HIGHLIGHTED TOPIC | Reflexes from the Lungs and Airways

CO₂ relaxes parenchyma in the liquid-filled rat lung

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Emery MJ, Eveland RL, Kim SS, Hildebrandt J, Swenson ER. CO₂ relaxes parenchyma in the liquid-filled rat lung. J Appl Physiol 103: 710–716, 2007. First published May 10, 2007; doi:10.1152/japplphysiol.00128.2006.—CO₂ regulation of lung compliance is currently explained by pH- and CO₂-dependent changes in alveolar surface forces and bronchomotor tone. We hypothesized that in addition to, but independently of, those mechanisms, the parenchyma tissue responds to hypercapnia and hypcapnia by relaxing and contracting, respectively, thereby improving local matching of ventilation (VA) to perfusion (Q̇). Twenty adult rats were slowly ventilated with modified Krebs solution (rate = 3 min⁻¹, 37°C, open chest) to produce unperfused living lung preparations free of intra-airway surface forces. The solution was gassed with 21% O₂, balance N₂, and CO₂ varied to produce alveolar hypocapnia (PCO₂ = 26.1 ± 2.4 mmHg, pH = 7.56 ± 0.04) or hypercapnia (PCO₂ = 55.0 ± 2.3 mmHg, pH = 7.23 ± 0.02). The results show that lung recoil, as indicated from airway pressure measured during a breathhold following a large volume inspiration, is reduced ~30% when exposed to hypercapnia vs. hypcapnia (P < 0.0001, paired t-test), but stress relaxation and flow-dependent airway resistance were unaltered. Increasing CO₂ from hypo- to hypercapnic levels caused a substantial, significant decrease in the quasi-static pressure-volume relationship, as measured after inspiration and expiration of several tidal volumes, but hysteresis was unaltered. Furthermore, addition of the glycolytic inhibitor NaF abolished CO₂ effects on lung recoil. The results suggest that lung parenchyma tissue relaxation, arising from active elements in response to increasing alveolar CO₂, is independent of (and apparently in parallel with) passive tissue elements and may actively contribute to VA/Q matching.

alveolar; pulmonary mechanics; ventilation-to-perfusion matching

Delivery of air flow and blood flow to discrete alveolar regions in the proper proportions is of central importance for efficient pulmonary gas exchange, but our understanding of mechanisms that match local alveolar ventilation (VA) to perfusion (Q) is still incomplete (28). Hypoxic pulmonary vasoconstriction (HPV), known to divert blood flow away from poorly oxygenated regions (12), is one mechanism known to improve matching of VA and Q (VA/Q). However, local changes in HPV are not expected to significantly affect vascular tone in normoxic lungs (2, 19).

Adjustment of local alveolar ventilation in response to alveolar perfusion is a potential mechanism for improving VA/Q that has not been well explored. Previous investigation of humans and dogs found evidence for decreased ventilation to large lung regions made hypocapnic by unilateral main or lobar pulmonary artery occlusion, which could be prevented by adding CO₂ to the inspired air (26, 29, 31). Experiments in dogs suggest that changes in alveolar CO₂ alter heterogeneity of ventilation distribution between regions on the scale of acini and larger (9), and global VA/Q (10, 30). CO₂-dependent influences on regional compliance (and therefore regional ventilation) and VA/Q matching have been hypothesized to result from 1) CO₂- and/or pH-dependent changes in the tone of conducting airways, 2) properties of pulmonary surfactant, and/or 3) the extent of collateral ventilation (9, 10, 26, 28, 29, 31). CO₂-dependent changes in airway tone are likely responsible for some changes in parenchyma compliance via bronchial-parenchymal tethering (22). However, several studies have concluded that significant mechanical interactions between conducting airways and surrounding parenchyma must be limited to closely adjacent regions (11, 17, 18, 23). Also, a known agonist of smooth muscle contraction (atropine) has been shown to influence uniformity of ventilation distribution between large airway regions (separated by branches in the conducting airways) but not influence ventilation heterogeneity between smaller regions that branch in the lung periphery (7). Of particular interest is work showing responsiveness of human parenchymal tissue compliance to acetylcholine independent of large airways (8), allowing that other regulating agents could also directly alter mechanical properties of the lung parenchyma.

