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Regional ventilation in statically and dynamically hyperinflated dogs

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Hubmayr, Rolf D., and Susan S. Margulies. Regional ventilation in statically and dynamically hyperinflated dogs. J. Appl. Physiol. 81(4): 1815–1821, 1996.—Using the parenchymal marker technique in normal anesthetized dogs, we compared the dynamics of regional lung expansion between two ventilation strategies designed to increase mean thoracic volume. Dynamic hyperinflation (DH) was produced by ventilating the lungs at a rate of 50 breaths/min and with a duty cycle of 0.5. Static hyperinflation (SH) was produced through the application of extrinsic positive end-expiratory pressure while the lungs were ventilated at a rate of 15 breaths/min and with a duty cycle of 0.15. Regional tidal volume (VT,r), regional functional residual volume, and the time delay between regional expansion and the flow signal at the common airway were computed for up to 100 regions/lobe in 5 animals. Ventilation strategy had no effect on the overall variance of VT,r within lobes. Although the VT,r measured during SH correlated with VT,r measured during DH, the average correlation coefficient was only 0.69. Ventilation rate-related differences in VT,r and regional functional residual capacity varied with the regional time delay in ways qualitatively consistent with parallel inhomogeneity of unit time constants. However, a large component of frequency-dependent behavior remains unexplained by established mechanisms. We conclude that DH and SH should not be considered equivalent lung unit recruitment strategies.

EXPERIMENTAL METHODS

The parenchymal marker technique has been described in detail previously (15, 25). In brief, 10–15 radiopaque markers were implanted in the right upper and right caudal lobes of five beagles, and the dogs were allowed to heal for 6 wk. On the morning of the study, the animals were anesthetized with pentobarbital sodium (25 ml/kg), intubated with a no. 9 endotracheal tube, and placed in either the right or left lateral decubitus posture on a fluoroscopy table. A balloon catheter was introduced under fluoroscopic guidance into the esophagus for the subsequent recording of pressure. The lungs were ventilated with a Siemens 900C ventilator set to deliver a tidal volume (VT) between 15 and 20 ml/kg at a constant inspiratory flow. Flow and airway pressure were measured at the oral end of the endotracheal tube, and volume was computed by integration of the flow signal. Electrocardiogram, body temperature, and expired CO2 tensions were monitored to assure the stability of the preparation. Pressures, flow, and volume were recorded on a strip-chart recorder (Hewlett-Packard), and their electrical analogues were encoded on videotape in synchrony with the biplane images.

Biplane fluoroscopic images of the static thorax were recorded on videotape at several volumes between total lung capacity (TLC) and relaxation volume (Vrel) and during mechanical ventilation of the lungs at two rate and duty cycle settings. TLC was defined as the lung volume at a respiratory system recoil of 30 cmH2O. Measurements were made in the right and left lateral decubitus postures with the beaded lobes either dependent or nondependent. During so-called DH runs, the ventilator rate and duty cycle were set to 50 breaths/min and 0.5, respectively. Trapped volume above Vrel was measured directly from the volume trace and inferred from changes in end-expiratory recoil pressure of the lungs and respiratory system. During SH runs, the ventilator rate...
and duty cycle were reduced to 15 breaths/min and 0.15, respectively. Expiratory airway pressure was raised with an underwater seal system until overall FRC and recoil pressure equaled those of the DH runs.

The two-dimensional locations of markers in \approx 60 image pairs obtained at a sampling rate of 33 Hz and taken at equal intervals from 3 breaths were calculated with an operator-interactive computer-based video-tracking system. The three-dimensional locations of markers were determined from the two-dimensional views, and the volumes of the tetrahedra formed by taking four markers as the apexes of the tetrahedra were computed. The volume of tissue per tetrahedron was also computed assuming that the lung at TLC contains 15.8 ml air/kg tissue. A few hundred tetrahedra could be formed by combining different markers, of which up to 60 were chosen based on previously established size and shape criteria (15).

Data analysis. Tetrahedron data yielded between 10 and 61 regional spirometry/lobe from which VT, r, rFRC, regional mean volume (VR mean), and regional TLC (rTLC) were derived. VR mean is defined as the volume of gas contained in a tetrahedron midway between end inspiration and end expiration; it is not time weighted. The time delay between flow delivered to the common airway and regional volume change was computed with a cross-correlation analysis. Regional and whole lung spirometry were offset relative to each other in nine 30-ms time increments and decrements. Correlation coefficients (r) between the two time series were computed at each interval, and a parabola was fit to r with respect to the time from the onset of a ventilator breath. The time at which r was predicted maximum defined the time delay of a region or tetrahedron. Frequency dependence of regional lung function was inferred from differences in regional behavior between DH and SH runs, yielding parameters such as \((VR, r/VR_{mean})_{DH} - (VR, r/VR_{mean})_{SH}\) for each tetrahedron. Such indexes of frequency dependence were regressed against time delay with data sets grouped by lobe and posture. Data are presented as means ± SD. Unless stated otherwise, the sample size was considered 10 (lobes as opposed to dogs) and statistical significance was assumed with 95% confidence.

