ANALYSIS OF THE RESPIRATORY RESPONSE TO CARBON DIOXIDE INHALATION IN VARYING CLINICAL STATES OF HYPERCAPNIA, ANOXIA, AND ACID–BASE DERANGEMENT

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Individuals with cor pulmonale secondary to chronic pulmonary emphysema tend to have pulmonary ventilation which is less than normal both at rest and during exercise, despite the presence of factors ordinarily making for increased ventilation such as anoxemia and acidosis (1), and despite the fact that these ventilatory levels may be appreciably less than the observed maximum breathing capacity. Moreover, the ventilatory response to increased CO_2 in the inspired air may be less than normal in certain patients with pulmonary emphysema (2–5). These observations have been interpreted as indicating a disorder of the chemical regulation of respiration associated with emphysema.

The present study was undertaken to define more specifically the nature of this disorder in terms of the sensitivity of the neural regulatory mechanism to the carbon dioxide-hydrogen ion stimulus, and to characterize the conditions under which such a disorder might exist. Sensitivity of the neural regulatory mechanism to CO_2 and/or hydrogen ion has been evaluated quantitatively by correlation of arterial blood hydrogen ion concentration and CO_2 tension with effective alveolar ventilation when changes are brought about by varying amounts of carbon dioxide in the inspired air.

In the present investigation, the effects of CO_2 inhalation in normal subjects have been compared with those in emphysematous subjects having disease of varying severity.

In order to evaluate separately the possible effects of chronic anoxemia, chronic acidosis, and chronic hypercapnia in conditioning the response of patients with advanced pulmonary emphysema, patients without pulmonary disease who exhibited such derangements have also been studied. For investigation of the effects of chronic anoxemia, patients with cyanotic congenital heart disease were chosen; for the effects of chronic acidosis patients with long standing renal failure and nitrogen retention; and for the effects of hypercapnia patients with chronic metabolic alkalosis secondary to hyperadrenalism.

MATERIALS AND METHODS

Material for study comprised twelve normal subjects, thirteen patients with chronic pulmonary emphysema, three patients with cyanotic congenital heart disease, three patients with chronic renal disease and uremia, and two patients with Cushing's syndrome and chronic metabolic alkalosis.

Subjects were studied in the post-absorptive state. Observations at rest and during a standard exercise test were carried out as outlined by Baldwin, Cournand, and Richards (6). To determine sensitivity to the carbon dioxide-hydrogen ion stimulus, three sets of observations were made on each subject, allowing the determination of three points on the stimulus response curve. In each instance the subject breathed in succession room air, 3 per cent CO_2 in air, and 5 per cent CO_2 in air through a two-way low resistance respiratory valve with a dead space of 60 ml. The CO_2 mixture was supplied continuously from a tank through an anesthesia bag which was in turn connected to the inspiratory side of the respiratory valve. As previously reported by Nielsen (7), it was found that for both normal subjects and patients approximately twenty to twenty-five minutes' inhalation of the CO_2 gas mixtures used was required to achieve a steady state in terms of pulmonary ventilation,

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respiratory frequency, and respiratory exchange ratio. Therefore observations were made only after twenty to thirty-five minutes of continuous inhalation of CO_2. Expired air was collected for a three-minute period, and a steadily and continuously drawn sample of arterial blood was obtained during the middle minute from an indwelling needle in a brachial artery.

If it is assumed that in a steady state there is a consistent relationship between the arterial blood concentrations and those intra- or extracellular concentrations of certain chemical agents acting at receptor and integrative levels on the nervous system, simultaneous measurement of blood concentrations and pulmonary ventilation permits estimation of the sensitivity of the respiratory nervous regulatory mechanism as a whole to these stimuli. The values relating effective alveolar ventilation, either in terms of ventilation ratio (VR) or alveolar ventilation per square meter body surface area ($\dot{V}A/M^2$), to changes in arterial CO_2 tension ($PaCO_2$) and hydrogen ion concentration $(H^+)a$ were obtained from graphs in which VR and $\dot{V}A/M^2$ were plotted against $PaCO_2$ and $(H^+)a$, respectively. For both $PaCO_2$ and $(H^+)a$ the relationship was found to be essentially linear, so that a straight line best fitting the three points could be drawn. The slopes of the lines so constructed have been utilized to determine the changes in arterial CO_2 tension or hydrogen ion concentration required to double the effective alveolar ventilation ($PaCO_2/VR$, $(H^+)a/VR$) and to determine the increase in effective alveolar ventilation per square meter body surface area associated with unit rise in arterial CO_2 tension or hydrogen ion concentration ($\dot{V}A/M^2/PaCO_2$, $\dot{V}A/M^2/(H^+)a$). To arrive at a figure representing the change in arterial CO_2 tension or hydrogen ion concentration necessary to double the effective alveolar ventilation when the latter did not actually occur, the observed slope was extrapolated.

Oxygen consumption and respiratory exchange ratios were calculated in the usual way from expired air analyses. Physiological dead space ventilation was obtained using the Bohr relationship for carbon dioxide (8) assuming the arterial CO_2 tension to be equivalent to the mean alveolar CO_2 tension (9, 10). Effective alveolar ventilation was taken as the difference between total pulmonary ventilation and dead space ventilation. Mean alveolar oxygen tensions were calculated from the usual "alveolar" equation when the inspired gas mixture was room air, and from a generalized form of the same relationships when carbon dioxide was added to the inspired air.[4] Arterial whole blood buffer base was calculated from the Singer-Hastings nomogram (13). A list of the symbols used (14) in this report appears in Table I.

TABLE I

Symbols

B.S.A.	Body Surface Area, square meters.
R_E	Respiratory exchange ratio (RQ), expired air.
R_A	Respiratory exchange ratio (RQ), alveolar air.
$\dot{V}o_2$	Oxygen consumption, ml. per min. STPD (Standard temperature and pressure, dry).
M^2	Square meters of body surface area.
$\dot{V}_E$	Total ventilation (expired air), liters per minute, BTPS (Body temperature and pressure, saturated with water vapor).
V_D	Ventilatory dead space total, *i.e.*, instrumental plus personal, ml. BTPS.
PAO_2	"Effective" alveolar oxygen tension, mm. Hg
$\dot{V}_A$	Effective alveolar ventilation, liters per min. BTPS.
VR	Alveolar ventilation ratio, *i.e.*, observed effective alveolar ventilation divided by resting effective alveolar ventilation.
pHs	Arterial blood pH (serum).
$(H^+)a$	Hydrogen ion concentration, arterial blood, in billionths of moles per liter.
$Csco_2$	Serum carbon dioxide content, arterial blood, volumes per cent.
$Paco_2$	Carbon dioxide tension, arterial blood, mm. Hg
Sao_2	Oxygen saturation, arterial blood, per cent.
V_C	Hematocrit, arterial blood.
$(B_{B+})b$	Buffer base, whole blood, mEq. per liter.
f	Respiratory frequency as breaths per minute.
VC	Vital capacity, ml. BTPS.
V_T	Tidal volume, ml. BTPS.
FRC	Functional residual capacity, liters BTPS.
$\frac{RV}{TC}$	Residual volume to total capacity ratio.
MBC	Maximum breathing capacity, liters per min. BTPS.
$\frac{Paco_2}{VR}$	Change in arterial CO_2 tension, mm. Hg, necessary to double the effective alveolar ventilation.
$\frac{\dot{V}_A/M^2}{Paco_2}$	Increase in effective alveolar ventilation, liters per minute BTPS per sq. meter BSA, associated with a rise of 1 mm. Hg in arterial CO_2 tension.
$\frac{(H^+)a}{VR}$	Change in arterial hydrogen ion concentration, billionths of moles per liter, necessary to double the effective alveolar ventilation.
$\frac{\dot{V}_A/M^2}{(H^+)a}$	Increase in effective alveolar ventilation, liters per minute BTPS per sq. meter BSA, associated with a rise in arterial hydrogen ion concentration of 1 billionth of a mole per liter.

