Regional distribution of ventilation at residual volume in induced bronchospasm

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DEL AUNOIS, L., R. BOILEAU, J. DIODATTI, J. GAUTHIER, AND R. R. MARTIN. Regional distribution of ventilation at residual volume in induced bronchospasm. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 53(2): 361–366, 1982.—The regional distribution of a bolus of gas inhaled at residual volume (RV) is attributed to regional airway closure and is responsible for the phase IV of the single-breath washout during the following deflation. As bronchospasm increases the range of airway opening pressures through the lung, the regional distribution of the bolus could change with effects on the shape of the single-breath washout. We investigated the regional distribution of boluses inhaled at RV and their single-breath washouts during methacholine-induced bronchospasm in prone dogs. With increasing total lung resistance (RL) we first observed in five out of eight animals a preferential “redistribution” of the bolus to the upper caudal regions of the lung, which could be partially attributed to the increased lung volume at RV. When maximal RL was attained, the bolus was evenly distributed through all regions of the lung in these animals with disappearance of phase IV and increased slope of phase III, and a final decrease of tracer concentration at low lung volumes was observed. We conclude from these data that increased bronchomotor tone in dogs results in a less homogeneous intraregional distribution of the bolus with increased slope of phase III and in a more even interregional distribution leading to disappearance of phase IV. In severe bronchospasm the downward slope at low lung volume suggests intraregional closed lung units emptying through collateral pathways into still open neighboring units.

SINCE ITS FIRST DESCRIPTION by Milic-Emili et al. (15), the distribution of a bolus of gas inhaled at residual volume (RV) to the nondependent zones of the human lung has been attributed to airway closure in the dependent zones. This regional concentration gradient causes the phase IV of the single-breath washout (5). Induced bronchospasm in human subjects increases the range of opening pressures, renders uniform the distribution of the bolus, and decreases the size of the phase IV (8).

However, in the dog in the prone position at RV, the regional volume is evenly distributed and all airways are closed (2). Nevertheless, a bolus injected at RV is mostly distributed to the ventral cephalic and the dorsal caudal zones of the lung (1), probably due to changes in local transpulmonary pressure due to regional chest wall mechanics. We therefore investigated the regional distribution of a bolus injected at RV in prone dogs during induced bronchospasm and its consequences on the single-breath washout and phase IV.

METHODS

Eight mongrel dogs (mean wt 20 kg) were anesthetized with chloralose (25 mg/kg) and urethan (75 mg/kg) and paralyzed with succinylcholine chloride (2 mg/kg). The animals, intubated and placed in prone position in a constant-pressure body plethysmograph, were ventilated via a Harvard Pump. Functional residual capacity (FRC) was measured according to Boyle’s law before and after periods of paralysis induced by succinylcholine.

Total lung capacity (TLC) was defined as the lung volume at 30 cmH2O transpulmonary pressure (PL), and RV as the lung volume when ~30 cmH2O pressure was applied at the airway opening.

Airway opening pressure was measured at the endotracheal tube outlet by a Validyne MP 45-2 transducer, and esophageal pressure was measured with a similar transducer from a balloon (5 cm length, 0.5 ml air content) in the lower third of the esophagus. Electric subtraction gave PL. PL was recorded as a function of volume on an XYY recorder for quasi-static pressure-volume (PV) curves during slow inflation and deflation maneuvers (flow ≈ 150 ml/s). Maximal opening pressure (Pao,max), defined as the point on the inflation PV curve where all airways are open, was assumed to be the pressure at which the inflation PV curve takes on the exponential form (11). Minimal opening pressure (Pao,min) was defined as the point on the inflation PV curve where the initial volume change with increasing pressure was observed.

The total lung resistance (RL) was measured by the oscillation technique: for a frequency of 4 Hz a linear relationship between flow and pressure was obtained on an XY scope by subtracting or adding to PL an electrical signal proportional to the volume signal (6). Expired Xenon-133 (133Xe) concentration was monitored at the endotracheal tube outlet and recorded as a function of volume on the XYY recorder for single-breath washout measurement. Each curve was standardized according to its surface area and the slope of phase III expressed as percent change of 133Xe concentration per liter of volume.