Our experiments were therefore designed to test the hypothesis that CO₂ directly influences compliance of parenchymal tissue in a manner that would serve to improve VA/Q matching. To that end, we utilized isolated rat lungs in situ (widely opened chest) that were unperfused but maintained viable by slow liquid ventilation with modified Krebs solutions that were saturated with gas to be either hypocapnic or hypercapnic. In this manner, potential CO₂-dependent effects on surface forces at the air-liquid interface, or structures external to the lung structure (e.g., chest wall), were removed. In addition, pressure-volume relationships were obtained for dynamic and stop-flow conditions to better understand the relative roles of altered bronchial tone vs. parenchymal tissue recoil in determining the effects of CO₂ on lung compliance. Some experiments were repeated with and without inhibition of glycolysis by addition of 2 mM NaF (5) to better understand the roles of energy-
dependent active cellular processes vs. chemical influences on passive tissue elements in determining the potential parenchymal response to CO2.

METHODS
Apparatus and General Procedures

All procedures were reviewed and approved by the Animal Care Committee of the Veterans Administration Puget Sound Health Care System.

Anesthesia was induced in 21 adult rats of either sex (350–500 g) by bolus injection of pentobarbital (40 mg/kg ip) to maintain a deep surgical plane. The animals were then intubated and mechanically ventilated (model 683, Harvard Apparatus, South Natick, MA) with room air in a quasi-sinusoidal pattern with fixed tidal volume (VT) of 8 ml/kg, respiratory rate (f) of 40 min−1, and zero positive end-expiratory pressure (PEEP). Tracheal airway pressure (Paw) was continuously monitored throughout all subsequent procedures via an endotracheal tube side port, and the measured values were sampled at 100 Hz and stored in computer files for later analysis. The airway pressure transducer was calibrated by water manometer (0 and 10 cmH2O) before each procedure and checked for drift at the end of each experiment. Calibration pressure transducer signals were stable over the course of the experiments, and corrections were not necessary. The respiratory gas mixture was changed to 100% O2, and after sternotomy the chest was held wide open with a rib spreader. PEEP was then increased to 1 cmH2O, and the preparation was equilibrated for 15 min to ensure nearly complete washout of alveolar N2. Ventilation was then stopped, and the lungs were degassed by O2 absorption. Simultaneously, the lungs were slowly filled with 6 ml of a modified Krebs solution (120 mM NaCl, 4 mM KCl, 1.2 mM MgSO4, 2.5 mM CaCl2, 1.2 mM KH2PO4, 25 mM NaHCO3, 11 mM dextrose) with 4% Ficoll 70 (Sigma) and saturated with the normocapnic gas mixture (7% CO2, 21% O2, balance N2; 37°C) from a reservoir elevated 10 cm above the animal. Complete liquid filling was confirmed by visualization of lungs free of air bubbles (1–3 min following cessation of ventilation). Ventilation was then resumed using the liquid under the conditions described below. Cardiac ventricular arrest occurred within 15 min of the lungs being filled with liquid. Intrathoracic temperature and humidity were maintained by fashioning a cellophane vapor barrier over the open chest, with a warm surgical lamp directed toward the entire preparation from ~1 m.

Experiment 1: Pressure Relaxation at End Inspiration

For 10 of the animals, liquid ventilation (rate = ~3 min−1, VT = 6 ml, PEEP = 1 cmH2O) was continued for 1 h to equilibrate the preparation. Inspired liquid was sampled for dissolved gas partial pressures (model ABL-500, Radiometer, Copenhagen, Denmark), and the equilibrating gas mixture then altered (in a random manner) to be either hypocapnic [fraction of CO2 (Fco2) = 3%] or hypercapnic (Fco2 = 10%), with normoxia [fraction of O2 (Fo2) = 21%] and balance N2. Ventilation was continued for 45 min to reequilibrate the preparation before sampling the inhaled fluid for gas partial pressures. Flow was then stopped at end inspiration for at least 40 s. Twice more, ventilation was resumed for ~5 min, and the end-inspiration, stop-flow condition was repeated. The alternate condition of CO2 was then applied, the preparation was reequilibrated (~45 min), and three more repetitions of the stop-flow procedures were performed. Throughout these procedures, the pleural surface and chest cavity were continuously superfused with the ventilating liquid. For five of these preparations, the testing procedures were repeated under both conditions of Fco2.