Total pulmonary ventilation per unit time and respiratory frequency were measured with a Tissot gasometer and suitable recording apparatus. Fractions of CO_2 and

[4] The general form of the alveolar equation may be readily derived by expressing the alveolar respiratory exchange ratio in terms of fractions of oxygen and CO_2 in alveolar and inspired air, converting certain of these dry fractions to gas tension, and solving the expression for alveolar oxygen tension (11, 12). The form used in the present study was as follows:

$$PAO_2 = \frac{(P_B-47)(R_A \cdot FIO_2+FICO_2)+PACO_2[1-FICO_2(1-R_A)]}{R_A+FICO_2(1-R_A)}$$

This reduces to the usual alveolar equation in the special case where CO_2 in the inspired air is negligible. R_A was taken as equivalent to R_E.

oxygen in inspired and expired air were determined by the Scholander technique (15). Arterial blood oxygen content, CO_2 content, and oxygen capacity were determined on the Van Slyke manometric apparatus. Arterial blood pH was measured with a Cambridge glass electrode pH meter at 38° C. within ten minutes of removal from the vessel, transfer of blood from artery to glass electrode being accomplished without exposure to air. Arterial serum CO_2 content was calculated from the diagram of Van Slyke and CO_2 tension from the Henderson-Hasselbalch relationship. Lung volumes and maximum breathing capacity were measured with a Benedict-Roth respirometer. The open circuit method was used for determining functional residual capacity (16).

RESULTS

Normal group

The data obtained from observations on twelve normal subjects appear in Tables II–V, with the spirometric and ventilatory data in Tables II and III. Respiratory exchange ratios showed only small variation, there being an average change of 0.06 from the resting value with inhalation of 3 per cent CO_2 and 0.05 with 5 per cent CO_2. Respiratory frequency tended to increase only slightly with CO_2 inhalation, usually not more than about five breaths per minute. In two instances the rate was slower with 5 per cent CO_2 inhalation than with 3 per cent CO_2. A greater tidal volume largely accounted for the increased pulmonary ventilation with CO_2 inhalation, rising to 158 per cent of the resting tidal volume on 3 per cent CO_2, and to 232 per cent on 5 per cent CO_2. Oxygen consumption per square meter body surface area showed no consistent or marked change with 3 per cent CO_2 inhalation, and only an inconstant tendency to rise with 5 per cent CO_2 (average increase 11 ml.). Average total pulmonary ventilation rose to 202 per cent of the resting value with 3 per cent CO_2 inhalation, and to 329 per cent with 5 per cent CO_2. In all instances but two, the physiological dead space increased appreciably with 5 per cent CO_2 inhalation. If the three instances in which a large dead space flutter valve was used are excluded, and the personal dead space is determined by deducting the instrumental dead space (60 ml.) from the observed total dead space (V_D), then there was an average increase in the personal physiological dead space of 39 ml. or 47 per cent with 3 per cent CO_2 inhalation, and of 75 ml. or 61 per cent with 5 per cent CO_2. The average personal physiological dead space was 92 ml. The average values for calculated mean alveolar oxygen tension were 97 mm. Hg at rest, 117 mm. Hg with 3 per cent CO_2 inhalation, and 125 mm. Hg with 5 per cent CO_2. An increase of 3 per cent and 5 per cent CO_2 occurred in each instance, with little individual variation from the average figures. Average effective alveolar ventilation rose to 222 per cent of the resting value with 3 per cent CO_2 inhalation, and to 382 per cent with 5 per cent CO_2.

Table IV contains the data from arterial blood analyses. The pH values are also expressed in terms of absolute hydrogen ion concentration as billionths of moles per liter [5] in order that the

[5] Hydrogen ion concentration as billionths of moles per liter is related to pH in the following way: (H^+) = antilog (9-pH).

TABLE II

Spirometric data in twelve normal subjects *

Subject	Sex	Age	B.S.A.	Vital capacity		Maximum breathing capacity		
				ml.	*% pred.*	*L./min.*	*L./min./M²*	*% pred.*
T. J.	F	43	1.99	3,340	100	78	39	78
J. R. W.	M	35	1.91	4,200	100	144	75.4	100
J. A. W.	M	30	1.96	5,380	100	174	89	100
J. K. A.	M	32	2.10	7,050	100	182	87	100
H. J.	M	17	1.89	4,670	100	106	56	74
J. D.	M	37	1.73	4,685	100	107	62	93
H. M.	M	35	1.79	5,030	100	120	67	100
P. P.	M	35	1.68	4,130	100	121	71.9	100
V. M.	M	18	1.67	4,360	100	137	82.2	100
N. B.	F	27	1.70	3,610	100	151	89	100
B. O.	M	32	1.76	4,530	100	122	69.5	100
M. B.	F	24	1.52	3,050	100	108	72	100

* A value of 100 for per cent predicted vital or maximum breathing capacity indicates that the observed value was 100 per cent or above.

TABLE III

Physiologic data relative to pulmonary ventilation at rest and during CO_2 inhalation in twelve normal subjects

Subject	Inspired gas mixture	Time on mixture (*min.*)	f	R_E	$\dot{V}_{O_2}/M^2$	V_T	$\dot{V}_E$	V_D *ml.*	V_D % $\dot{V}_E$	Calc. $P_{A_{O_2}}$
T. J.	Room air	—	17.7	0.70	125	381	6.76	163	42.8	96
	3% CO_2	20	31	0.72	147	487	15.10	183	37.7	117
	5% CO_2	24	33.3	0.72	165	891	29.65	321	36	128
J. R. W.*	Room air	—	8.7	0.77	123	592	5.16	192	32.3	94
	3% CO_2	26	12.4	0.87	130	982	12.16	382	38.9	117
	5% CO_2	21	14	0.82	133	1,377	19.26	520	37.7	125
J. A. W.*	Room air	—	9	0.75	127	595	5.36	218	36.7	96
	3% CO_2	27	12	0.76	117	838	10.07	311	37.1	116
	5% CO_2	30	13.7	0.76	149	1,420	19.48	408	28.7	126
J. K. A.	Room air	—	11	0.73	96	433	4.76	149	34.3	96
	3% CO_2	26	11	0.73	122	836	9.20	170	20.3	115
	5% CO_2	32	13.7	0.77	149	1,274	17.43	161	12.6	124
H. J.*	Room air	—	18	0.86	137	425	7.64	170	39.9	100
	3% CO_2	29	21.3	0.83	139	600	12.80	175	29.2	117
	5% CO_2	29	22.3	0.76	125	912	20.35	380	41.7	124
J. D.	Room air	—	15.3	0.74	140	422	6.44	185	43.8	91
	3% CO_2	28	17	0.74	118	586	9.96	237	40.6	111
	5% CO_2	28	19	0.84	125	729	13.87	148	20.3	122
H. M.	Room air	—	24.3	0.83	120	296	7.09	149	50.6	92
	3% CO_2	26	25	0.96	108	504	12.60	217	43.1	115
	5% CO_2	28	27.7	0.84	115	658	18.24	300	45.6	120
P. P.	Room air	—	19.7	0.83	107	282	5.53	129	45.8	91
	3% CO_2	26	25.7	0.95	112	471	12.10	195	41.5	118
	5% CO_2	26	26.3	0.74	123	593	15.60	227	38.4	122
V. M.	Room air	—	9.3	0.77	96	424	3.94	133	31.3	97
	3% CO_2	25	13.7	0.86	141	959	13.14	246	25.7	120
	5% CO_2	27	17.7	0.77	121	1,193	21.13	382	32.1	127
N. B.	Room air	—	15.3	0.86	110	419	6.42	164	39.2	105
	3% CO_2	30	24	0.96	105	549	13.17	171	31.2	124
	5% CO_2	26	21.3	0.85	116	922	19.68	201	21.8	128
B. O.	Room air	—	15	0.83	115	405	6.07	166	41	101
	3% CO_2	30	17.3	0.88	118	626	10.83	162	26	120
	5% CO_2	31	18.3	0.77	114	948	17.35	116	12	128
M. B.	Room air	—	20.7	0.77	116	272	5.62	128	47.2	99
	3% CO_2	33	23	0.80	109	376	8.64	136	36.1	117
	5% CO_2	37	22.3	0.70	111	632	14.10	181	28.7	126

* Large dead space flutter valve used.

changes in ventilation may be related to these concentrations after the manner of Gray (17). Average values for arterial blood pH were 7.42 at rest, 7.41 with 3 per cent CO_2 inhalation, and 7.38 with 5 per cent CO_2. Hydrogen ion concentrations expressed as billionths of moles per liter corresponding to the above pH values are 37.9, 38.8, and 41.7, respectively. Average values for arterial CO_2 tension in mm. Hg were 41.5 at rest, 44 with 3 per cent CO_2 inhalation, and 46.5 with 5 per cent CO_2. Although tending to rise with CO_2 inhalation, the changes in oxygen saturation of the arterial blood were somewhat less consistent, presumably because of inability to measure accurately with the Van Slyke technique the small changes in oxygen saturation associated with increased oxygen tension in this region of the dissociation curve. Arterial hematocrit showed no appreciable change. No direct observations on urinary constituents were made to evaluate possible renal adjustments to the respiratory acidosis induced during the thirty-minute period of CO_2

breathing. However, the absence of any appreciable change in the whole blood buffer base at the end of the CO_2 inhalation period suggests that such adjustments as may have occurred were not significant.

