Vdef volume/imaged lung volume</td>
<td>0.41±0.21</td>
<td>0.25±0.14*</td>
</tr>
</tbody>
</table>

Values are means ± SD. R\(_{low}\), low-frequency resistance; E\(_{low}\), low-frequency elastance; covV, coefficient of variation of specific ventilation; devia- tion, fraction of total \( x\), \( y\), or \( z\)-dimension with positive assigned to ventral, right, and caudal directions; Vdef, ventilation defect; V\(_{\text{Vdef}/out}\), specific ventilation inside Vdef vs. outside; \( F_{\text{gas}} \), fractional gas content. %Change refers to the change from baseline to post-methacholine. *\( P < 0.05 \) compared with supine.
In the prone position, the F_{gas,Vdef/out} before MCh was lower than 1 ($P < 0.05$, Fig. 4, bottom), indicating that, at baseline, areas that were to become Vdefs after MCh were less expanded than those that did not. This systematic behavior was not present in the supine position. However, $F_{gas,Vdef/out}$ increased after MCh in all subjects supine, and in all but one subject prone became greater than unity ($P < 0.0005$, Fig. 4, bottom), indicating that MCh-induced bronchoconstriction was associated with relative overexpansion of Vdef regions with respect to the rest of the lung. In contrast, the relative ventilation of Vdefs with respect to the rest of the lung ($V_{Vdef/out}$) was not systematically different from unity at baseline in either body position.

DISCUSSION

The main result of this study is that, compared with the prone position, the supine position resulted in equally hypoventilated, but larger, ventilation defective regions during bronchoconstriction with MCh. Given that all subjects inhaled MCh in the prone position, these findings suggest that factors other than agonist distribution favored the formation of larger Vdefs in the supine position. One obvious candidate is gravitational effects on regional lung volume, where reduced lung expansion, particularly of dependent areas, decreased lung parenchymal tethering forces on airways, making them smaller and more prone to severe constriction as smooth muscle tone increased.

Before discussing these findings, experimental and methodological limitations of the study should be acknowledged. General experimental limitations of our PET imaging technique have been discussed in previous reports (10, 17, 25, 35). We decided not to randomize the initial body position to minimize the chance of incomplete studies where, having completed a first imaging session, the subject would withdraw...
before or during the second session. Given the ~2-h duration of the study and because lying prone in the scanner was less comfortable than lying supine, we reasoned that, if a subject were able to complete the prone session, he or she would be more likely to complete the supine session. This proved correct, and all subjects who completed the first session went on to complete the second one. It could be argued the lack of randomization in the order of body position may have intro-
duced systematic bias in the study. However, the studies were conducted at least 1 wk apart, minimizing carryover effects, and we found no systematic differences in lung function between the two imaging sessions at baseline (Table 2). One could argue that differences in response could be due to changes in baseline lung volume on the 2 imaging days. We could find no relationship between the upright FEV₁ or FVC and the resulting Vdef size, despite excellent correlations between upright and recumbent spirometric values (Fig. 5).

What then predisposes a region to become a Vdef? Our laboratory has previously published a lung model of airway constriction that includes both long-range (through redistribution of tidal volume) and short-range (through airflow wall stretch by transmural pressure and local parenchymal tethering) feedback mechanisms in an integrative, computational model (34). This model showed that, at low levels of smooth muscle activation, these interactions are self-limiting, and the distribution of ventilation is fairly uniform. However, as smooth muscle activation is higher than a critical level, any small perturbation can trigger a positive feedback that propagates up and down the airway tree, resulting in the formation of large Vdefs. Thus, even minor differences in airway properties (e.g., airway wall thickness, smooth muscle contractile strength, mucus, or reduced parenchymal tethering forces) can be enough to trigger Vdefs in such an airway tree. The model also demonstrated that decreasing end-expiratory lung volume can trigger the formation of Vdefs at lower levels of smooth muscle activation or increase their size, if Vdefs are already present (36). In the present study, we postulate that one of such “small perturbations” could have been the heterogeneity in regional lung volume in the gravitational direction, predisposing Vdef formation in more dependent locations. This is also consistent with the reduced levels of regional lung volume (Fgas,Vdef/out) seen at baseline in the prone position, suggesting that locally reduced lung volume predisposed areas to become Vdefs during bronchoconstriction (Fig. 4). Although, in the supine position at baseline (Fgas,Vdef/out) was not always <1 (i.e., regions that became Vdefs were not necessarily less expanded than the rest of the lung), this does not negate the above hypothesis, because, in this condition, MCh was inhaled by the subjects prone, a position different than that during imaging: the supine Fgas,Vdef/out at baseline did not assess the relative degree of lung expansion that the lung had during exposure to MCh. As a result, Vdefs could have formed before the subject had turned back to the supine position. After reanalyzing the data from 11 subjects previously studied who where imaged and received MCh in the supine position (10), we found that 9 of the 11 subjects had a Fgas,Vdef/out < 1 at baseline, a result consistent with the current findings in the prone position.

In a previous study of MCh-induced bronchoconstricted sheep (33), we reported that the relative ventilation distribution, and thus the deposition of MCh, could have been associated with Vdef formation. Areas that were to become Vdefs had higher ventilation relative to areas outside before administration of the MCh. This is not the case in the present study, since the areas that became Vdefs in the prone position were not statistically more ventilated than the rest of the imaged lung (Vmax/Vdef/out at baseline = 0.96, Table 1). Although Vmax/Vdef/out at baseline was greater than unity in the supine position, we do not have ventilation data in the position that the MCh was delivered. From the data in the present study, it appears that the distribution of lung volume, and not the distribution of ventilation, could be the important determinant of Vdef formation. The extent to which regional lung volume could be related to regional ventilation per unit volume could explain our previous finding in the sheep.

