

CARBON DIOXIDE AND THE WORK OF BREATHING *

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It is well-known that within certain concentration limits carbon dioxide increases the work of breathing simply by acting on the respiratory center to stimulate hyperventilation. There is evidence that CO_2 also affects work of breathing by virtue of its tendency to cause bronchoconstriction with increased airway resistance.

Einhoven (1) demonstrated in dogs ventilated with a pump that end-inspiratory pressure increased when the gas mixture ventilating the lungs contained high concentrations of CO_2 . Dixon and Brodie (2) found that when animals were similarly ventilated with gases containing high concentrations of CO_2 , the expiratory phase was prolonged and the lungs trapped air. They noted that vagotomy prevented these changes. Daly, Lamberton, and Schweitzer (3) studied the resistance to inflation of the lungs in cross-circulation experiments in which the blood returning from one dog's lungs was used to perfuse another dog's brain. They demonstrated that an animal whose brain received blood with a high pCO_2 developed increased resistance to lung inflation as determined by the method of Konsett and Rossler (4). Peters (5), using the same method, showed that the increase in resistance to lung inflation was proportional to arterial pCO_2 when dogs were ventilated with gases with high CO_2 . Atropine and vagotomy prevented these changes.

These studies showed that CO_2 affected lung mechanics, but gave no information about whether the change was in the elastic or viscous (flow-resistive) properties of the lung. Roy and Brown in 1885 (6) found that the pressure in an endobronchial balloon increased with asphyxia, presumably owing to bronchoconstriction; vagotomy prevented this increase. Kilburn (7) demonstrated with bronchograms that inhalation of 5% CO_2 decreased the bronchial diameter by 15%.

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These last two studies suggest that the alteration in pulmonary mechanics associated with CO_2 breathing is due to bronchoconstriction with increased airway resistance. In contrast, in isolated perfused lungs, Nisell (8) and others have shown that increased CO_2 in the ventilating gas causes bronchodilatation.

Attinger (9) measured the pulmonary compliance, transpulmonary resistance, and functional residual capacity in dogs with an esophageal balloon to measure intrathoracic pressure and a plethysmograph to determine the flow and volume changes. With administration of 5 and 10% CO_2 , minute volume increased and functional residual capacity decreased, but the changes in compliance and resistance were not considered significant. Butler, Caro, Alcalá, and DuBois (10), using DuBois's closed-plethysmograph method in humans, found that ventilation with 4 to 10% CO_2 caused no change in airway resistance.

We undertook this investigation to determine more specifically the nature of the effects of hypercapnia on respiratory mechanics and the work of breathing.

METHODS

In order to determine the effect of CO_2 on the mechanical properties of the lung alone, the other effects of CO_2 had to be controlled. Any method allowing the animals to breathe spontaneously during CO_2 administration would inevitably lead to an alteration in the rate and depth of respiration. If the position or depth of respiration were altered, the end-inspiratory or end-expiratory volume might be outside the range of linear pressure-volume relationship. This would cause an apparent change in compliance without any actual change in the elastic properties of the lung. Changes in lung volume and in the rate of air flow would also introduce uncontrollable variations in airway resistance due to changes in bronchial caliber and in the ratio of turbulent to laminar flow. The use of controlled respiration in animals given muscle-paralyzing agents was unsatisfactory, since these agents cause an increase in bronchial secretions unless atropine or atropine-like drugs are given. Therefore,

the best method available was measurement of pulmonary mechanics in experimental animals with lungs exposed at thoracotomy and ventilation at all times carefully controlled by respirator pump. A pump was constructed to withdraw at all times exactly the volume of gas delivered without causing the animal to rebreathe its own expired gas.¹ The pump was equipped with two solenoid valves so timed that during one pump cycle, the animal was ventilated and during the next, the pump was evacuated and refilled. Thus, there was a pause equal to one respiratory cycle at the end of each expiration and no inspiratory pause. The tidal volume of this pump could be varied from 0 to 1,000 ml, and the frequency, from 0 to 22 respiratory cycles per minute. The inspiratory and expiratory flow rates could be controlled independently. Signals for volume and flow rate were generated respectively by a potentiometer and generator attached to the piston of the pump. The accuracy of the volume and flow measurements made with this respirator was checked by recording the flow rate simultaneously with a parallel plate flow resistor (linear range, 0 to 100 L per minute). Across this was connected a Statham ± 0.05 pounds per inch² differential manometer. The signal from this flowmeter was electronically integrated to give volume. Conditions occurring in most of these experiments were then simulated, and recordings made and analyzed. The discrepancy in time between the volume and flow measurements recorded by the pump and those by the flow integrator system was never greater than 0.03 seconds. Plots of data made from both recording systems coincided almost exactly when superimposed. Although this pump was designed to withdraw at all times exactly the volume delivered, it still did not assure maintenance of the same lung volume. In a system of this type, any deviation of RQ from unity might be expected to cause a progressive change in the lung volume over the course of the experiment. When a gas mixture high in CO₂ is administered to a previously normocapnic animal, one might expect an acute decrease in RQ, as CO₂ accumulates in the animal's tissues, until equilibrium is attained. The opposite effect would be expected on return to room air. Since the pressure in the pump during inspiration and expiration would not be exactly the same, it was also possible for this to cause the lungs to change volume. This would occur because the pump would fill itself at atmospheric pressure and force this air into the animal's lungs at an increased pressure; then it would withdraw air at less than atmospheric pressure and refill at atmospheric pressure. To detect changes in volume due to any of these factors, a total-body plethysmograph was used in some of the experiments as described below.