Observations on changes in effective alveolar ventilation, and correlation of these changes with hydrogen ion concentration and CO_2 tension in the arterial blood are described in Table V. If the effective alveolar ventilation is measured in terms of liters per minute per square meter body surface area, the average value at rest is 1.93. Body surface area has been arbitrarily chosen here as a reference point which would permit some comparison of alveolar ventilation, oxygen consumption, and sensitivity to chemical respiratory stimuli among the normal subjects and the other groups studied. The age range in this group of normal subjects was 17 to 43 years, average age 30.4. Robinson's data (18) for the closest average age group (35.1 years) yield a figure of 2.07 liters per minute per square meter body surface area for effective alveolar ventilation. Typical stimulus-response curves or sensitivity slopes of a

TABLE IV

Physiologic data relative to the arterial blood at rest and during CO_2 inhalation in twelve normal subjects

Subject	Inspired gas mixture	pHs	$(H^+)a$	Cs_{CO_2}	Pa_{CO_2}	Sa_{O_2}	Vc	Calc. $(B_B{}^+)b$
T. J.	Room air	7.42	38.0	58.1	39	92	33	47
	3% CO_2	7.41	38.9	58.6	40.5	97	33	47
	5% CO_2	7.37	42.6	59.2	45	95	34	47
J. R. W.	Room air	7.42	38.0	66.3	45	96	41	51
	3% CO_2	7.41	38.9	67.0	46.5	96	42	51
	5% CO_2	7.39	40.7	67.8	49.5	100	41	51
J. A. W.	Room air	7.40	39.8	61.4	43	98	42	49
	3% CO_2	7.39	40.7	61.8	45	98	42	49
	5% CO_2	7.37	42.7	63.5	48	99	43	49
J. K. A.	Room air	7.45	35.5	64.1	40.5	97	37	50
	3% CO_2	7.42	38.0	64.6	43	100	37	50
	5% CO_2	7.40	39.8	66.3	47.5	100	39	50
H. J.	Room air	7.42	38.0	63.3	42.5	99	40	50
	3% CO_2	7.41	38.9	63.5	43.5	98	40	50
	5% CO_2	7.40	39.8	64.1	45	97	41	50
J. D.	Room air	7.44	36.3	67.3	43	97	41	52
	3% CO_2	7.42	38.0	66.1	44.5	99	41	51
	5% CO_2	7.40	39.8	66.4	47	96	42	51
H. M.	Room air	7.40	39.8	62.7	44.5	96	41	49
	3% CO_2	7.39	40.7	62.7	46	96	42	50
	5% CO_2	7.37	42.7	63.6	48	96	42	49
P. P.	Room air	7.42	38.0	64.9	43.5	95	39	50
	3% CO_2	7.41	38.9	66.4	45.5	95	39	51
	5% CO_2	7.39	40.7	64.7	47	97	40	49
V. M.	Room air	7.40	39.8	56.1	39.5	97	42	47
	3% CO_2	7.39	40.7	57.7	41.5	98	43	47
	5% CO_2	7.38	41.7	57.1	42.5	99	43	46
N. B.	Room air	7.43	37.2	55.4	37	98	37	47
	3% CO_2	7.40	39.8	56.6	40	99	38	47
	5% CO_2	7.36	43.7	59.6	46	99	38	47
B. O.	Room air	7.44	36.3	60.3	40.5	98	47	51
	3% CO_2	7.42	38.0	65.1	43.5	96	47	51
	5% CO_2	7.40	39.8	64.9	45.5	97	48	51
M. B.	Room air	7.43	37.2	59.6	40	99	37	49
	3% CO_2	7.39	40.7	61.6	44.5	99	36	48
	5% CO_2	7.35	44.7	60.6	47	96	36	47

TABLE V

Physiologic data relative to effective alveolar ventilation and sensitivity to the carbon dioxide-hydrogen ion stimulus in twelve normal subjects

Subject	Inspired gas mixture	$\dot{V}_A$	$\dot{V}_A/M^2$	VR	$\frac{Pa_{CO_2}}{VR}$	$\frac{\dot{V}_A/M^2}{Pa_{CO_2}}$	$\frac{(H^+)a}{VR}$	$\frac{\dot{V}_A/M^2}{(H^+)a}$
T. J.	Room air	3.86	1.94	1				
	3% CO_2	9.40	4.72	2.33	1.5	1.4	1.2	1.8
	5% CO_2	19.	9.55	4.92				
J. R. W.	Room air	3.48	1.82	1				
	3% CO_2	7.43	3.89	2.13	1.7	1.2	1.1	1.9
	5% CO_2	12.	6.28	3.44				
J. A. W.	Room air	3.38	1.72	1				
	3% CO_2	6.33	3.23	1.87	1.6	1.1	0.9	1.9
	5% CO_2	13.88	7.08	4.12				
J. K. A.	Room air	3.13	1.49	1				
	3% CO_2	7.33	3.49	2.33	1.8	0.9	1.2	1.5
	5% CO_2	15.25	7.26	4.87				
H. J.	Room air	4.58	2.42	1				
	3% CO_2	9.05	4.79	1.97	1.5	1.6	1.1	2.2
	5% CO_2	11.83	6.26	2.58				
J. D.	Room air	3.62	2.09	1				
	3% CO_2	5.91	3.42	1.63	2.0	1.0	1.7	1.1
	5% CO_2	11.10	6.42	3.06				
H. M.	Room air	3.50	1.96	1				
	3% CO_2	7.17	4.01	2.05	1.9	1.1	1.5	1.4
	5% CO_2	9.92	5.54	2.84				
P. P.	Room air	3.	1.79	1				
	3% CO_2	7.07	4.21	2.36	1.5	1.2	1.1	1.7
	5% CO_2	9.60	5.71	3.19				
V. M.	Room air	2.71	1.62	1				
	3% CO_2	9.75	5.84	3.60	0.8	2.3	0.5	3.8
	5% CO_2	14.30	8.56	5.27				
N. B.	Room air	3.90	2.30	1				
	3% CO_2	9.06	5.33	2.32	2.7	0.9	2.0	1.1
	5% CO_2	15.40	9.06	3.95				
B. O.	Room air	3.58	2.03	1				
	3% CO_2	8.02	4.56	2.24	1.5	1.3	0.9	2.2
	5% CO_2	15.23	8.65	4.25				
M. B.	Room air	2.97	1.95	1				
	3% CO_2	5.53	3.64	1.86	2.2	0.8	2.9	0.7
	5% CO_2	10.04	6.60	3.38				
				Average:	1.7	1.2	1.3	1.8
				Range	0.8–2.7	0.8–2.3	0.5–2.9	0.7–3.8
				S.D.	±0.5	±0.3	±0.6	±0.7

normal subject, constructed in the manner previously indicated, are shown in Figures 1 and 2.