Eight collimated scintillation counters were placed laterally, four in the cephalic and four in the caudal zones, for regional volume- and ventilation-distribution measurements. Regional counts were measured at TLC after...
inhaling of a $^{133}$Xe bolus at RV, the washout being recorded during the following slow deflation to RV. Ventilation per alveolus ($V_A$) was computed for each counterfield using the following equation

$$V_A = \frac{CR_{(\text{bolus})} \times \Sigma CR_{(\text{eq})}}{CR_{(\text{eq})} \times \Sigma CR_{(\text{bolus})}}$$

where $CR_{(\text{bolus})}$ is the regional count rate at TLC after inhalation of the bolus, $CR_{(\text{eq})}$ is the corresponding regional count rate after equilibration (background counts being subtracted) and $\Sigma$ denotes the sum of respective counts (eq or bolus) from all the counters. The ventilation index would be 1 in all regions if the distribution of the bolus were uniform.

On the single-breath $^{133}$Xe-washout curve, the lung volume at the onset of phase IV was measured and expressed as percent of the vital capacity (VC). The closing capacity (CC) is the sum of that volume and RV, expressed as percent of the TLC (CC/TLC).

The dogs were then reinflated to TLC with room air, and residual counts were measured for calculation of the RV/TLC ratio, with correction for dead space on the basis of bolus distribution.

Methacholine chloride was aerosolized for 2 min with concentrations increasing from 0.75 to 100 mg/ml. Measurements of $R_L$, quasi-static PV curves, bolus distribution, and regional volumes were performed 2 min after each concentration, and the challenge was stopped when $R_L$ did not increase with increasing methacholine dose.

**RESULTS**

In all dogs, $R_L$ increased progressively to a plateau while methacholine aerosol concentration was increased (mean control $R_L$ 2.9, range 2–4, maximal mean $R_L$ 8.8, range 5–16 cmH$_2$O.l$^{-1}$.s$^{-1}$).

In four dogs, we were able to obtain FRC measurements when maximal resistance was attained. The following pattern of lung volume changes was observed: an insignificant change of TLC (98% of control TLC), a small increase of FRC (from 48 to 55% of control TLC), but a large increase of RV (13 to 28% of control TLC).

In five out of eight dogs, the increase of $R_L$ was accompanied by a redistribution of regional ventilation. An example (dog 4) is shown in Fig. 1 where cephalic and caudal ventilation indices are plotted against $R_L$. It is obvious that a small increase in $R_L$ is associated with a more uniform distribution of the bolus in the cephalic zones and a more uneven distribution in the caudal zones [see Fig. 1: cephalic indices (top panel) ranging from 0.5 to 2 in control conditions and from 0.7 to 1.2 in period $R_1$ (more uniform distribution); caudal indices (middle panel) ranging from 0.4 to 1.4 in control conditions and from 0.5 to 1.8 in period $R_2$ (more uneven distribution)].

We called this period $R_1$ when the ventilation indices of the cephalic counters were rendered more uniform while no tendency for uniformity had yet been recorded in the caudal zones.

However, at maximal $R_L$, nearly even bolus distribution is achieved both in caudal and cephalic zones. We called this period $R_2$. The single-breath $^{133}$Xe-washout curves for the three periods (control, $R_1$, and $R_2$) are shown on the lower panel. With increasing resistance, the phase IV disappears, the slope of the phase III becomes steeper, and a downward slope appears at the end of the phase III.

The five dogs that behaved similarly were labeled "responsive," the three others "unresponsive." The re-
gional ventilation indices (computed per alveolus) of the five responsive dogs are shown on Fig. 2. The upper panel shows the typical distribution in a prone dog, with higher values for the lower cephalic and the upper caudal zones. In period R₁, ventilation indices decrease in dependent zones (D and H) [zone D from 1.7 ± 0.28 (SE) to 1.25 ± 0.18, zone H from 0.75 ± 0.1 to 0.55 ± 0.05] and increase in upper cephalic (E and F) [zone E from 1.45 ± 0.05 to 1.55 ± 0.1, zone F from 1.1 ± 0.15 to 1.3 ± 0.05]. In period R₂, ventilation indices are nearly even in all zones (lower panel: all indices are nearly 1).

The mean ventilation indices for four representative zones of the lung (upper caudal, upper cephalic, lower caudal, lower cephalic) are shown for the five responsive dogs in Table 1. Each zone contains two scintillation counters, and each value is the mean of the indices of the two counters. In control, lower cephalic and upper caudal zones have the highest indices (1.26). In period R₂, all regions have nearly the same index. Even though indices became uniform, mean CC/TLC increases from 24 to 36%. Despite this fact, the onset of phase IV expressed as percent of VC decreases in period R₁ and disappears in four dogs in period R₂.