Mongrel dogs weighing between 8 and 16 kg were anesthetized with intravenous chloralose, 125 mg per kg. In one instance, pentobarbital was used instead. Each dog was placed on its back, and a large, curved, tracheostomy tube tied securely into the cervical trachea. A mid-line sternotomy was then carried out with electrocautery to

control bleeding and the Stryker saw to divide the sternum. The tracheal cannula was connected to the pump described above just before the chest was opened. The two edges of the sternum were widely retracted with the rib spreader, and both phrenic nerves clamped and divided. In those experiments in which the vagus nerve was to be stimulated, the carotid sheath in the neck was opened, and the nerve was isolated so that it could be divided and its distal end stimulated electrically. The femoral artery was exposed and cannulated with a polyethylene catheter, which was attached to a 3-way stopcock so that blood samples could be withdrawn and blood pressure monitored with a Statham P23D manometer. Transpulmonary pressure was measured with a Statham ± 2 pounds per inch² differential manometer. One chamber of this instrument was connected to the tracheal cannula, and the other was left open to the atmosphere. The volume, transpulmonary pressure, flow rate, and blood pressure were all suitably amplified and simultaneously recorded on an Offner multichannel recorder. The manometer used to measure airway pressure was calibrated against water after each experimental period. Cervical vagotomy was done in two of the dogs, and the vagus was stimulated with a Harvard apparatus stimulator using 15 v at 100 cycles per second.

In five studies, once the chest had been opened and the lungs exposed, the dogs were placed in an airtight, 50-gallon plethysmograph. When thermal equilibrium was reached, the plethysmograph was sealed, and gains or losses in the dog's lung volume were recorded as pressure changes in the plethysmograph with a Statham ± 0.15 pounds per inch² manometer. In experiments with the plethysmograph, transpulmonary pressure was measured as the difference between the pressure in the airway and that within the plethysmograph.

In these experiments, after the operative procedure, the position, rate, and volume of respiration were adjusted so that the lungs seemed to be in a normal mid-position and not over- or underinflated. After all adjustments, volume, flow rate, transpulmonary pressure, plethysmographic pressure, and blood pressure were recorded with the dog breathing air. Three to four complete respiratory cycles were included. The time of this first reading was that from which all times noted in Tables I and II were calculated. The test gas—25% O₂, 10 to 20% CO₂, and nitrogen to make 100%—was then administered for 3 to 10 minutes, and recordings were repeated once or more during this period, usually at 3-minute intervals. The dog was then ventilated with air long enough to allow arterial pCO₂ to return to normal. Recordings were repeated, and then another test gas administered. Samples of arterial blood were drawn within 30 seconds of each recording. Oxygen saturation was determined with a Waters double-scale oximeter, total CO₂ with a Van Slyke-Neill apparatus, and pH with a radiometer pH-meter at 37.5° C. pCO₂ was calculated from the Henderson-Hasselbalch equation after correction of pH and pK to the dog's temperature.

From those recordings, graphs were drawn with transpulmonary pressure plotted against the volume of gas in

¹ Custom Engineering & Development Co., St. Louis, Mo.