To double the effective alveolar ventilation at rest an average increase of 1.7 mm. Hg (range 0.8 to 2.7, S.D. ± 0.5) in arterial CO_2 tension was required, associated with an average increase in arterial hydrogen ion concentration of 1.3×10^{-7} moles per liter (range 0.5 to 2.9, S.D. ± 0.6). For each mm. Hg rise in CO_2 tension of the arterial blood there was an average increase in effective alveolar ventilation per square meter body surface area of 1.2 liters per minute (range 0.8 to 2.3, S.D. ± 0.3). For an increase of 1.0×10^{-7} moles per liter in hydrogen ion concentration of the arterial blood an average increase in effective alveolar ventilation per square meter body surface

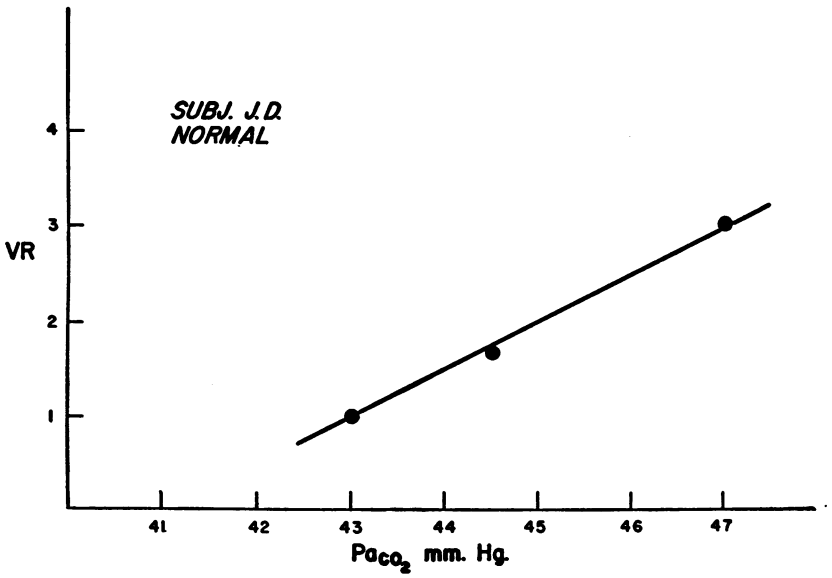

FIG. 1. STIMULUS RESPONSE CURVE IN A NORMAL SUBJECT, RELATING ARTERIAL CO_2 TENSION TO ALVEOLAR VENTILATION RATIO

area of 1.9 liters per minute (range 0.7 to 3.8, S.D. ± 0.7) occurred.

Pulmonary emphysema

Thirteen patients with chronic pulmonary emphysema were studied. All tolerated the CO_2 inhalation well, without respiratory distress. A few complained of mild headache following the procedure. The patients have been separated into three groups according to the classification of Baldwin, Cournand, and Richards (1). Those in Group II were found to have arterial oxygen un-

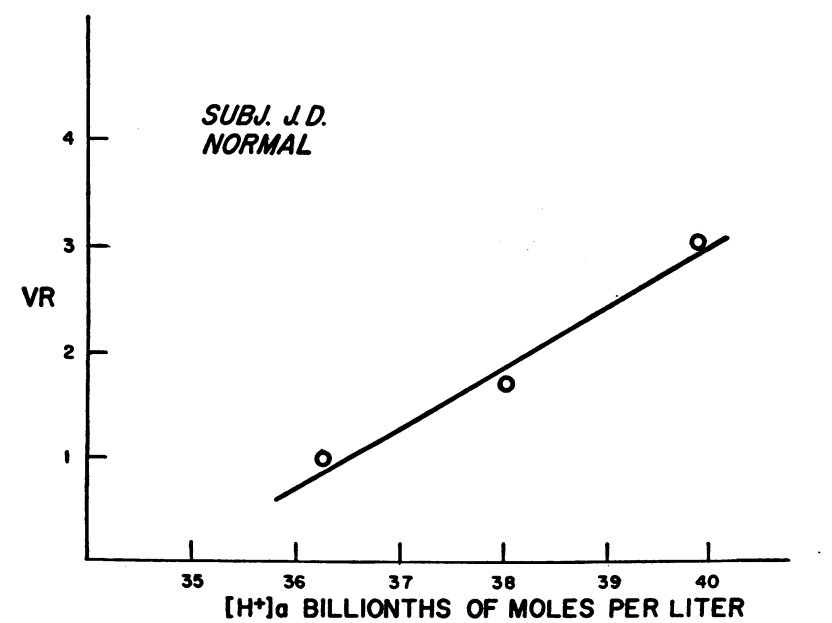

FIG. 2. STIMULUS RESPONSE CURVE IN A NORMAL SUBJECT, RELATING ARTERIAL HYDROGEN ION CONCENTRATION TO ALVEOLAR VENTILATION RATIO

TABLE VI

Physiologic data relative to pulmonary ventilation and arterial blood under conditions of rest and standard exercise in thirteen emphysematous subjects *

Subject			$\dot{V}_E/M^2$		$\dot{V}_{O_2}/M^2$		Arterial blood					
							pHs		Sa_{O_2}		Pa_{CO_2} mm. Hg	
Sex	Age	B.S.A.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.
					Emphysema IV							
F A. M.	47	1.65	4.30	—	137	—	7.33	—	59	—	54	—
M F. J.	47	1.75	3.45	11.15	134	—	7.38	7.28	78	75	54	64
M W. D.	58	1.64	5.00	12.60	160	306	7.46	7.42	87.6	54.8	45	50
M R. C.	74	1.81	4.79	7.91	141	242	7.44	7.43	86	75.8	49.5	51.5
M J. R.	52	1.79	3.74	5.88	139	207	7.38	7.32	81.6	53.8	59	66
M C. M.	70	1.53	5.95	12.67	145	306	7.36	7.36	88.1	84.7	55	52
					Emphysema III							
M G. R.	56	1.82	5.05	16.9	141	575	7.40	7.39	97.6	93	48	49
M R. D.	75	1.54	3.99	10.15	119	301	7.39	7.36	90.4	86.4	48	53
M J. Y.	46	1.83	4.83	12.60	143	405	7.40	7.29	80.6	67.7	47	60
					Emphysema II							
M D. C.	48	1.61	5.70	12.61	127	374	7.43	7.42	93	90	40	40
M G. B.	69	1.46	7.36	19.60	166	486	7.40	7.40	89	89	41	37
F R. F.	54	1.60	4.69	15.12	134	436	7.40	7.38	96.2	90.5	36	36.5
M A. H.	48	1.89	5.63	14.47	133	402	7.44	7.45	92.2	92.7	36	35

* In some instances these studies were done on a different day than those recorded in Tables VIII and IX, so that resting values are not exactly the same.

saturation at rest or following standard exercise, but no CO_2 retention. In addition to anoxemia, those in Group III had elevation of the arterial CO_2 tension at rest or following exercise, but no evidence of congestive heart failure. Finally, patients in Group IV suffered from anoxemia, CO_2 retention and cor pulmonale, with chronic congestive failure. The data obtained relative to ventilation, oxygen consumption, and arterial blood in these patients under conditions of rest and exercise appear in Table VI. Indices of intrapulmonary mixing, lung volumes, maximum breathing capacities, and serum electrolytes where available, are shown in Table VII. All were found to have reductions in vital and maximum breathing capacities. Both the index of intrapulmonary gas mixing and the residual volume to total capacity ratio were increased in all instances except one.

The response of the emphysematous subjects to the CO_2 stimulus was determined in the same manner as was done with the normal individuals. The data so derived are shown in Tables VIII, IX, and X. Similar results were obtained in Groups III and IV, and they may be considered together. Certain of these results, with the average normal values for comparison, are summarized in Table XI. As indicated by the respiratory exchange ratios in Table VIII, it was possible to achieve steady states during CO_2 inhalation which were comparable to those in normal individuals. The average percentage increases in tidal volume and total pulmonary ventilation were approximately half the normal values. As in the normal group, there was little change in oxygen consumption with CO_2 inhalation, but the average oxygen consumption of 137 ml. per square meter body surface area at rest for the emphysematous pa-

TABLE VII

Physiologic data relative to intrapulmonary gas mixing, lung volumes, and maximum breathing capacity with clinical findings in thirteen emphysematous subjects