From control to period R₂, mean RL increases from 3.02 to 9.3 cmH₂O·l⁻¹·s⁻¹ and the slope of phase III (expressed as the percent increase of ¹³³Xe concentration per liter of expired volume) becomes steeper. (Each bolus was standardized according to the surface underneath the single-breath washout curve.) Both Pao₅max and Pao₅min increase.

The results for the three unresponsive dogs are shown on Table 2. The ventilation distribution remains unchanged at three levels of RL corresponding to those of the three periods of responsive animals. The CC/TLC ratio increases, but the phase IV does not disappear despite a large increase in resistance (from 2.9 to 7.99 cmH₂O·l⁻¹·s⁻¹), in slope of phase III, and in both opening pressures.

Changes of regional RV are shown in Fig. 3. For all the dogs, although there is a progressive increase of RV/TLC ratio in all regions, the relative interregional homogeneity of volume at RV is little changed between the control and phase R₂ (from nearly 20 to nearly 30% TLC). A transient increase of regional RV in the lower caudal zone is noted at R₁.

During bronchospasm, with the disappearance of phase IV, a downward slope of the ¹³³Xe-washout curves is found at low lung volume. An example for dog 1 is

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**TABLE 1. Evolution of all parameters for five responsive dogs in three periods**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ce</td>
<td>Ca</td>
<td>Ce</td>
</tr>
<tr>
<td>Upper</td>
<td>0.73</td>
<td>1.26</td>
<td>0.99</td>
</tr>
<tr>
<td>Lower</td>
<td>1.26</td>
<td>0.75</td>
<td>1.08</td>
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<tr>
<td>CC/TLC, %</td>
<td>24</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Onset phase IV, %VC</td>
<td>12</td>
<td>6.5</td>
<td>0.4</td>
</tr>
<tr>
<td>RL, cmH₂O·l⁻¹·s⁻¹</td>
<td>3.02</td>
<td>4.85</td>
<td>9.3</td>
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<tr>
<td>Phase III, %/l</td>
<td>6</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>Pa₅max, cmH₂O</td>
<td>5.5</td>
<td>10.3</td>
<td>9.8</td>
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<tr>
<td>Pa₅min, cmH₂O</td>
<td>-6</td>
<td>0.2</td>
<td>5.2</td>
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</tbody>
</table>

(See Table 1 for abbreviations.)

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**TABLE 2. Evolution of all parameters for three unresponsive dogs in three periods**

<table>
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<th>Control</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ce</td>
<td>Ca</td>
<td>Ce</td>
</tr>
<tr>
<td>Upper</td>
<td>0.62</td>
<td>1.60</td>
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</tr>
<tr>
<td>Lower</td>
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<td>35</td>
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<tr>
<td>Onset phase IV, %VC</td>
<td>8</td>
<td>5</td>
<td>5</td>
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<tr>
<td>RL, cmH₂O·l⁻¹·s⁻¹</td>
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<td>7.99</td>
</tr>
<tr>
<td>Phase III, %/l</td>
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<td>32</td>
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<tr>
<td>Pa₅max, cmH₂O</td>
<td>8</td>
<td>11.3</td>
<td>14.3</td>
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<tr>
<td>Pa₅min, cmH₂O</td>
<td>-8</td>
<td>-3</td>
<td>4</td>
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</tbody>
</table>

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**FIG. 2.** Distribution of bolus at residual volume for our 5 responsive animals for the 3 periods. On vertical ordinate from top to bottom are cephalic zones A-D, on right ordinate are caudal zones E-H. On abscissa are ventilation indices. Ventilation index would be 1 in every region if bolus distribution were perfectly uniform.
presented in Fig. 4. The control \(^{133}\)Xe-washout curve has a normal configuration, whereas the one obtained during maximal bronchospasm shows a sharp rising of phase III followed by a downward slope instead of the normally occurring upward phase IV. This pattern was observed qualitatively in every responsive dog.

DISCUSSION

The fact that a bolus of \(^{133}\)Xe injected at RV is mostly distributed into the nondependent regions of human lung was first described by Milic-Emili and co-workers (12, 15), who proposed that airways were closed in the dependent zones at RV. This vertical gradient of bolus distribution was assumed to be the cause of the phase IV of the single-breath washout (5).