TABLE I
Measurements in dogs ventilated with air and with CO₂*

Dog	TTG	T _p C	Test gas	Arterial pCO ₂	Resistance	Compliance	Nonelastic work	Elastic work	Transpulm. end-expir. pressure
	<i>min</i>	<i>min</i>	% CO ₂	<i>mm Hg</i>	<i>cm H₂O/L/sec</i>	<i>ml/cm H₂O</i>	<i>dyne-cm × 10⁶</i>	<i>dyne-cm × 10⁶</i>	<i>cm H₂O</i>
1	15	0	Air	24	5.19	39	2.67	4.08	
	10	19	15	116	12.80	28.7	6.95	5.25	
	10	29	Air	28	5.37	33.0	2.84	4.49	
	5	35	20	151	13.33	33.0	6.75	4.62	
	5	45	Air	29	3.85	34.9	1.92	4.14	
2	15	0	Air	33	9.76	21.4	3.90	6.69	
	10	12	15	104	13.33	23.1	4.82	5.87	
	16	28	Air	29	8.54	23.0	2.98	5.81	
	9	40	15	102	13.56	22.8	4.80	5.61	
	10	52	Air	26	4.94	26.3	1.73	5.26	
	12	67	20	127	10.14	26.8	3.52	4.69	
	10	80	Air	27	6.52	25.4	1.82	5.98	
3	15	0	Air	25	2.58	51.6	1.67	5.51	3.0
	9	10	15	96	8.16	38.9	6.14	6.26	0.0
	10	21	Air	27	1.62	44.7	1.33	5.90	2.0
	3	26	20	129	9.18	39.5	6.96	6.43	0.0
	10	37	Air	33	1.26	51.6	.94	5.59	3.0
	9	53	10	82	7.02	42.7	5.34	6.12	0.0
	9	64	Air		1.62	44.7	1.22	6.41	3.0
4	15	0	Air	16	2.76	30.0	1.55	6.84	3.0
	10	13	10	57	9.90	28.5	4.92	6.41	0.0
	1	15	Air	42	3.42	33.7	1.96	5.81	2.0
	10	24	Air	19	1.74	30.0	1.47	6.94	3.0
	10	35	20	125	6.81	30.9	3.43	6.18	1.0
	10	45	Air	21	3.48	32.7	1.37	5.96	2.0
	3	49	15	94	4.62	30.0	2.65	6.61	0.0
	8†	54	15†		3.42	33.8	1.59	6.04	1.0
	10	64	Air	20	2.98	33.8	1.53	6.32	1.0
5	15	2	Air	20	2.34	55.0	1.31	6.39	4
	3	8	10	61	3.30	62.5	2.06	5.59	4
	4	13.5	Air	20	2.34	52.0	1.51	7.02	4.5

* TTG = time dog breathed test gas, and T_pC = time elapsed since initial control study.

† Atropine, 0.03 mg per kg, iv, 4 minutes before this determination.

With very few exceptions, the viscous resistance and nonelastic work were considerably higher with CO₂ breathing and with the resulting hypercapnia than when the dog was ventilated with air. The few exceptions and those instances where viscous resistance was slightly to moderately elevated tended to occur late in the experiments. Simple inspection of the data shows no striking or obvious change in compliance or elastic work. The end-expiratory transpulmonary pressure decreased in all experiments with CO₂ breathing.

Table II shows results in studies where changes in end-expiratory volume were determined by making all measurements with the dog in a body plethysmograph. In dog 7, where changes in viscous resistance were smaller than in any other

experiment, there was a slight fall in end-expiratory volume. In all other experiments where changes in mechanics were similar to those presented in Table I, the end-expiratory volume increased after a transient fall when CO₂ was administered. As in the initial studies, this was associated with a fall in end-expiratory transpulmonary pressure.

Table III shows the results of one of a number of studies in which vagal interruption was followed by vagal stimulation. Ten per cent CO₂ was associated with a threefold increase in nonelastic work, and vagotomy returned this to normal. Vagal stimulation increased the nonelastic work in a manner similar to CO₂ with the exception that end-expiratory pressure rose.

One experiment (not included in tables) was done on a 20-pound pig. Changes in respiratory mechanics were similar to those observed in dogs.

To test the significance of the changes in mechanics of breathing with hypercapnia, data were subjected to statistical analysis. These rather elaborate analyses were necessary to determine the relation between changes in lung mechanics and the arterial $p\text{CO}_2$, and to determine whether this was affected by the time on any given test gas and the total duration of the experimental period. This type of analysis also served to correct for the unavoidable variations among dogs.