Subject	Index of intrapulmonary mixing RV/TC	Vital capacity ml.	Vital capacity % pred.	Total capacity ml.	Total capacity % pred.	Max. breathing cap. L./min.	Max. breathing cap. L./min./M²	Max. breathing cap. % pred.	Serum electrolytes mEq./L. Na	K	Cl	BUN mg. %	Notes
						Emphysema IV							
A. M.	—	—	1,570	59	—	—	17.8	10.8	22	142.3	5.1	101.4	14	Marked congestive failure. Could not be exercised. FRC not done. Marked exp. prolongation. VC & MBC increased p bronchodilator.*
F. J.	3.33	46	2,230	60	4,160	86	27.9	16	26	—	—	—	15	Chronic congestive failure. Marked exp. prolongation. VC & MBC increased p bronchodilator.
W. D.	5.98	72	1,520	42	5,540	106	14.1	8.6	14	145	5.0	95	(NPN 38)	Mild congestive failure. Exp. prolongation. VC & MBC increased p bronchodilator.
R. C.	11.56	57	1,784	54	4,142	87	15.4	8.5	18	—	—	98.6	19	Exercise 18 steps only in one min. Mild congestive failure. Exp. prolongation. VC & MBC increased p bronchodilator.
J. R.	5.82	50	2,470	65	4,962	90	22.8	12.9	22	—	—	—	—	Exercise 25 steps in one min. Chronic congestive failure, mild. Exp. prolongation. Little improvement p bronchodilator.
C. M.	5.99	50	1,898	59	3,823	82	48.7	32	64	143.6	5.0	94.0	33	Mild congestive failure. Exp. prolongation. MBC increased p bronchodilator.
						Emphysema III							
G. R.	3.49	48	2,540	68	4,163	77	92.2	50.6	88	—	—	—	16.5	Diffuse infiltration both lungs by x-ray consistent with clinical diagnosis of asbestosis.
R. D.	6.93	59	1,992	67	4,815	112	27.5	17.8	40	—	—	—	18	Exercise 26 steps in one min. Exp. prolongation. VC & MBC increased p bronchodilator.
J. Y.	9.93	58	2,755	68	5,290	125	49.5	27	43	—	—	—	—	Modest increases in VC & MBC p bronchodilator.
						Emphysema II							
D. C.	3.42	30	3,340	89	4,785	98	54.1	33.6	55	—	—	—	—	Expiratory prolongation. MBC increased p bronchodilator.
G. B.	5.15	54	2,860	75	6,220	110	52.2	37.8	75	136.6	5.0	98	23	Exercise 25 steps in one min. Exp. prolongation. Little improvement p bronchodilator.
R. F.	2.06	41	1,520	57	2,597	68	28.2	17.6	44	—	—	—	23	Bronchiectasis. Slight exp. prolongation. VC and MBC increased p bronchodilator.
A. H.	4.07	54	1,860	46	5,190	78	43.9	23.5	38	135	4.5	95.6	10	Congestive circulatory failure secondary to constrictive pericarditis, the latter suspected on basis of cardiac catheterization data, confirmed by pericardial biopsy. Marked improvement in VC and MBC p bronchodilator.

* Bronchodilator agent used in these studies was "Vaponefrin," a 2.25 per cent solution of racemic epinephrine hydrochloride.

TABLE VIII

Physiologic data relative to pulmonary ventilation at rest and during CO_2 inhalation in thirteen emphysematous subjects

Subject	Inspired gas mixture	Time on mixture (*min.*)	f	R_E	$\dot{V}_{O_2}/M^2$	V_T	$\dot{V}_E$	V_D *ml.*	V_D % $\dot{V}_E$	Calc. $P_{A_{O_2}}$
					Emphysema IV					
A. M.	Room air	—	21.3	0.73	137	332	7.10	207	62.3	80
	3% CO_2	30 min.	24	0.70	145	392	9.41	226	57.6	97
	5% CO_2	24 min.	24	0.67	178	563	13.50	322	57.2	103
F. J.	Room air	—	15.7	0.70	131	366	5.74	163	44.6	88
	3% CO_2	28 min.	16.3	0.83	118	610	9.95	302	49.5	107
	4% CO_2	33 min.	17.8	0.65	143	656	11.68	328	50.2	109
W. D.	Room air	—	17	0.76	160	483	8.20	253	52.3	91
	3% CO_2	26 min.	17.2	0.80	153	683	11.74	317	46.3	107
	4% CO_2	26 min.	21.2	0.76	179	691	14.62	306	44.2	111
R. C.	Room air	—	23.7	0.73	141	366	8.67	227	62.1	84
	3% CO_2	30 min.	24.7	0.73	137	483	11.92	293	60.6	98
	5% CO_2	25 min.	26.7	0.64	163	572	15.28	349	61.0	100
J. R.	Room air	—	13.7	0.79	139	483	6.62	275	57.0	77
	3% CO_2	32 min.	15	0.81	130	543	8.15	288	53.0	93
	5% CO_2	30 min.	15.7	0.84	125	655	10.28	344	52.5	102
C. M.	Room air	—	19.7	0.74	145	462	9.10	329	71.4	79
	3% CO_2	25 min.	25	0.77	128	487	12.17	353	72.7	95
	5% CO_2	25 min.	24	0.78	135	644	15.45	455	70.6	103
					Emphysema III					
G. R.	Room air	—	20.67	0.77	135	430	8.90	262	60.7	92
	3% CO_2	25 min.	20.34	0.79	127	653	13.25	387	59.3	111
	5% CO_2	22 min.	21	0.73	153	950	19.95	493	51.8	118
R. D.	Room air	—	13.7	0.82	119	448	6.14	250	55.8	91
	3% CO_2	30 min.	16.7	0.88	113	633	10.55	354	55.9	109
	5% CO_2	28 min.	20	0.70	123	758	15.17	463	61.2	113
J. Y.	Room air	—	20.3	0.85	128	458	9.30	286	62.4	89
	3% CO_2	26 min.	18.7	0.77	140	643	12.	347	54.0	105
	5% CO_2	25 min.	20.7	0.78	159	814	16.85	424	52.2	107
					Emphysema II					
D. C.	Room air	—	23.0	0.76	146	403	9.27	224	55.7	102
	3% CO_2	28 min.	24.7	0.74	159	696	17.20	272	39	110
	4% CO_2	28 min.	28.3	0.83	161	868	24.60	267	30.7	130
G. B.	Room air	—	23.7	0.80	166	453	10.73	281	61.8	99
	3% CO_2	28 min.	25.3	0.91	147	662	16.76	347	52.5	120
	5% CO_2	28 min.	26	0.84	178	975	25.30	396	40.7	125
R. F.	Room air	—	22.3	0.77	134	337	7.51	158	47.1	104
	3% CO_2	30 min.	27.7	0.75	130	513	14.23	202	39.3	124
	5% CO_2	28 min.	32	0.81	117	722	23.10	213	29.6	131
A. H.	Room air	—	16	0.75	132	519	8.30	764	50.9	98
	3% CO_2	29 min.	23.7	0.75	138	694	16.45	338	48.6	117
	5% CO_2	25 min.	25.3	0.78	162	1,054	26.68	431	40.8	123

tients was higher than the average figures for the normal group by 19 ml. Although the changes in physiological dead space with CO_2 inhalation were approximately the same as the normal percentagewise, the average personal dead space at rest of 208 ml. was twice the normal, and the absolute changes were almost twice as great. The alveolar oxygen tensions were consistently lower at rest than in the normal group, with a lesser degree of change during CO_2 inhalation.

The relationships between effective alveolar ventilation and arterial blood CO_2 tensions and hy-

drogen ion concentration are found in Table X. The data were handled in the same way as in the normal group, and the stimulus response relationships obtained were found to be linear. Although the age groups are not comparable, it may be noted that the average effective alveolar ventilation per square meter body surface area at rest (1.84 liters) in the Group III and IV emphysema categories was slightly lower than that of 1.93 liters for the normal group. Thus the elevated arterial CO_2 tension at rest in the emphysematous groups would presumably stem from the effects of

TABLE IX

Physiologic data relative to the arterial blood at rest and during CO_2 inhalation in thirteen emphysematous subjects