Airway closure at RV was proven later by Engel et al. (7). They injected a bolus of \(^{133}\)Xe at RV in breath-holding subjects after rapid equilibration with \(\text{N}_2\text{O}\); \(\text{N}_2\text{O}\) absorption by blood was expected to aspirate the bolus toward lung units with open airways. As the bolus was mostly distributed to the upper zones of the lung, they concluded that most of the airways were closed at RV in the lower zones of the lung.

Methacholine, a cholinergic drug known to increase the opening pressure of airways (16), was used by Engel et al. (8) to increase the range of opening pressure in humans; in such a case they observed a more even distribution of a \(^{133}\)Xe bolus given at RV and of regional RV and a decrease in the size of phase IV (8).

But the dog is a quite different model from the upright human: in a prone dog, a \(^{133}\)Xe bolus injected at RV is mostly distributed to the lower cephalic and the upper caudal zones probably because of differences in regional chest wall compliance (1), and the regional volume at RV is nearly evenly distributed through the lung. Using the same \(\text{N}_2\text{O}\) technique of Engel et al. (7), Amyot et al. (2) were unable to demonstrate bolus movement into the lung and concluded that all airways are closed at RV in
DISTRIBUTION OF A BOLUS AT RV DURING BRONCHOSPASM

Dogs. After three vital capacities of 80% N₂O-20% O₂ had been given, anesthetized, paralyzed, and intubated animals were aspirated to RV (-30 cmH₂O mouth pressure) and put in free communication with a N₂O-O₂-containing circuit where the pressure was also -30 cmH₂O. A 1-mCi bolus of ¹³³Xe was placed in the orifice of the endotracheal tube. With the N₂O of the alveolar air being absorbed into the bloodstream continuously, if some airways had been opened at RV: 1) lung volume would have remained the same; 2) airway opening and pleural pressures would have remained the same; and 3) ¹³³Xe would have been carried into the open alveoli by the flux of N₂O. But they observed that while the animals were kept at RV: 1) lung volume decreased; 2) mouth pressure remained the same but pleural pressure became more negative, confirming the diminution of lung volume; and 3) ¹³³Xe inserted at the airway orifice stayed there, and no radioactivity appeared in the different regions of the lung.

They concluded that all the airways were closed at RV in dogs. Further, using the classic method of Milic-Emili et al. (15), they measured the regional lung volume in seven dogs and found neither a vertical nor a cephalo-caudal gradient of regional volume of RV. Their results are corroborated by ours (see Fig. 3). It then follows that the phase IV observed during single-breath N₂ washouts should be due to unequal distribution of the dead space N₂. They verified this hypothesis by flushing the common endotracheal tube. With the N₂O of the alveolar air being absorbed into the bloodstream continuously, if some airways had been opened at RV: 1) lung volume would have remained the same; 2) airway opening and pleural pressures would have remained the same; and 3) ¹³³Xe would have been carried into the open alveoli by the flux of N₂O. But they observed that while the animals were kept at RV: 1) lung volume decreased; 2) mouth pressure remained the same but pleural pressure became more negative, confirming the diminution of lung volume; and 3) ¹³³Xe inserted at the airway orifice stayed there, and no radioactivity appeared in the different regions of the lung.

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Knowing that all airways were closed at RV, and that at RV there is no vertical or cephalo-caudal gradient of regional distension, they used boluses of radioactive ¹³³Xe to define the distribution of ventilation in the prone position, the distribution of airway opening pressure, the influence of the abdominal content on these two, and the difference as well as the similarity that might exist between the prone and the supine positions.

In the prone position, contrary to what would be predicted based on the human data, the region receiving the most ¹³³Xe is a dependent one, the ventral cephalic region. Progressively less goes to the dorsal caudal region, the dorsal cephalic region, and finally least to the ventral caudal region. This is corroborated by our results as can be seen in Fig. 2, top panel.

The action of methacholine on dog airways has been previously described: increased RV, increased airway closure and opening pressure, and obvious spasm of all bronchi examined (16). The increase of RL and RV we observed is in full agreement with these studies. The variation in RL responses we saw from one animal to another was described previously (16).