Data were analyzed by means of four model equations taking each index of lung mechanics (resistance, compliance, and viscous and elastic work) as a dependent variable and assuming each to be

a linear function of the effect of the individual dog plus the differing combination of the following three independent variables: arterial $p\text{CO}_2$ ($p\text{CO}_2$), the time in minutes the dog had been breathing the test gas (TTG), and the time in minutes elapsed since the initial control study ($T_p\text{C}$). Combinations of the independent variables included each term as well as its square and logarithm to measure quadratic effects and deviations from pure linearity. Individual terms were also combined by multiplication to discover the importance of interactions among the independent variables. Each equation included a parameter to measure the effect of the individual dog. This has the effect of considering each observation as a change in the individual dog and allows the individual variation among the dogs to be removed

TABLE II
*Measurements in ventilated dogs in a whole-body plethysmograph**

Dog	TTG	$T_p\text{C}$	Test gas	Arterial $p\text{CO}_2$	Resistance	Compliance	Nonelastic work	Elastic work	Transpulm. end-expir. pressure	End-expir. volume change
	<i>min</i>	<i>min</i>	% CO_2	<i>mm Hg</i>	<i>cm H₂O/L/sec</i>	<i>ml/cm H₂O</i>	<i>dyne-cm × 10⁶</i>	<i>dyne-cm × 10⁶</i>	<i>cm H₂O</i>	<i>ml</i>
6	15	0	Air	23	2.69	17.8	0.96	5.66	1.0	0
	2	8	10	58	9.57	17.4	3.18	5.53	0.4	+25
	3	18	Air	24	3.16	18.2	1.10	5.66	1.2	-35
	5	24	15	77	8.24	17.4	2.94	5.63	0.3	-15
	9	34	Air		2.15	17.4	0.88	5.70	1.0	-50
	1.5	36	15		4.89	17.8	2.23	5.43	1.0	-35
7	15	0	Air	19	4.83	17.7	2.37	7.27	1.0	0
	2	4	15	95	4.17	19.6	1.90	6.66	0.0	-25
	6	8	15		3.33	20.0	1.72	6.55	1.0	0
	4	13	Air		3.33	20.4	1.45	6.45	1.5	0
	2	15.5	15		3.75	22.4	1.61	5.70	0.0	-40
	3	19	Air		2.92	20.4	1.43	6.84	1.5	-40
8	15	0	Air		6.25	16.2	0.92	2.67	1.0	0
	1.5	2.5	10		10.71	14.2	1.55	3.02	0.5	+35
	2.0	3	10	64	13.75	14.9	1.86	2.78	1.5	+200
	3	4	10		10.53	14.5	1.47	2.98	2.0	+275
	2.5	7	Air	34	7.02	14.9	0.98	3.04	1.5	+85
	5.5	13.5	10		9.30	15.8	1.41	2.98	2.5	+275
8	22	Air	35	9.65	14.5	1.43	2.21	1.5	0	
9	15	0	Air	32	4.24	13.2	0.31	2.49	0.0	0
	4.5	5	10	67	8.47	11.3	2.10	2.78	0.0	+75
	2.5	9	Air		3.39	12.5	0.43	2.49	0.0	+25
	5.5	15	15	97	8.47	11.5	1.06	2.70	0.0	+60
	6	23	Air		6.78	11.8	0.82	2.65	0.0	+10
10	15	0	Air		1.54	33.3	0.69	2.13	2.0	0
	5	6	15	103	2.69	26.9	1.28	2.64	.75	+100
	6	13	Air		1.54	33.3	0.78	2.16	1.5	+110
	22†	29	Air	26	1.54	30.4	0.73	2.42	1.5	+75
	7	37	15	100	1.54	30.4	0.69	2.55	1.5	+75
	5	43	Air		1.15	29.2	0.76	2.59	2.0	+10

* Abbreviations as in Table I.

† Atropine, 0.06 mg per kg, iv, 6 minutes before this determination.

TABLE III
Effect of vagotomy in a ventilated dog*

TTG	T _p C	Test gas	Resistance	Compliance	Nonelastic work	Elastic work	Transpulm. end-expir. pressure
<i>min</i>	<i>min</i>	% CO ₂	<i>cm H₂O/L/sec</i>	<i>ml/cm H₂O</i>	<i>dyne-cm × 10⁶</i>	<i>dyne-cm × 10⁶</i>	<i>cm H₂O</i>
15	0	Air	3.96	27.3	0.82	2.02	1.5
0.5	3.5	10	11.58	22.2	2.33	2.35	0.5
1†	4	10	5.28	22.2	1.08	2.39	0.5
1.5‡	4.5	10	18.18	18.2	3.50	2.63	1.5
3	6	10	4.5	27.3	0.82	1.90	0.5
7	14	Air	3.0	26.1	0.67	2.18	1.5
8‡	15	Air	17.88	18.2	4.06	2.72	2.0
10	17	Air	3.24	31.6	0.61	1.76	1.6

* Abbreviations as in Table I.

† Vagus cut.

‡ Vagus stimulated by 15 v, 100 cycles per second.

statistically from the analysis. It also allows combination of the results from Tables I and II without any further adjustment of the data.