Subject	Inspired gas mixture	pHs	$(H^+)a$	Cs_{CO_2}	Pa_{CO_2}	Sa_{O_2}	Vc	Calc. $(B_{B^+})b$
			Emphysema IV					
A. M.	Room air	7.33	46.8	65.3	54	59	47	49
	3% CO_2	7.30	50.1	65.3	58	77	50	49
	5% CO_2	7.28	52.5	69.0	64	77	55	49
F. J.	Room air	7.41	38.9	64.0	44	79	48	51
	3% CO_2	7.35	44.7	65.4	52	87	48	50
	5% CO_2	7.33	46.8	65.2	54	87	49	49
W. D.	Room air	7.46	34.7	72.6	45	88	55	56
	3% CO_2	7.45	35.5	78.6	50	91	55	58
	5% CO_2	7.43	37.2	79.7	53	91	56	58
R. C.	Room air	7.44	36.6	76.0	49.5	86	41	55
	3% CO_2	7.39	41.0	78.9	57.5	92	42	55
	5% CO_2	7.35	44.9	80.5	64	92	45	55
J. R.	Room air	7.38	41.6	79.8	59	82	52	55
	3% CO_2	7.36	44.0	81.8	64	89	51	56
	5% CO_2	7.34	45.7	81.8	67	92	52	56
C. M.	Room air	7.36	43.7	71.4	55	88	60	52
	3% CO_2	7.32	47.8	72.0	61	94	60	52
	5% CO_2	7.30	50.1	73.5	65	95	59	52
			Emphysema III					
G. R.	Room air	7.42	38.0	69.0	47	88	41	53
	3% CO_2	7.39	40.7	68.4	50	95	41	52
	5% CO_2	7.37	42.7	70.2	53	—	42	51
R. D.	Room air	7.39	40.9	66.1	48	90	40	52
	3% CO_2	7.36	43.3	67.3	52	95	40	50
	5% CO_2	7.34	45.8	68.8	56	94	41	50
J. Y.	Room air	7.37	42.6	66.1	50	87	48	51
	3% CO_2	7.36	43.7	68.6	53	94	48	51
	5% CO_2	7.29	51.2	68.5	62	99	48	50
			Emphysema II					
D. C.	Room air	7.46	34.7	61.1	38	90	41	50
	3% CO_2	7.45	35.5	61.1	39	91	41	50
	5% CO_2	7.43	37.2	62.0	41	95	42	50
G. B.	Room air	7.40	39.8	58.0	41	89	46	48
	3% CO_2	7.39	40.7	60.0	43	91	47	49
	5% CO_2	7.37	42.7	61.4	46	97	47	49
R. F.	Room air	7.40	40.1	50.3	36	96	39	45
	3% CO_2	7.39	40.9	51.8	37.5	96	40	45
	5% CO_2	7.33	46.6	51.8	42	95	42	44
A. H.	Room air	7.44	36.3	62.4	40	92	43	50
	3% CO_2	7.43	37.2	62.2	41.5	95	44	50
	5% CO_2	7.38	41.7	63.9	47	96	47	50

TABLE X

Physiologic data relative to effective alveolar ventilation and sensitivity to the carbon dioxide-hydrogen ion stimulus in thirteen emphysematous subjects

Subject	Inspired gas mixture	$\dot{V}_A$	$\dot{V}_A/M^2$	VR	$\frac{Pa_{CO_2}}{VR}$	$\frac{\dot{V}_A/M^2}{Pa_{CO_2}}$	$\frac{(H^+)a}{VR}$	$\frac{\dot{V}_A/M^2}{(H^+)a}$
				Emphysema IV				
A. R.	Room air	2.68	1.62	1				
	3% CO_2	3.99	2.42	1.49	8.6	0.2	5.7	0.3
	5% CO_2	5.78	3.50	2.15				
F. J.	Room air	3.18	1.82	1				
	3% CO_2	5.02	2.87	1.57	13.0	0.1	9.6	0.2
	5% CO_2	5.82	3.33	1.83				
W. D.	Room air	3.91	2.38	1				
	3% CO_2	6.32	3.85	1.61	7.4	0.3	2.3	1.1
	5% CO_2	8.16	4.98	2.08				
R. C.	Room air	3.29	1.82	1				
	3% CO_2	4.70	2.60	1.43	17.0	0.1	10.1	0.2
	5% CO_2	5.98	3.30	1.81				
J. R.	Room air	2.85	1.59	1				
	3% CO_2	3.83	2.14	1.34	12.0	0.1	6.7	0.3
	5% CO_2	4.88	2.72	1.71				
C. M.	Room air	2.60	1.70	1				
	3% CO_2	3.33	2.18	1.28	14.0	0.1	9.7	0.2
	5% CO_2	4.55	2.97	1.75				
				Emphysema III				
G. R.	Room air	3.48	1.91	1				
	3% CO_2	5.38	2.96	1.55	4.4	0.5	2.9	0.6
	5% CO_2	9.60	5.27	2.75				
R. D.	Room air	2.72	1.77	1				
	3% CO_2	4.66	3.03	1.71	6.5	0.3	4.0	0.5
	5% CO_2	5.90	3.83	2.17				
J. Y.	Room air	3.50	1.91	1				
	3% CO_2	5.52	3.02	1.58	8.4	0.2	5.0	0.4
	5% CO_2	8.04	4.39	2.30				
				Emphysema II				
D. C.	Room air	4.11	2.55	1				
	3% CO_2	10.33	6.42	2.52	0.9	2.9	0.8	3.4
	5% CO_2	17.02	10.57	4.14				
G. B.	Room air	4.10	2.81	1				
	3% CO_2	7.98	5.46	1.94	1.9	1.5	1.1	2.6
	5% CO_2	15.00	10.28	3.67				
R. F.	Room air	3.97	2.48	1				
	3% CO_2	8.66	5.41	2.18	1.7	1.3	1.5	1.6
	5% CO_2	16.25	10.17	4.10				
A. H.	Room air	4.07	2.15	1				
	3% CO_2	8.45	4.47	2.08	2.1	1.0	1.8	1.2
	5% CO_2	15.80	8.37	3.88				

diminished effective alveolar ventilation and some slight increase in CO_2 production, possibly related to greater respiratory work. The average percentage increases in effective alveolar ventilation with 3 per cent and 5 per cent CO_2 inhalation were less than half the average normal values. To double the effective alveolar ventilation, which was accomplished in only five of the nine cases, an increase of 4.4 to 17 mm. Hg in the arterial CO_2 tension was required. The changes were well out of the normal range in all instances, usually several times the average normal value. The as-

sociated change in hydrogen ion concentration necessary to double the effective alveolar ventilation was usually three or more times the average normal value, although in two instances it fell at the upper limit of the normal range. For each mm. Hg rise in the arterial CO_2 tension there was an increase in effective alveolar ventilation per square meter body surface area of only 0.1 to 0.5 liter per minute, as compared with an average increase of 1.2 liters per minute in the normal group. The smallest increase in the normal group was 0.8 liter per minute. For a billionth of a mole per liter increase in arterial blood hydrogen ion concentration, the effective alveolar ventilation per square meter body surface area rose only 0.2 to 1.1 liters per minute. The average value in the normal group was 1.9 liters per minute, and in only one instance was the value of a Group III or IV emphysema patient within the normal range.

Observations on four emphysematous patients without CO_2 retention (Group II) are shown in Tables VIII, IX and X. The findings at rest and changes with CO_2 inhalation are roughly comparable to the normal with regard to respiratory exchange ratio, respiratory frequency, oxygen consumption, tidal volume, total pulmonary ventilation, and calculated mean effective alveolar oxygen tension. The physiological dead space at rest is greater than normal as would be expected. Except for lowered oxygen saturation, the results of arterial blood analyses differ little from those described in the normal group. Effective alveolar ventilation per square meter body surface area at rest was greater than the average normal value in all instances. Nevertheless the changes in effective alveolar ventilation with CO_2 inhalation were essentially the same as in the normal group, *i.e.*, roughly two times the resting value with 3 per cent CO_2 inhalation, and four times the resting value with 5 per cent CO_2. Relationships between effective alveolar ventilation and arterial CO_2 tension or hydrogen ion concentration obtained in the manner previously described, fell within the normal range, indicating a normal ventilatory response to the carbon dioxide-hydrogen ion stimulus.

Cyanotic congenital heart disease

Of the patients with cyanotic congenital heart disease, the diagnosis of pulmonic stenosis and interatrial defect had been made in one, and that of Eisenmenger's Complex in two, on the basis of cardiac catheterization studies. Spirometric data and clinical notes on these patients are shown in Table XII. Vital and maximum breathing capacities were within the normal range except in one instance where moderate kyphosis probably accounted for some reduction in the vital capacity. Observations on ventilation and arterial blood at rest and during CO_2 inhalation appear in Tables XIII, XIV, and XV. All three patients had arterial oxygen unsaturation and polycythemia of appreciable degree. In addition two had lowered arterial CO_2 tensions and a tendency to alkalosis. Oxygen consumption per square meter body surface area, total pulmonary ventilation, and ef-

TABLE XI

Response of emphysematous subjects (groups III and IV) and normal subjects to CO_2 inhalation. Comparison of sensitivity to the carbon dioxide-hydrogen ion stimulus

Inspired gas mixture	pH average values		Pa_{CO_2} average increase		PA_{O_2} average values		$\dot{V}_E$ average increase		$\dot{V}_A$ average increase	
	Normal	Emphysema	Normal	Emphysema	Normal	Emphysema	Normal	Emphysema	Normal	Emphysema
			mm. Hg		*mm. Hg*		%		%	
Room air	7.42	7.40	—	—	97	86	—	—	—	—
3% CO_2 in air	7.41	7.36	2.5	5.1	117	102	202	144	222	151
5% CO_2 in air	7.38	7.34	5.0	9.6	125	107	329	192	382	206