Our study showed, in both body positions, a systematic tendency of Vdefs to occur in dependent regions of the lung despite that MCh was inhaled prone in both cases. This supports the notion that the posture one assumes during bronchial challenge may not be as important as that assumed after exposure in the pattern of the resulting bronchoconstriction (16). However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. Despite not controlling other factors that may influence heterogeneous deposition, such as inhalation rate, we still found a systematic dependent location of Vdefs. Gravitational effects on regional lung volume could have also created localized reduction in parenchymal tethering forces on the airways. It is well known that gravitational forces on lung parenchyma and chest wall are responsible for a gradient of lung volume decreasing from nondependent to dependent zones (19, 26). The larger size of the Vdefs observed in supine compared with prone is consistent with this hypothesis, since the gradient in regional lung volume of the prone position was greater than that in the supine position, and the value of Fgas in the most dependent parts of the lung for both positions was nearly the same before MCh (−0.60−0.65, Fig. 6). The larger overall lung volume prone would tend to increase outward tethering forces on airways and limit the size of Vdefs for a given amount of airway smooth muscle constriction. This is consistent with prior data obtained without imaging, demonstrating that airway hyperresponsiveness is inversely related to lung volume (7). In addition to the larger overall lung volume at baseline in the prone position compared with supine, another possible reason for the smaller size of Vdefs could have been the smaller fraction of the lung in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. Despite not controlling other factors that may influence heterogeneous deposition, such as inhalation rate, we still found a systematic dependent location of Vdefs. Gravitational effects on regional lung volume could have also created localized reduction in parenchymal tethering forces on the airways. It is well known that gravitational forces on lung parenchyma and chest wall are responsible for a gradient of lung volume decreasing from nondependent to dependent zones (19, 26). The larger size of the Vdefs observed in supine compared with prone is consistent with this hypothesis, since the gradient in regional lung volume of the prone position was greater than that in the supine position, and the value of Fgas in the most dependent parts of the lung for both positions was nearly the same before MCh (−0.60−0.65, Fig. 6). The larger overall lung volume prone would tend to increase outward tethering forces on airways and limit the size of Vdefs for a given amount of airway smooth muscle constriction. This is consistent with prior data obtained without imaging, demonstrating that airway hyperresponsiveness is inversely related to lung volume (7). In addition to the larger overall lung volume at baseline in the prone position compared with supine, another possible reason for the smaller size of Vdefs could have been the smaller fraction of the lung in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position.

Our study showed, in both body positions, a systematic tendency of Vdefs to occur in dependent regions of the lung despite that MCh was inhaled prone in both cases. This supports the notion that the posture one assumes during bronchial challenge may not be as important as that assumed after exposure in the pattern of the resulting bronchoconstriction (16). However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position. However, because regions of Vdefs not only formed in dependent zones (Fig. 3), it suggests that the trigger for Vdef formation could be multifactorial. One factor that could influence the location of Vdefs is heterogeneous deposition of agonist. We attempted to minimize this factor by inhaling the MCh in the same body position.
reported in our laboratory’s previous study (10). What is thus notable is that, despite a greater increase in the lung volume in response to MCh of subjects in the supine position, the fraction of lung occupied by Vdefs was still larger in the supine position. Thus, if the increase in lung volume in response to MCh was a protective response to an increase in residual volume, the increase in lung volume undergone by the subjects supine was not enough to reduce the size of the Vdefs. In addition to the overall increase in lung volume, we also found a relative increase in regional lung volume of the ventilation defective regions by bronchoconstriction (Fgas,Vdef/fout increased in all supine and all but one prone). As our laboratory previously observed (10), this relative increase in Fgas in Vdefs compared with the rest of the lung may be due both to a relative reduction in local blood volume or to dynamic hyperinflation of these regions.

There are several potential clinical implications of these findings. First, patients who are mechanically ventilated with asthma could benefit from the prone position. Second, it is known that the supine position results in greater bronchial hyperresponsiveness compared with the erect position (28), and many patients with asthma often exhibit increased symptoms at night (14). Our data showing reduced lung volume at baseline and larger Vdefs supine compared with prone during bronchoconstriction for the same dose of MCh could be consistent with those findings. Indeed, studies using nocturnal continuous positive airway pressure in asthma have shown improved nocturnal asthma symptoms (5) and quality of life (15).

In conclusion, independent of body position, bronchoconstriction with MCh resulted in ventilation defective areas that tended to be located in gravitationally dependent regions of the lung with the prone position, resulting in smaller Vdefs than those of the supine position. These findings could have important implications for mechanically ventilated patients with asthma or for preventing, or reducing, nighttime asthma symptoms.

ACKNOWLEDGMENTS

The authors thank S. A. Barrow and S. B. Weise for technical assistance with image acquisition and processing; Dr. R. J. Callahan and A. Bruce for the development of the radioisotope; and Dr. J. A. Correa, W. M. Buzelwicz, and D. F. Lee for preparation of the radioisotope.

GRANTS

This study was supported in part by National Heart, Lung, and Blood Institute Grants HL-068011 and HL-086717.

REFERENCES