Preliminary analyses showed that in addition to the dog-to-dog variation, five terms in the regression equations were adequate to explain almost all the observed residual variation in the four dependent variables. These were: pCO₂, natural logarithm of pCO₂ (ln pCO₂), T_pC, TTG interacting with pCO₂ (TTG × pCO₂), and T_pC interacting with pCO₂ (T_pC × pCO₂). The time the dog breathed the test gas appeared to have no direct effect on the four dependent variables, but had some effect only when considered together with the concentration of arterial pCO₂.

Analysis of variance for resistance based upon

these five factors plus the variation among dogs is shown in Table IV. The five factors plus the dog-to-dog variation accounted for 924.891/1,152.663 = 80.2% of the variability among all observations. The major source of variation, as expected, was the difference among dogs. The F ratio for this factor was significant at the 1% level. Despite the large variation among dogs, however, the direct effect of pCO₂ upon resistance was highly significant, and the F ratio of 19.069 is associated with a probability beyond the 1% level. The other two significant factors were T_pC and TTG × pCO₂. The latter was negative, indicating that at higher pCO₂ long TTG would tend to lower resistance.

The effect of dog-to-dog variation was much

TABLE IV
Analysis of variance for resistance*

Source	Degrees of freedom	Sum of squares	Mean square	F ratio
Total	71	1,152.663		
Regression on all variables	14	924.891	66.064	16.532
Dogs†	9	471.815	52.424	13.119‡
pCO ₂ and ln pCO ₂	2	152.403	76.201	19.069‡
T _p C†	1	18.230	18.230	4.562§
pCO ₂ × TTG†	1	35.996	35.996	9.008‡
pCO ₂ × T _p C†	1	0.012	0.012	0.003
Residual error	57	227.771	3.996	

* Abbreviations as in Table I.

† Values adjusted for other variables.

‡ Significant at 1% level.

§ Significant at 5% level.

TABLE V
Analysis of variance for compliance*

Source	Degrees of freedom	Sum of squares	Mean square	F ratio
Total	71	9,426.999		
Regression on all variables	14	9,054.860	646.776	99.066†
Dogs‡	9	7,976.202	886.245	136.745†
pCO ₂ and ln pCO ₂ ‡	2	86.716	43.358	6.641†
T _p C	1	8.827	8.827	1.352
pCO ₂ × TTG‡	1	1.678	1.678	0.257
pCO ₂ × P _p C‡	1	49.588	49.588	7.595†
Residual error	57	372.138	6.529	

* Abbreviations as in Table I.

† Significant at 1% level.

‡ Values adjusted for other variables.

greater upon the observations of compliance than resistance, but the influence of pCO₂ was nonetheless significant. Results are presented in Table V.

Because most of the variation among the compliance observations is attributed to the individual differences of the ten dogs, the model explained $9,054.860/9,426.999 = 96.1\%$ of the variation. After adjustment for or removal of the individual effects, however, analysis shows that the influence of varying pCO₂ upon compliance is still significant. The F ratio for the latter test is 6.641 and is significant at a level of less than 1%. The only other significant term was T_pC × pCO₂; this was positive, so that compliance increased rapidly on very high levels of pCO₂ at the end of the experiment on each dog.

Analyses of variance for viscous work and elastic work followed closely the patterns established for resistance and compliance, respectively. The least satisfactory but still adequate fit was obtained with the viscous work. Numerical results are given below for all four dependent variables, and include a constant term to account for dog-to-dog variations in base-line values. Resistance = $-0.223 + 0.0345 \text{ pCO}_2 + 1.562 \ln \text{ pCO}_2 - 0.0561 \text{ T}_p\text{C} - 0.00306 (\text{TTG} \times \text{pCO}_2) + 0.00020 (\text{T}_p\text{C} \times \text{pCO}_2)$. Compliance = $18.265 - 0.1273 \text{ pCO}_2 + 4.339 \ln \text{ pCO}_2 - 0.0390 \text{ T}_p\text{C} - 0.00066 (\text{TTG} \times \text{pCO}_2) + 0.001277 (\text{T}_p\text{C} \times \text{pCO}_2)$. Viscous work = $-0.633 + 0.0126 \text{ pCO}_2$

+ $0.810 \ln \text{ pCO}_2 - 0.0241 \text{ T}_p\text{C} - 0.00123 (\text{TTG} \times \text{pCO}_2) + 0.000015 (\text{T}_p\text{C} \times \text{pCO}_2)$. Elastic work = $7.648 + 0.0240 \text{ pCO}_2 - 1.055 \ln \text{ pCO}_2 + 0.0075 \text{ T}_p\text{C} + 0.00029 (\text{TTG} \times \text{pCO}_2) - 0.000281 (\text{T}_p\text{C} \times \text{pCO}_2)$.