	Pa_{CO_2}/VR	$\frac{\dot{V}_A/M^2}{Pa_{CO_2}}$	$(H^+)a/VR$	$\frac{\dot{V}_A/M_2}{(H^+)a}$
Normal average value	1.7	1.2	1.3	1.9
Emphysema range	4.4–17	0.1–0.5	2.3–10.1	0.2–1.1

TABLE XII

Spirometric data and clinical findings in patients with cyanotic congenital heart disease, chronic acidosis, and chronic alkalosis

Patient Sex	Age	B.S.A.	Vital capacity ml.	Vital capacity % pred.	Maximum breathing cap. L./min.	Maximum breathing cap. L./min./M²	Maximum breathing cap. % pred.	Notes
				Cyanotic congenital heart disease				
M J. B.	23	1.67	4,630	108	124.5	75	100	Moderate reduction in exercise tolerance. Pulmonic stenosis with interatrial defect and right-to-left shunt.
M R. W.	28	1.64	2,170	57	97.3	59.3	83	Kyphosis of moderate degree. Eisenmenger's Complex.
M W. M.	26	1.86	5,880	137	170	91.3	126	Moderate reduction in exercise tolerance. Eisenmenger's Complex.
				Chronic acidosis				
F G. K.	30	1.58	2,590	89	72	45.6	80	Chronic glomerulonephritis since age 5. Nitrogen retention documented for 3 yrs. prior to study. At time of study serum electrolyte levels, mEq./L., Na 135.8, Cl 98.6, K 4.7; BUN 83 mg. %.
M J. K.	48	1.67	2,146	61	71.7	43	70	Nephritis since age 17 with documented nitrogen retention for 7 yrs. prior to study. Lowered venous serum CO_2 content found on occasion over several years. At time of study serum electrolyte levels, mEq./L., Na 131.4, Cl 104.6, K 5.6, BUN 96 mg. %.
M E. W.	51	1.91	2,695	80	71.5	37.4	62	Documented nitrogen retention for 3 yrs. prior to study. Presumed diagnosis arteriolar nephrosclerosis. At time of study serum electrolyte levels, mEq./L., Na 139, Cl 125, K 7.1, BUN 58 mg. %.
				Chronic alkalosis				
F K. S.	49	1.65	2,030	80	57.3	35	73	Functioning adrenal cortical carcinoma and secondary Cushing's syndrome. Documented hypochloremic alkalosis and CO_2 retention for two months prior to study. At time of study serum electrolytes, mEq./L., Na 138.2, Cl 96.2, K 3.9.
F J. T.	41	1.59	4,330	152	153.4	96.5	187	Adrenal cortical hyperplasia with documented hypochloremic alkalosis for two months prior to therapy. No CO_2 retention for approx. 4 mos. at the time of study.

fective alveolar ventilation [6] at rest were uniformly elevated. The effective alveolar ventilation per square meter body surface area was 50 per cent or more greater than the average normal value in all three patients. With CO_2 inhalation, the changes

[6] The effective alveolar ventilation in these cases, as in the normal group, was calculated on the assumption that alveolar CO_2 tension was equivalent to arterial CO_2 tension. This of course is not a valid assumption in these patients because of venous admixture to left ventricular blood through the right to left intracardiac shunt. Thus the actual effective alveolar ventilation at rest was somewhat higher than that recorded in Table XV. Since no pulmonary arterial blood samples were obtained at the time of the CO_2 inhalation study which would allow estimation of the degree of venous admixture, no calculations were carried out attempting to correct arterial CO_2 tension to alveolar CO_2 tension. This would introduce no error in the slope of the CO_2 response curve if the degree of shunt remained constant with CO_2 inhalation. However, even if the amount shunted were to change by as much as 10 per cent with CO_2 inhalation, the difference in the corrected alveolar CO_2 tension would be no greater than 1 mm. Hg. Thus, no appreciable error has been introduced into the measurement of the *change* in effective alveolar ventilation with CO_2 inhalation, a partial determinant of the slope of the stimulus response curve. Because of the lack of specific values for alveolar CO_2 tension, no calculations of mean effective alveolar oxygen tension were carried out.

in respiratory exchange ratio and frequency, tidal volume, ventilation, physiological dead space, pH, CO_2 tension, and buffer base were similar to those observed in the normal group. However, the increase in oxygen consumption per square meter body surface area with 5 per cent CO_2 breathing in these patients was consistent, and was presumably related to the high rates of ventilation observed. As expected, only a small increase in arterial oxygen saturation occurred with CO_2 inhalation, despite substantial increments in effective alveolar ventilation. As in the normal group, the relationships between changes in effective alveolar ventilation and arterial CO_2 tension or hydrogen ion concentration were found to be essentially linear. The observed changes in arterial CO_2 tension and hydrogen ion concentration associated with doubling of the effective alveolar ventilation fell within the normal range, although an increased response in terms of effective alveolar ventilation per square meter of body surface area occurred in one instance.

Chronic metabolic acidosis

Three patients with uremia and chronic metabolic acidosis secondary to renal failure were studied. Clinical findings, blood electrolyte levels at the time of study, and spirometric data appear in Table XII.

All showed a tendency to reduction in maximum breathing capacity which might well have been related to the presence of weakness and easy fa-

TABLE XIII

Physiologic data relative to pulmonary ventilation at rest and during CO_2 inhalation in patients with cyanotic congenital heart disease, chronic acidosis, and chronic alkalosis

Patient	Inspired gas mixture	Time on mixture (*min.*)	f	R_E	$\dot{V}_{O_2}/M^2$	V_T	$\dot{V}_E$	V_D *ml.*	V_D % $\dot{V}_E$	Calc. $P_{A_{O_2}}$
				Cyanotic congenital heart disease *						
J. B.	Room air	—	18	0.76	148	524	9.43	212	40.3	
	3% CO_2	26	20.3	0.88	158	1,265	25.70	187	14.7	
	4% CO_2	30	25	0.71	206	1,750	43.70	120	7.0	
R. W.	Room air	—	31.7	0.76	179	388	12.30	228	58.7	
	3% CO_2	26	33.3	0.71	151	666	22.15	422	63.3	
	4% CO_2	29	36.7	0.74	200	904	33.20	477	52.8	
W. M.	Room air	—	16	0.75	162	680	10.88	271	39.8	
	3% CO_2	27	20.2	0.87	137	1,362	27.50	604	44.3	
	4% CO_2	26	23	0.71	203	2,010	46.15	888	44.1	
				Chronic acidosis						
G. K.	Room air	—	15.7	0.81	131	424	6.66	172	40.5	105
	3% CO_2	27	20	0.82	138	717	14.35	258	36.1	124
	5% CO_2	27	20.7	0.94	139	1,300	26.90	345	26.6	131
J. K.	Room air	—	29.7	0.80	187	387	11.48	211	54.5	101
	3% CO_2	23	29.3	0.72	232	773	22.65	359	46.4	119
	5% CO_2	Tolerated only 8 min.	49	—	—	992	48.60	—	—	—
W. E.	Room air	—	16.7	0.82	119	514	8.59	231	44.9	106
	3% CO_2	30	25.7	0.76	136	795	20.43	369	46.4	121
	5% CO_2	Tolerated only 10 min.	26	—	—	1,345	34.97	—	—	—
				Chronic alkalosis						
K. S.	Room air	—	20	0.73	148	320	6.41	139	43.3	93
	3% CO_2	34	23.7	0.72	136	435	10.33	182	41.8	114
	5% CO_2	30	23	0.81	137	693	15.93	267	38.5	120
J. T.	Room air	—	8.3	0.72	145	651	5.41	234	36.0	95
	3% CO_2	26	10	0.70	143	915	9.15	364	39.8	111
	5% CO_2	25	14	0.80	141	1,232	17.26	610	49.5	120

* See footnote 6.