RESULTS

During SH, a pressure of 7 ± 1 cmH2O was applied to the airway during expiration to match the intrinsic PEEP present during DH. This raised the mean lobar FRC to 59 ± 12% of TLC, slightly below the mean lobar FRC of 61 ± 12% of TLC during DH (P < 0.05). The post hoc lobar-volume analysis derived from the means of the tetrahedron data revealed that the extrinsic PEEP required to match overall FRC between experimental conditions had been underestimated by a small amount in four of five dogs.

Figure 1 shows the VT, r distributions in each lobe at the two ventilation frequencies (DH and SH) and in the two postures (dependent and nondependent). VT, r values are expressed as a fraction of VR mean. Figure 1 emphasizes two findings: 1) VT, r/VR mean is greater when the lobes are dependent than when they are nondependent (this finding can be attributed to both a fall in VR mean and an increase in VT, r in the dependent posture) and 2) frequency has no effect on mean lobar VR or its variability within lobes. Table 1 summarizes these data in terms of mean VT, r/VR mean and its SD within each lobe.

As dictated by the experimental design, VT, r/VR mean when averaged across dogs, lobes, and postures was identical during DH and SH runs (0.28 ± 0.08 vs. 0.28 ± 0.08; P < 1.0). The VT of upper lobes averaged 0.26 ± 0.07 ml/kg during SH and 0.26 ± 0.06 during DH (P < 0.9). The VT of lower lobes averaged 0.31 ± 0.09 during SH and 0.30 ± 0.10 during DH (P < 0.8), indicating that the different means by which lung volume was raised had no effect on the lobar distribution of ventilation. The within-lobe heterogeneity of regional ventilation was estimated from the average SDs of VT, r/VR mean. These were also unaffected by rate, and thus mode, of raising FRC and averaged 0.044 ± 0.018 and 0.044 ± 0.013 during SH and DH, respectively (P < 0.9). The conclusions derived from Fig. 1 and Table 1 would have been identical had VT, r been normalized by rTLC or regional Vrel instead of VR mean (data not shown).

Figure 2 shows a comparison of lobar time delays in the two postures. Data were computed from the averages of all regions during DH and SH runs. The data are labeled according to lobe. The figure emphasizes two statistically significant findings: 1) expansion of the caudal lobe precedes that of the upper lobe by 44 ± 22 ms (P < 0.01) and 2) changing from the nondependent to the dependent posture delayed lobar filling by 13 ± 19 ms (P < 0.05). The tendency for time delays to decline with frequency, i.e., the difference in average time delays between SH and DH (51 ± 39 vs. 40 ± 21 ms) did not reach statistical significance (P < 0.11).

Figure 3 shows two representative examples of within-lobe correlations between regional time delays and the frequency dependence of VT, r (Fig. 3A) and rFRC (Fig. 3B).

Figure 3A illustrates that the relationship between the dependent variable (difference in regional ventilation during SH and DH runs) and the independent variable (regional time delay) has a positive slope. This means that regions with above average time delays (slow regions) received a relatively smaller VT during DH than during SH runs. In contrast, regions with below average time delays (fast regions) received a relatively larger VT during DH compared with during SH runs. Figure 3B illustrates that the relationship between the dependent variable (difference in rFRC between SH and DH) and the independent variable (regional time delay) has a negative slope. This implies that the FRC of regions with above average time delays (slow regions) was greater during DH than during SH runs. In contrast, the FRC of fast regions was greater during SH than during DH runs.

The slopes of the relationships between time delay and frequency dependence (see examples in Fig. 3) were computed for each lobe and experimental condition. Those slopes pertaining to frequency dependence of volume (FRC) and ventilation (VT) have been plotted against each other, as shown in Fig. 4.

Figure 4 demonstrates that 1) the frequency dependence of VT on time delay (analogous to the slope in Fig. 3A) had a positive value in most instances (P < 0.05), 2)
the frequency dependence of FRC on time delay (analogous to the slope in Fig. 3B) had a negative value in most instances (P < 0.05), and 3) the two parameters are correlated with each other. This means that the lobes with the most pronounced frequency dependence of regional ventilation also had the most pronounced frequency dependence of regional gas trapping.