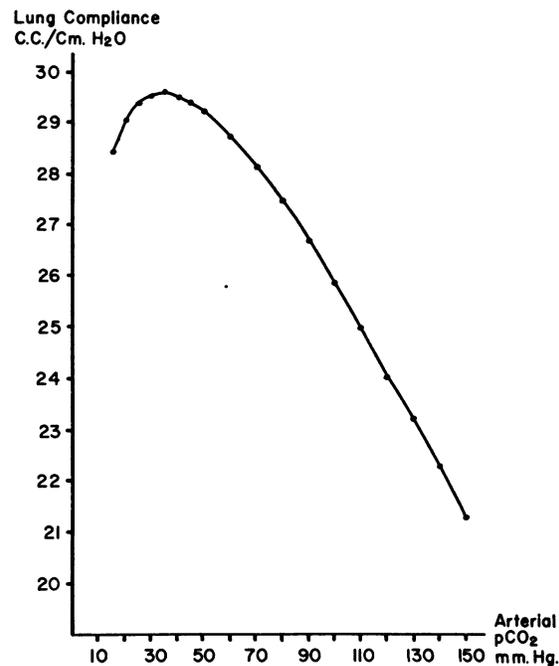


FIG. 2. CHANGE IN COMPLIANCE AS A FUNCTION OF pCO₂. Effects of individual dogs, total time on the test gas × pCO₂, and total time after control run × pCO₂ were held constant. Data points are not included because the effects of factors listed above cannot be held constant.

To summarize, analyses of variance showed that the models described were highly significantly related ($p < 0.01$) to the parameters of pulmonary mechanics. The joint effects of $p\text{CO}_2$ and $\ln p\text{CO}_2$ were significant as follows: resistance, $p < 0.01$; compliance, $p < 0.01$; viscous work, $p < 0.01$; and elastic work, $p < 0.05$.

Other variables with significant effects on the parameters of lung mechanics were as follows. Resistance showed a significant ($p < 0.05$) tendency to decrease with TpC . This was also true ($p < 0.01$) if $p\text{CO}_2$ was elevated for longer periods ($\text{TTG} \times p\text{CO}_2$). Compliance and elastic work were both highly correlated ($p < 0.01$) with $\text{TpC} \times p\text{CO}_2$. For compliance, the regression coefficient was positive and for elastic work, negative. This means that the lung's distensibility at elevated $p\text{CO}_2$ increased with the length of the experiment, whereas the elastic work decreased.

Figures 2, 3, and 4 plot the relationships expressed by these equations. The equation in each figure represents the pure relationship between the measured responses and the $p\text{CO}_2$ after adjustment for other factors such as variation among dogs and time. For example, Figure 3 shows the change in resistance expected as arterial $p\text{CO}_2$ is varied from 15 to 150 mm Hg and is adjusted for the average dog effect as well as

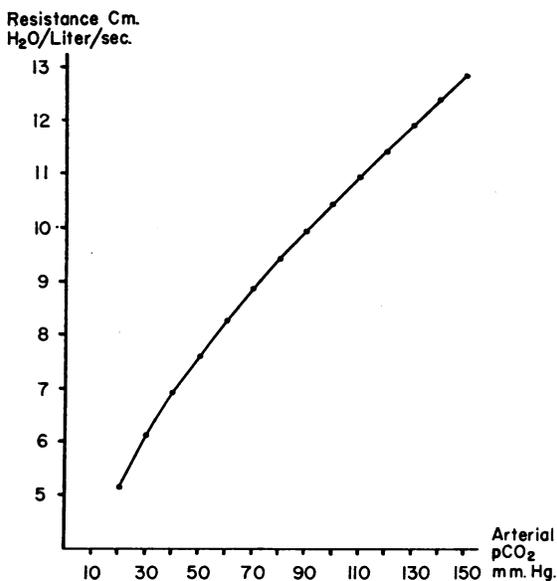


FIG. 3. CHANGE IN RESISTANCE AS A FUNCTION OF $p\text{CO}_2$. Same factors held constant as in Figure 3.