In five other animals, NaF (2 mM) was added to the liquid ventilate following the initial testing of 3% and 10% CO2, and testing procedures were then repeated as described above. To observe the degree to which 2 mM NaF blocks lung tissue metabolism, as indicated by altered O2 uptake, one additional preparation underwent 4 h of liquid ventilation under normocapnic conditions without NaF. As ventilation continued, and before addition of NaF, the dissolved gas partial pressures were measured three times in both the inhaled and end-exhaled liquids. NaF was then added to the ventilate, and 15 min later the inhaled and end-exhaled liquids were again sampled in triplicate for dissolved gas partial pressures and calculation of O2 uptake.

Experiment 2: Pressure Relaxation at Two Intermediate Volume Points and End Inspiration

This series utilized liquid ventilation applied by syringe pump (model 906, Harvard Apparatus) that produced a constant flow rate during inspiration and expiration. By this method, we assessed both the inflation- and deflation-limb portions of the quasi-static pressure vs. volume (PV) relationship of this preparation by interruption of flow at multiple points during a ventilatory cycle.

For 10 animals, liquid filling of the lung was followed by slow ventilation with the normocapnic mixture at ~ 0.5 min−1, PEEP = 0.5 cmH2O, and VT of 6 ml for rats <400 g or 7 ml for rats >400 g. Following 1 h equilibration, end-inspiration stop flow for 10 s was then performed at VT and two intermediate conditions of volume (V) following that present at Paw = 0.5 cmH2O (2 and 4 ml in rats <400 g, or 2 and 5 ml in rats >400 g), during both inhalation and exhalation (all conditions were varied in a random manner). Each assessment of Paw followed a return to the end-expiratory volume and then 1) inflation to the chosen level of added liquid for the inflation-limb measurements, or 2) inflation to VT and then deflation to the chosen level for the deflation-limb measurements, with each condition repeated three times. After testing under normocapnic conditions, the equilibrating gas mixture was altered to 3% CO2 (n = 5) or 10% CO2 (n = 5) condition, and all test procedures were repeated following 1 h liquid ventilation. Finally, normocapnic conditions were repeated for 1 h, followed by three repetitions of the stop-flow maneuver at VT. For these procedures, the pleural surface was periodically superfused with the liquid ventilate, and the thoracic cavity was then cleared of perfusate before continuing with the stop-flow maneuvers. (This was done to avoid variable effects of extrapulmonary thoracic fluid on Paw measured at the various conditions of VT.)

Data Analysis

Dynamic and static pressures, static compliance, stress relaxation, and leak. Figure 1A is a representative tracing of Paw vs. time during piston-pump liquid ventilation (dynamic) followed by stop-flow (static) conditions. Peak airway pressure (Pawmax) was measured over the last 2 s of inspiration, and mean Paw was quantified for stop flow of 1 to 3 s (Paw2s) and later at 39 to 41 s (Paw40s). Static compliance was estimated at 2-s stop flow as VT/(Paw2s − PEEP).

Pressure loss due to stress relaxation was quantified in two ways: as the best-fit linear slope of Paw vs. log time, and as a linear fit of log Paw vs. log time, both of these from 1 to 10 s of stop flow. Pressure loss due to leak was then estimated as the difference between the extrapolated best-fit and measured values of Paw40s (shown for linear plot of Paw vs. time, Fig. 1B).

Compliance curves. From experiment 2, PV curves were constructed separately for inhalation and exhalation measures of Paw2s. Best-fit third-degree polynomial solutions of Paw2s vs. VT were then determined by an iterative least-squares method. Hysteresis was determined as the area between best-fit inhalation and exhalation PV curves for each condition of Fco2. Time-dependent changes in lung recoil were assessed by comparing mean Paw2s results from initial vs. final stop-flow maneuvers at VT for each experiment (3 each).
Statistical Analysis

The three repeated measurements of \( P_{aw} \) from each period of dynamic and stop-flow testing were averaged for use in the analyses. For statistical comparisons, indexes of stress relaxation and leak were normalized by \( P_{aw,2s} \), and the averaged values of leak estimated by the two modeling methods were compared for every sample period by paired \( t \)-test. All comparisons of \( P_{aw} \) measured at high and low \( F_{CO_2} \) were made by paired \( t \)-test, and results were considered to be statistically significant with a \( P \) value <0.05.