The increase of RL induced a more even distribution of the bolus in five of our dogs. Normal interregional distribution of a bolus injected at RV is related to differing opening pressures of the airways. If bronchospasm increased the range of opening pressure of the airways intraregionally, it is possible that airways with low Pao, in regions where previously the bolus was not preferentially distributed, could open before airways with a high Pao in previously favored regions, and the bolus would be more evenly distributed. Then the enlarged interregional inhomogeneity would cause a more even interregional distribution.

The uniform distribution of the bolus during bronchospasm might have been due to the increased RV. Amyot et al. (1) showed that the nonuniform distribution of a bolus inhaled at RV could be changed into a uniform distribution if the bolus was inhaled at 52% TLC. At an intermediary level (30% TLC), the bolus was mostly distributed to the upper caudal zones of the lung. In our experiments, RV increased approximately to 28% TLC, and the distribution observed at period R₁ could be partially due to increased lung volume at RV. However, the uniform distribution of period R₂ cannot be explained by the increased RV, as no further increase of CC/TLC was recorded between periods R₁ and R₂, despite changes in regional distribution and phase IV: another mechanism such as increased range of Pao must be involved.

The disappearance of phase IV shows that phase IV in dogs is related to interregional distribution of the tracer gas. The increase of the slope of phase III might be due to interregional uneven distribution, as interregional distribution is even. Engel et al. (9) have shown a slope of phase III of N₂ plateau in very small units and estimated it to be 52% of total phase III at the mouth, corroborating that inhomogeneity still exists in small segments.

Some dogs did not show uniformity of ventilation indices, despite a large increase of Pao, slope of phase III, and RL. The reason is unclear but could be explained by regional differences in methacholine responsiveness, very large local differences in chest wall compliance that could not be overcome by changes in Pao distribution, or a homogeneous increase in intraregional Pao such that interregional differences would remain the same.

There is another possibility: differences in preferential distribution of the bolus can be seen in the control measurements (Table 1 and 2) of the two groups and could be due to differing chest wall mechanics, which could explain the different behavior: the responsive dogs have two privileged zones (lower cephalic and upper caudal in Table 1), and the spread in ventilation indices ranges only from 0.73 to 1.26. Unresponsive dogs have only one privileged zone of regional distribution of the bolus (upper caudal in Table 2). The differences between its index (1.6) and those of the other zones (0.62, 0.79, and 0.99, respectively) are so large that the relatively small differences in regional distribution of the bolus cannot make them more uniform.

We conclude then that in the unresponsive dogs differences in regional chest wall compliance may have been too large to allow their regional ventilation to become uniform during bronchospasm, and this nonuniformity is reflected by the fact that phase IV did not disappear in these animals.

Another point of interest is the appearance of a downward slope of the ¹³³Xe-washout curve at low lung volume during maximal bronchospasm. This slope was recently described in emphysematous patients by some authors (4, 10) and was attributed to a first-in-first-out mechanism. In our conditions of even regional distribution of the bolus, this downward slope must be attributed to intraregional distribution. One possible mechanism
would be the late emptying of lung units with constricted bronchi: these lung units could open later but also close later on account of an increased stability due to their smooth muscle contraction (18, 21). If the shortening of the smooth muscle were complete and insufficient to occlude the lumen with mucus, mucosa, and submucosa, there should be no further tendency for the muscle to produce narrowing, but the ratio of wall thickness to internal diameter would be increased and lead to an increased resistance to collapsing forces (13, 21). As bronchoconstriction by itself is able to close the airways (19, 20), particularly with methacholine induction (16), this explanation seems unlikely.

This phenomenon is perhaps better explained by the following model: some units have a high opening pressure and must open late. They are then “xenon poor.” As they close prematurely at high lung volume, they empty via collateral ventilation into still open zones that have a lower closing pressure. It has been proved that collateral ventilation is very effective in dogs (3) and is increased by inflation to TLC and slow deflation (17). As the time constant of collateral ventilation is short at high lung volumes and as collateral ventilation seems to be interrupted only below 3 cmH2O Pt (22), the closure of airways occurring at higher Pt should favor the emptying of these xenon-poor units through still open ones.

But premature airway closure and subsequent ventilation to collateral channels is only one possible mechanism. Bronchoconstriction can occur without any closure with increased time constants for emptying and filling. If certain alveoli have volume-dependent time constants such that their emptying and filling decrease sharply but do not cease completely at low lung volume, they would receive very little of the 133Xe bolus during inspiration and would be the last ones still emptying during the subsequent expiration.

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