**DISCUSSION**

We have shown that in normal mechanically ventilated dogs the distribution of regional lung volume and ventilation changes with the rate of breathing. Frequency dependence of regional lung expansion was observed over a physiological range of rates, and it followed predictions of linear models with parallel time-constant inhomogeneity (20). However, we also observed a large residual variability in regional lung dynamics that is not readily explained by established mechanisms.

Forty years ago, Otis et al. (20) pointed out that differences in regional lung properties produce frequency-dependent regional lung expansion and that

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<th>Table 1. Effect of frequency and posture on lobar tidal volumes</th>
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Values are averages ± SD of regional tidal volume normalized by regional mean volume during static (SH) and dynamic hyperinflation (DH). ULd, upper lobe dependent; LLd, lower lobe dependent; ULnd, upper lobe nondependent; LLnd, lower lobe nondependent.
This mechanism may account for rate-related changes in "effective" lung compliance. Otis et al. considered the dynamics of two parallel units each consisting of a resistive and a series elastic element [analogous to electrical resistance and compliance (RC) circuits]. The salient responses of such a system when it is driven with sinusoidal flow are as follows. At zero frequency, "inspired volume" is distributed in direct proportion to unit compliances. At infinite frequency, inspired volume is distributed in inverse proportion to unit resistances. The regional dynamics in the intermediate-frequency range are determined by the relative differences in unit impedances. Filling and emptying of the unit with the larger cross product of RC (or time constant) is delayed relative to the common flow source. Because of this delay, the slow unit's end-expiratory pressure (and volume) start to rise with rate, reducing the overall driving pressure for flow into the unit. Consequently the slow unit's VT decreases with rate, illustrating that the rate dependence of regional "gas trapping" and regional ventilation are linked on a fundamental level.

It has been known for some time that the normal dog lung expands nonuniformly in situ (14, 15, 23). Humayr et al. (15) and Rodarte et al. (22) have previously demonstrated that only a small fraction of the overall nonuniformity is topographic and explained by gravity's effects on lung/chest wall coupling. Consistent with a large body of literature (reviewed in Ref. 18), we show that a lobe receives more ventilation per unit volume when it is dependent than when it is nondependent. This observation is usually attributed to a decrease in lobar volume and thus an increase in lobar compliance in the dependent posture. In addition, we now demonstrate that the ventilation of dependent lobes is delayed relative to that of nondependent lobes. To the extent to which the decreased volume of dependent lobes is associated with a greater lobar compliance and resistance, this finding is also consistent with Otis-Mead-type models.

Although there remains considerable uncertainty about the relative importance of different mechanisms leading to nonuniform expansion, we now show that the heterogeneity of the normal dog lung contributes to frequency-dependent behavior in situ. The frequency dependence of regional lung expansion is not a random process because, as predicted, rate effects on VT, r and rFRC scaled with regional time delays. The time delay between regional expansion and the volume recorded at the mouth was measured as an index of in situ regional RC. The variance in time delays between regions served as a measure of heterogeneity in regional RCs.

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1 The closed system is being oscillated as opposed to being ventilated; in the latter instance, expiratory flow is a monoexponential function of time.

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Fig. 2. Comparison of mean regional or lobar time delay averaged across frequencies between dependent and nondependent postures. Solid line, line of identity. ○, Lower lobe; ●, upper lobe. For further explanation, see text.

Fig. 3. A: effect of rate on distribution of regional tidal volume shown by relationship between regional time delay and VTSH minus VTDH. B: rate effect on distribution of regional functional residual capacity (FRC) shown by relationship between regional time delay and difference in regional FRC between static and dynamic hyperinflation runs (FRCSH minus FRCDH). For further explanation, see text.
Regional dynamics were evaluated for two ventilation strategies during which the lungs were cycled at different rates but with the same VT and over the same absolute lung volume range. Both produced hyperinflation, albeit by different mechanisms. The difference in VT,r and rFRC between the SH and DH runs were taken as two measures of rate effect. We show that rate effects on VT,r and rFRC are linearly related to time delay as predicted by models with parallel nonuniformities in time constants. The VT values of regions with the smallest time delays (fast units) were greater during DH than during SH runs, whereas the opposite was true for regions with large time delays (slow units). This explains the positive slope of the relationship shown in Fig. 3A. Alternatively, the FRCs of regions with the smallest time delays tended to be lower during DH than during SH; the opposite was true for regions with large time delays. This explains the negative slope of the relationship shown in Fig. 3B. Considering that the strengths of these relationships are measures of frequency dependence on a sublobar scale, we note that the lobes with the greatest frequency dependence of rFRC also had the greatest frequency dependence of VT,r (Fig. 4).