RESULTS

Experiment 1: Pressure Relaxation at End Inspiration

Dynamic and static pressure and static compliance. Compared with experiment 1 results obtained under hypocapnic conditions, tracheal pressures measured under dynamic (\( P_{aw,max} \)) and static (\( P_{aw,2s}, P_{aw,40s} \)) conditions were significantly decreased when tested with hypercapnia (Fig. 2A), and by similar amounts (~3.2 cmH\(_2\)O, \( P \) = not significant (NS)). When expressed as compliance (Fig. 2B), the magnitude of the \( CO_2 \)-dependent increase (~30%) was similar for all animals.

Effect of time and NaF. Repeated measurements without addition of NaF to the ventilating liquid show that after 3–4 h under the conditions of these experiments, the lungs continued...
to show a significant effect of CO₂ on static airway pressure (Fig. 3). However, after addition of NaF the effect of CO₂ on Paw was completely eliminated, and Paw was maintained at hypocapnic levels even after ~45 min exposure to hypercapnia.

The demonstration of NaF effects on tissue metabolism and oxygen uptake showed that the mean difference in PO₂ levels between inhaled and exhaled liquid found at the beginning of the experiment (124.3 ± 1.4 vs. 84.2 ± 3.3 mmHg, respectively, mean ± SD) was essentially unchanged after 4 h (118.6 ± 2.0 vs. 82.5 ± 2.2 mmHg) but then greatly reduced when tested 15 min following addition of NaF (124.1 ± 3.7 vs. 114.1 ± 3.1 mmHg).

Stress relaxation and leak. Stress relaxation was similar for hypo- vs. hypercapnia initially, after 2 h, and after NaF (for all, \( P = \text{NS} \)), when determined by semilog or log-log best fits (Fig. 4, A and B), and a similar result was found for estimates of leak (Fig. 4C). For each lung, correlation of best-fit semilog and log-log descriptions of the measured Paw (vs. time) between 1- and 10-s stop flow was excellent in all instances (\( R^2 = 0.98 \)). However, as suggested in Fig. 1B, leak estimated at 40-s stop flow was, on average, ~20% greater when estimated by the log-log best fit (\( P < 0.0001 \)).

Experiment 2: Pressure Relaxation at Two Intermediate Volume Points and End Inspiration

Measurements of Paw, as assessed for V₁, were found to consistently increase by ~5% over the ~5-h time course of these experiments (0.39 ± 0.07 cmH₂O). Therefore, assuming the effect of time on Paw to be a linear function, measured Paw values at each condition of V were corrected (reduced) in proportion to the time of the measurement and fraction of V₁ (V/V₁).

PV curves constructed from inhalation and exhalation stop-flow results are shown for hypocapnia and hypercapnia in Fig. 5A. Loops were notable for almost uniform shift to a higher recoil pressure of ~0.3 cmH₂O in conditions of reduced FCO₂ (except the PEEP point, which was fixed at 0.5 cmH₂O).

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![Fig. 3. Grouped results from experiment 1 showing the influences of time (+2 h) and time plus metabolic inhibition by NaF (+2 h, +NaF) on Paw measured during hypo- and hypercapnia.](image)

![Fig. 4. Grouped results from experiment 1 showing the influences of time and NaF on stress relaxation as determined by semilog (A) and log-log (B) best-fit methods, and leak as determined by both methods (C), measured during hypo- and hypercapnia. (The negative values of slope are shown as positive.)](image)
Figure 5 shows the degree of increased compliance with hypercapnia compared with hypocapnia for inspiration and expiration. At each applied volume, increasing FCO2 significantly decreased quasi-static Paw, while decreasing FCO2 significantly increased Paw. The greatest increase in compliance when hypercapnic compared with hypocapnic occurs during deflation at the lower lung volume. Hysteresis area was unaltered by exposure of the lungs to hypocapnic vs. hypercapnic conditions.

DISCUSSION

Potential Sites of Parenchymal CO2 Sensitivity

Several mechanisms may explain the influence of CO2 on parenchymal compliance in these experiments, including:

1) changes in bronchomotor tone translated to the parenchymal tissue due to tethering; 2) CO2- or pH-sensitive properties of passive structural support elements of lung tissue, such and collagen and other proteins of the extracellular matrix; and 3) CO2-sensitive changes in contractile elements that are contained within or influenced by alveolar interstitial cells.