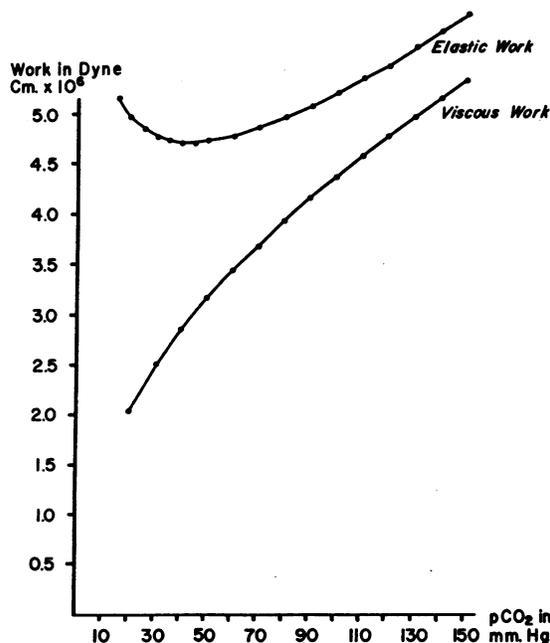


FIG. 4. CHANGE IN VISCIOUS AND ELASTIC WORK AS A FUNCTION OF $p\text{CO}_2$. Corrected for same factors as in Figures 3 and 4.

TTG. Resistance steadily increased over the measured range of $p\text{CO}_2$ about $2\frac{1}{2}$ times. Compliance increased slightly until the $p\text{CO}_2$ reached the normal range of 35 to 50 and then steadily fell. Viscous work increased $2\frac{1}{2}$ times, but elastic work increased only 20%.

DISCUSSION

Although the results clearly demonstrate an increase in resistance with hypercapnia under the conditions of these experiments, such changes may occur from a variety of causes. (Since animal size, position of respiration, tidal volume, and flow rate were different in individual dogs, the principal variation among all observations would be that from dog to dog. Flow rate and tidal volume were unaltered in the individual dogs. It is well-known that airway resistance increases with change in the position of breathing toward a lower part of the respiratory curve. To ascertain that change in position of respiration toward a lower part of the respiratory curve was not increasing the resistance, the body plethysmograph was used in the last five experiments.) A transient, slight

fall occurred in end-expiratory volume with CO_2 breathing, and seems likely to be due to an acute change in RQ owing to the dog's rapid uptake of CO_2 . The transient fall in volume was followed by an increase in volume on CO_2 associated with an increase in resistance. This observation indicates that the alterations in respiratory mechanics reported here were due to a change in airway size, not to volume change alone. Changes observed with vagotomy confirm that some factor other than the volume change was effective.

Volume and pressure changes observed in these dogs seem best explained as follows. When the high concentration of CO_2 was first administered, the base-line lung volume decreased transiently owing to rapid uptake of the CO_2 by the tissues. As the bronchioles constricted, airway resistance increased markedly from the effect of CO_2 . Since flow rates remained unchanged, the difference between mean transpulmonary pressure during inspiration and expiration increased. The volumes of gas delivered and withdrawn remained fixed and equal, but the pressure in the pump cylinder during inflation tended to rise, and during deflation the cylinder pressure tended to fall. During the exhaust phase, the withdrawn gas was expelled into the atmosphere and at this pressure, occupied progressively less volume than the gas taken in for delivery to the animal's lungs. This explains the system's tendency to accumulate gas in proportion to the level of airway resistance. The expected accumulation was calculated from pump volume and the mean difference in inspiratory and expiratory transpulmonary pressures; the observed changes agreed closely with the calculated ones. This mechanism probably explains the system's tendency slowly to accumulate gas during long periods of ventilation with air, since the normal airway resistance had to be overcome.

Changes in compliance were small and subject to error, since there was no pause in the pump on change from inspiration to expiration so that a difference between alveolar and mouth pressure could exist. The small increase in compliance could have been due to the increase in volume exceeding the limits of straight-line relationship between change in pressure and in volume. Unless dogs were at the upper limit of inspiratory reserve during the control periods, this seems unlikely.

The inherent inaccuracy in determination of compliance and elastic work when only two points on the compliance curve are known dictates caution in the interpretation of changes in elastic properties. These dynamic curves do, however, reflect accurately the resistive properties of the lungs.

The changes in nonelastic work with hypercapnia could be due to increased airway resistance or to increased tissue resistance. The methods of this study cannot distinguish between the effects of narrowed airway lumen and the decreased pliability of the lung tissues. The combination, however, of increased lung volume and decreased end-expiratory pressure after the administration of CO_2 can best be explained by air trapping in the distal portion of the lungs as a result of constricted airways. In earlier studies where the lungs were allowed to empty themselves during the expiratory phase, massive air trapping occurred when CO_2 was administered. Kilburn (7) and Roy and Brown (6) have shown that bronchial lumen decreases in response to hypercapnia in the intact animal. It is unlikely that the change is due to alteration of pulmonary vascular tone, since CO_2 does not effect this in dogs (12).