The frequency dependence in regional expansion of normal canine lungs is not as large as Hubmayr et al. (13) had previously observed in methacholine-constricted canine lungs. This is not surprising in view of the considerably greater heterogeneity in airway dimensions (and presumably time constants) after broncho-provocation (19). The difference in frequency dependence between normal and constricted lungs may also reflect differences in the mechanisms responsible for hyperinflation. In the normal lung, DH is the result of a high endotracheal tube and ventilator circuit resistance, whereas in the constricted lung, it is caused by flow limitation in small parallel airways (13). Figure 4 illustrates that the frequency dependence was greatest in dependent lower lobes. In this posture, lower lobes have decreased end-expired volumes so that in some regions expiratory flow could have been maximal and contributed to dynamic airway collapse.

Compared with SH induced with PEEP, the ventilator-delivered minute volume was substantially greater during runs associated with DH. This undoubtedly produced alveolar hypocapnia. Alveolar hypocapnia causes pneumoconstriction that, in turn, could have promoted frequency-dependent behavior (24). The combined effects of hypocapnia and rate of lung inflation on regional airway and tissue impedance have not been delineated. It is, therefore, not clear to what extent the topographic distribution of regional ventilation-perfusion, alveolar CO₂, and regional mechanical constants could have differed between the two frequency settings.

Because there appears to be a great deal of variability in frequency dependence of regional volume and ventilation that is not explained by linear RC models, we must address methodological limitations and consider biological sources of nonlinear behavior. The parenchymal marker technique was developed and originally validated in the 1970s (4, 25). Since then, we have implemented many upgrades in imaging and analysis hardware and software that have improved the accuracy and precision of the technique. With the current system, the error of a single intermarker distance measurement made on a stationary object with known dimensions is <0.5 mm 95% of the time.

The volume and ventilation data presented in this paper were computed from spiromgrams (tetrahedron volume vs. time traces) that contain information from...
up to 1,000 projection images/region and experimental condition. Even by most conservative estimates, the random marker tracking error explains <25% of the observed interregional variability in VT. To test whether breath-to-breath variability of a region’s VT estimate accounts for the apparent interregional variability in VT, we generated spirograms of 10 lower lobe tetrahedra during volume-preset ventilation by sampling regional volumes for 2 min at a rate of 8.2 Hz. Ninety-five percent of single-breath VT estimates fell within ±16% of the 40-breath VT averages, and the variability in VT seemed to be randomly distributed over time.

In light of these precision estimates, it seems remarkable that there is not greater agreement between VT,r measurements across breathing rates. The average correlation coefficient between the VT,r estimates in Fig. 1 is 0.69, indicating that VT,r measurements made at one frequency explain only 47% of the variability in VT at another frequency. Although we are convinced by the data provided in Figs. 3 and 4 that the general principles first outlined by Otis et al. (20) apply in our experimental system, we do not believe that linear RC heterogeneity can explain all of the remaining 53% of total variability. There is ample evidence from parenchymal-strip preparations and from alveolar capsule measurements on whole lungs that tissue mechanics are nonlinear (1, 3, 7, 11, 12). These studies have identified lung parenchyma as the major site of flow resistance and have deemphasized small-scale heterogeneity in airway dimensions as a source of frequency-dependent behavior. The conclusions follow logically from alveolar capsule pressure measurements, which show that alveolar pressure changes uniformly in the physiological range of breathing frequencies. However, recent observations have raised questions about the validity of the alveolar capsule technique, at least when it is used in constricted lungs (13, 17). Alveolar pressure values from capsules may be weighted toward low-impedance pathways and may underestimate regional heterogeneity. Because currently available experimental techniques for measuring regional pressure and volume have a limited resolution, conclusions as to the site and nature of nonuniform regional lung dynamics are, by necessity, inferential.

It would be inappropriate to make recommendations about the ventilatory management of humans with injured lungs on the basis of our findings on normal dog lungs. However, our data emphasize that the choice between SH and DH strategies for recruiting lung units may not be a trivial one. The distribution of injury and edema in patients with adult respiratory distress syndrome is nonuniform (10). Most analyses of regional lung function after injury have been restricted to statics and have focused on the topographic distribution of edema. Accordingly, Gattinoni and colleagues (8, 9) view the injured lung as having three compartments: a nondependent compartment of air-filled and recruited lung units, a dependent compartment of fluid-filled and nonrecruitable lung units, and an intermediate compartment of partially edematous (and potentially recruitable) lung units. Little, if anything, is known about the mechanical properties of lung units and their dynamics within or across these compartments so that, at present, ventilation strategies for alveolar recruitment cannot be based on time-constant considerations.

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