Effects of airway-parenchymal tethering (interdependence) might occur when bronchial tone is altered by the known sensitivity of airway smooth muscle to CO2. If the CO2-dependent changes in bronchial tone were significant in our preparation, evidence of CO2-dependent changes may be found in the comparison of airway pressure before vs. 2 s after stop flow (Pawmax vs. Paw2s). This flow-dependent portion of Pawmax identifies mainly the effect of airways flow resistance on the total pressure measurement because potential contributions of tissue resistance are largely absent during low-frequency ventilation. However, these results failed to show differences in the flow-dependent portion of airway pressure when tested during hypocapnia (7.13 ± 0.95 cmH2O) vs. hypercapnia (7.31 ± 1.02 cmH2O, P = NS; see Fig. 2A), suggesting that any indirect effects of CO2 on the parenchyma via bronchial tethering should be small. Overall, if changes in CO2 did influence the caliber of conducting airways under the conditions of these experiments, the effect was not sufficient to alter flow resistance.

The results from experiments using NaF to block glycolysis suggest that normal cellular function is required for CO2 to produce altered pulmonary compliance, as opposed to a mechanism where CO2 affects tissue elements only through passive chemical alterations in protein structure. For example, osmolarity-dependent changes in the stress-strain relationship of parenchymal tissue, shown to be mediated by proteoglycans (6), may result from altered pH when CO2 level is altered. Disruption of metabolism would not be expected to produce changes in passive properties of lung tissue maintained for 2 h in Krebs solution under physiological conditions of temperature and gas content. Indeed, measures of stress relaxation and leak were essentially unchanged under all conditions of these experiments, and the lack of CO2 effect on hysteresis area adds to evidence for a lack of CO2 effect on tissue structural elements. Also, the result showing lack of change in any measure of airway pressure during hypocapnia before vs. after application of NaF further suggests that passive properties determining pulmonary compliance are probably unaltered by the conditions of these experiments.

Taken together, these results support a primary role for energy-dependent, active contractile elements within the parenchyma in producing the CO2 response. The living parenchyma has recently been shown to contract when acetylcholine levels are increased within the physiological range (8), allowing that other agents may also result in reflex regulation of the parenchyma. Alveolar interstitial cells in humans and rats contain actinlike filaments (16, 33), and the contractile response of guinea pig parenchymal strips to applied acetylcholine was blocked by calmidazolium, an inhibitor of myosin light chain phosphorylation (25). Further research is needed to more fully understand how these or other contractile proteins produce a response to altered CO2.

Fig. 5. Grouped results of experiment 2. A: pressure-volume curves for inhalation and exhalation during hypocapnia [fraction of CO2 (FCO2) = 3%] and hypercapnia (FCO2 = 10%), produced by the best-fit 3rd-degree polynomial solutions of Paw2s vs. V/VT (measured at 0.33, 0.67, and 1.0 VT, where VT is tidal volume). B: change (Δ) in compliance for hypocapnia compared with hypercapnia for V/VT = 0.33 and 0.67, measured during inhalation and exhalation.
Limitations of the Methods

Characteristics of PV relationships found for these liquid-filled lungs were similar to those previously described for several mammalian species, including the greatly reduced hysteresis that occurs after transition from air to liquid breathing due to elimination of the air-liquid interface (4). However, in contrast to earlier studies of liquid ventilation that utilized room-temperature normal saline with ambient room-air gas content, our preparations were maintained viable using Krebs solution containing physiological levels of respiratory gases and other compounds at body temperature. This may explain why we found essentially no change in baseline compliance over the course of these experiments (Figs. 3 and 4), while earlier experiments found compliance to increase with duration of experiment time to a large degree (4).

The apparatus that we used to deliver liquid ventilation in the first experiment series was designed for gas delivery in a quasi-sinusoidal pattern. Therefore, our measures of stress relaxation were less than optimal, and likely underestimated, because inspiratory flow was already decreasing before application of the complete “stop-flow” condition at peak inspiration. In addition, the experiment records demonstrate low-amplitude, nonrandom variations in Paw during inspiration (see Fig. 1A), which likely resulted from mechanical effects of fluid or increased flow resistance on the ventilator piston mechanism.