These changes in mechanics are not the result of a local effect on the lung. Daly and co-workers (3) clearly demonstrated in cross-circulation experiments in dogs that this was a central reflex and that the vagus nerve had to be intact. Previous experiments (5) and the present findings confirm that this is a vagal reflex. The observed effect of hypercapnia on pulmonary mechanics seems on the surface to be at variance with certain observations suggesting the bronchodilator effect of CO_2 . Since the studies of Nisell (8) were on isolated lungs, any reflex bronchoconstriction of the type reported here would not have been in effect. Severinghaus and associates (13) observed unilateral bronchoconstriction associated with occlusion of one pulmonary artery. Since administration of CO_2 reversed this, they concluded that low alveolar pCO_2 causes bronchoconstriction. Since arterial pCO_2 would not have been altered in these experiments, the bronchoconstrictive effect of hypercapnia would be absent. In their experiments, unilateral pulmonary artery occlusion had little effect on ventilation under chloralose anesthesia. To establish that

the alterations in lung mechanics seen in our dogs were not due to the pharmacologic effects of chloralose, a study was done under pentobarbital anesthesia. The changes observed were similar in magnitude and direction to those seen with chloralose anesthesia.

Attinger (9) reported in dogs that during spontaneous breathing, 5 and 10% CO₂ caused an increase in functional residual capacity of 90 to 100 ml and some increase in the lung's compliance. The airway resistance rose slightly, although Attinger postulated that this was no more than would be expected with the increased flow rate and decreased functional residual capacity. Since the airway resistance was calculated by the method of Cook and co-workers (11), an upward change in mid-position of respiration may have occurred owing to a greater inspiratory volume. If this was the case, a change in respiratory work per unit of ventilation might have been obscured. Butler and associates (10) used the body-plethysmographic method to measure airway resistance in human subjects during rapid panting respiration after up to 10 minutes of breathing 4 to 10% CO₂. There was no change in position of ventilation, and the effect on airway resistance was variable. Arterial pCO₂ was not determined. Their failure to show a consistent increase in viscous resistance may have been due to the method used. In our studies, it was not clear whether elevated pCO₂, total CO₂, or depressed pH was principally responsible for the alterations in lung mechanics, since all changed simultaneously. Arterial pCO₂ was chosen arbitrarily as the independent variable since it was directly altered. Further investigation will be necessary to determine the importance of the changes in pH and the total CO₂ content.

If these acute experiments are valid examples of the response to be expected, then certain clinical implications are suggested. The work of Sealy, Young, and Harris (14) and Young, Monroe, and Craige (15) has demonstrated that a rapid fall in arterial pCO₂ may be associated with serious cardiac arrhythmias and often, ventricular fibrillation. In such situations, bronchoconstriction associated with hypercapnia might be visualized as a mechanical buffer against a rapid decrease in tissue pCO₂. Despite the possible usefulness of this reflex, it has certain obvious de-

leterious effects. Acute and chronic respiratory acidosis is being recognized more and more frequently in clinical situations. Acute respiratory acidosis often occurs in postoperative periods, particularly after open-heart surgery and major pulmonary resections. Chronic respiratory acidosis most often occurs in patients with pulmonary emphysema, and acute, severe CO₂ retention may result from complicating infections. Since all of these situations are associated with elevated arterial pCO₂, if bronchoconstriction resulted from hypercapnia, increased work would be required of the respiratory system to maintain ventilation at a time when the patient could ill afford it. A number of investigators (16-19) have shown that the ventilatory response to pCO₂ decreases when the work required for a given level of ventilation increases. Thus, an increase in the viscous work of breathing associated with hypercapnia would lead to less than the normal increase in alveolar ventilation, thereby resulting in a vicious cycle leading to further elevation of pCO₂ and further decrease in efficiency of the ventilatory effort. These interactions offer one explanation for progressive, severe respiratory acidosis. The association of these two phenomena also explains how mechanical ventilation can, by correcting hypercapnia, restore respiratory compensation and enable the patient to maintain this compensation unassisted (20). If this increase in airway resistance depends on a change in pH as much as on pCO₂, metabolic acidosis after major cardiac or pulmonary surgery might be the initiating factor in the development of acute, postoperative respiratory failure.

SUMMARY

In dogs with opened chest and controlled respiration, an increase in CO₂ in the inspired air decreased compliance and increased elastic work, resistance, and viscous work; the increase in viscous work was 2½ times that of the elastic work. Vagotomy prevented these changes.

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