Beyond these mechanical limitations of the equipment, the method used to estimate the rate of decline in Paw due to stress relaxation and leak did reveal a highly significant but minor increase in estimated leak (~20%), when determined by the log-log vs. semilog curve-fit method. However, although previous studies of pulmonary tissue relaxation have found experimental results to be best fit by solutions from either the semi-log (14) or log-log method (3, 13), we found that both methods gave equally excellent descriptions of pressure decay from 1 to 10 s following stop-flow (and differences remained small at 40-s stop flow). Although limitations of the equipment and differences in the curve-fit method may have influenced the magnitude of estimated stress relaxation and leak, they are not expected to influence comparisons and conclusions based on altered CO2. Also, to avoid effects of airway collapse and overstretch on the results, we maintained preinspiration Paw at restricted VT to 6 or 7 ml. Therefore, results shown in Fig. 5 experiment 2 measured in inspiratory stop flow in experiment 1 only partially describe the compliance characteristics of these lungs filled with normal saline when measured at 2 s following stop-flow (and differences remained small at 40-s stop flow). Although limitations of the equipment and differences in the curve-fit method may have influenced the magnitude of estimated stress relaxation and leak, they are not expected to influence comparisons and conclusions based on altered CO2. Also, to avoid effects of airway collapse and overstretch on the results, we maintained preinspiration Paw at restricted VT to 6 or 7 ml. Therefore, results shown in Fig. 5 experiment 2 measured in inspiratory stop flow in experiment 1 only partially describe the compliance characteristics of these liquid-filled lungs.

Compared with static Paw measured at 2 s following end-inspiratory stop flow in experiment 1, the same parameter measured in experiment 2 using similar VT was substantially lower, as was the magnitude of changes in Paw after altering FCO2 (see Fig. 2A vs. Fig. 5A). A large portion of those differences likely resulted from a substantially elevated preinspiratory Paw in experiment 1 and therefore increased preinspiratory volume (~0.5 to 1 ml). Also, the slower rate of ventilation in experiment 2 vs. experiment 1 probably resulted in a greater alveolar CO2 (and therefore increased reduction of Paw) and reduced influence of viscoelastic forces on stop-flow Paw results. Therefore, the experiment 2 stop-flow results measured at 2 s may be more comparable to those obtained in experiment 1 after longer periods of stop flow (see Fig. 2A).

Functional Significance of CO2-Mediated Compliance Within the Parenchyma

VA/Q matching is consistently found to be better than predicted from separately measured distributions of Va and Q, when measured in several species under varied conditions of activity and inspiratory gas content (19–21, 24). Although HPV has been long studied as a mechanism to facilitate VA/Q matching, CO2 regulation of parenchymal tissue compliance may be a more potent mechanism for improved matching of VA to Q under more normal (i.e., normoxic) conditions. By this mechanism, alveolar gas exchange units that become overperfused would relax to facilitate increased ventilation with subsequent reduction of CO2, and reduced local Q would result in decreased VA. Although hypoxia was not found to directly influence mechanics of pulmonary tissue in one study (27), potential effects of reduced alveolar Po2 on the pulmonary parenchymal response to varied CO2 remain unexplored.

The degree to which CO2 influences regional compliance in air-filled lungs is likely similar to liquid-filled lungs during exhalation but not inhalation. Compared with liquid breathing, air breathing decreases compliance during inflation substantially (4), likely reducing the relative influence of CO2-dependent relaxation. However, the deflation limb of the PV curves over the range of normal breathing is essentially unaltered by air vs. liquid breathing (4). Also, CO2-dependent change in tissue recoil may not be expected to influence hysteresis of air-filled lungs. In these studies, we found tension but not hysteresis to be altered by varying CO2, in general agreement with a previous study of parenchymal strips showing increased tension but a lack of altered hysteresivity in response to acetylcholine (25).

In conclusion, the results of this study support a potentially important role for CO2 in local matching of alveolar VA/Q, because CO2-dependent changes in parenchymal tissue compliance would serve to increase VA in lung regions with low VA/Q and reduce VA in lung regions with high VA/Q. This mechanism may have considerable functional significance, because compliance was found to decrease ~30% over a range of alveolar CO2 that likely occurs within lungs of humans and other animals under various conditions of health and disease (1, 15, 32). In addition, loss of the compliance response to CO2 following NaF demonstrates that, as opposed to effects on passive tissue elements, CO2-dependent relaxation of parenchyma requires normal cellular function.

GRANTS

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REFERENCES