TABLE XIV

Physiologic data relative to the arterial blood at rest and during CO_2 inhalation in patients with cyanotic congenital heart disease, chronic acidosis, and chronic alkalosis

Patient	Inspired gas mixture	pHs	$(H^+)a$	Cs_{CO_2}	Pa_{CO_2}	Sa_{O_2}	Vc	Calc. $(Bb_+)b$
			Cyanotic congenital heart disease					
J. B.	Room air	7.45	35.4	45.7	29	86	62	48
	3% CO_2	7.44	36.3	49.1	32	87	62	48
	4% CO_2	7.40	39.8	49.7	35	88	62	47
R. W.	Room air	7.40	39.8	53.7	38.5	83	75	50
	3% CO_2	7.39	40.7	56.0	41	85	76	49
	4% CO_2	7.36	43.6	55.9	43	88	77	48
W. M.	Room air	7.49	32.3	51.4	30	87	61	51
	3% CO_2	7.42	38.0	52.0	35	89	61	49
	4% CO_2	7.40	39.8	54.2	38.5	90	62	49
			Chronic acidosis					
G. K.	Room air	7.36	43.6	47.5	37	95	26	41
	3% CO_2	7.35	44.7	49.0	38.5	98	27	41
	5% CO_2	7.30	50.1	49.5	43	100	28	41
J. K.	Room air	7.32	47.4	50.1	41.5	94	33	42
	3% CO_2	7.32	48.3	49.3	42	96	35	42
	5% CO_2	—	—	—	—	—	—	—
W. E.	Room air	7.20	63.2	32.0	34.5	94	26	32
	3% CO_2	7.19	64.6	33.1	37	100	27	32
	5% CO_2	—	—	—	—	—	—	—
			Chronic alkalosis					
K. S.	Room air	7.47	33.9	69.2	42.5	91	38	54
	3% CO_2	7.45	35.5	70.5	45	96	38	54
	5% CO_2	7.42	38.0	73.2	50	96	37	54
J. T.	Room air	7.40	39.8	60.1	42	94	43	48
	3% CO_2	7.38	41.7	63.3	47	97	43	49
	5% CO_2	7.35	44.6	65.1	52	97	44	49

tigability. The lowered vital capacity in patient J. K. was possibly associated with the presence of moderate pulmonary congestion.

Observations on the response of these uremic patients to the CO_2 stimulus are found in Tables XIII, XIV, and XV. At rest all had an elevated effective alveolar ventilation per square meter body surface area, reduced arterial pH, and anemia. One patient had an elevated oxygen consumption per square meter body surface area. The other two had a somewhat lowered arterial CO_2 tension. Two of the three patients were not able to tolerate the 5 per cent CO_2 inspired gas mixture for longer than a few minutes, a finding confirmatory of Peabody's experience (19). In these two instances the ventilation measured near the end of this short period on 5 per cent CO_2 was 50 per cent or more of the maximum breathing capacity, suggesting that intolerance may result when the ventilatory drive exceeds the patient's physical capacity to respond. The sensitivity to the carbon dioxide-hydrogen ion stimulus in these two cases has been determined, therefore, on the basis of only two points on the stimulus response curve. There was a deficit in the calculated buffer base, as found by Yeomans and Stueck (20) in their uremic subjects, and no change in buffer base occurred with CO_2 inhalation.

It can be seen that the response to the carbon dioxide-hydrogen ion stimulus when evaluated in terms of either the alveolar ventilation ratio or effective alveolar ventilation per square meter body surface area fell within the normal range in two patients, but was distinctly increased in a third (J. K.).

Chronic metabolic alkalosis

Clinical notes on the two patients with chronic metabolic alkalosis and CO_2 retention secondary

to hyperadrenalism appear in Table XII. In both instances the anatomical diagnosis is based on gross and microscopic examination of the operative pathological specimen. It should be noted that there was no disturbance of blood acid-base balance in patient J. T. at the time of study. Although CO_2 retention was documented in this patient only for the two-month period of observation prior to therapy, clinical symptoms had been present for a year or more. The venous serum CO_2 content, previously about 35 mEq. per liter, fell to normal shortly after subtotal adrenalectomy, and remained so during the ensuing four months prior to study.

The spirometric observations on these two patients are shown in Table XII. The slight reductions in vital and maximum breathing capacities found in patient K. S. were probably the result of old pleural disease.

Tables XIII, XIV, and XV contain the data obtained during CO_2 inhalation in these two patients. The first was found to have an elevated arterial blood pH and serum bicarbonate level at rest, with a somewhat lowered oxygen saturation. Resting values for the second patient were within normal limits at the time of study. In both cases the ventilatory responses to 3 per cent and 5 per cent CO_2 inhalation were less than normal, and sensitivity to the carbon dioxide-hydrogen ion stimulus was one-half to one-third that represented by the average normal values.

DISCUSSION

The effects of CO_2 inhalation on the normal subjects were comparable to those found previously (21–25). In this study the average value of 1.7 mm. Hg change in arterial CO_2 tension required

TABLE XV

Physiologic data relative to effective alveolar ventilation and sensitivity to the carbon dioxide-hydrogen ion stimulus in patients with cyanotic congenital heart disease, chronic acidosis, and chronic alkalosis

Patient	Inspired gas mixture	$\dot{V}_A$	$\dot{V}_A/M^2$	VR	$\frac{Pa_{CO_2}}{VR}$	$\frac{\dot{V}_A/M^2}{Pa_{CO_2}}$	$\frac{(H^+)a}{VR}$	$\frac{\dot{V}_A/M^2}{(H^+)a}$
			Cyanotic congenital heart disease					
J. B.	Room air	5.63	3.37	1				
	3% CO_2	21.80	13.05	3.88	1.0	3.5	0.7	5.5
	4% CO_2	40.7	24.36	7.22				
R. W.	Room air	5.08	3.10	1				
	3% CO_2	8.12	4.95	1.60	2.2	1.5	1.8	1.7
	4% CO_2	15.68	9.56	3.08				
W. M.	Room air	6.54	3.53	1				
	3% CO_2	15.33	8.24	2.34	2.7	1.3	2.6	1.4
	4% CO_2	25.80	13.87	3.94				
			Chronic acidosis					
G. K.	Room air	3.96	2.50	1				
	3% CO_2	9.16	5.80	2.32	1.4	1.7	1.4	1.6
	5% CO_2	19.75	12.50	5.				
J. K.	Room air	5.22	3.13	1				
	3% CO_2	12.14	7.27	2.33	0.4	8.0	0.7	4.8
	5% CO_2	—	—	—				
W. E.	Room air	4.74	2.48	1				
	3% CO_2	10.98	5.75	2.31	2.0	1.4	1.0	2.0
	5% CO_2	—	—	—				
			Chronic alkalosis					
K. S.	Room air	3.63	2.20	1				
	3% CO_2	6.03	3.65	1.66	4.3	0.5	2.5	0.9
	5% CO_2	9.78	5.93	2.69				
J. T.	Room air	3.46	2.18	1				
	3% CO_2	5.51	3.46	1.59	6.6	0.3	3.2	0.7
	5% CO_2	8.70	5.47	2.51				

to double the effective alveolar ventilation in normal subjects is not much different from the value of 1.5 mm. Hg obtained by Haldane and Priestley (21) as early as 1905, using alveolar air samples. Gray (17) arrived at an average figure of 2.5 mm. Hg using 200 determinations reported in the literature under both steady and unsteady conditions, and based on alveolar air CO_2 tensions. The buffering capacity of normal human blood, measured *in vivo* under conditions of CO_2 inhalation and voluntary hyperventilation, has previously been reported by Shock and Hastings (26). It was found that when arterial hydrogen ion concentration is plotted against arterial CO_2 tension in mm. Hg, an almost linear relationship is obtained which is approximated in the hypercapnial range by the equation $(H^+)a = 0.652\ PaCO_2 + 13.5$ (17). When plotted in the same way, the data obtained in this study using normal subjects also yield a linear relationship, the equation for which is $(H^+)a = 0.714\ PaCO_2 + 8.3$.

The increase in physiological dead space to CO_2 (Bohr) accompanying the hyperpnea of CO_2 inhalation in normal subjects has long been recognized (24), and the magnitude of change observed in this study is comparable to that previously reported. Changes of this order of magnitude in the respiratory dead space with comparable increases in tidal volume have not been found using the nitrogen analysis technique (27). However, the size of the Bohr dead space to CO_2 is subject to changes in ventilation perfusion relationships in the lung, and may be increased, for example, when the lung contains appreciable numbers of well ventilated but poorly perfused alveoli. The increase in physiological dead space observed in this study with CO_2 inhalation is interpreted as suggesting a change in ventilation perfusion relationships under these conditions, perhaps secondary to changes in alveolar volume, or in respiratory air flow velocity, or possibly resulting from an effect of increased CO_2 tension on the pulmonary capillaries or bronchioles.

In evaluating the reduction in sensitivity to the carbon dioxide-hydrogen ion stimulus found in the Group III and IV emphysema patients, the possible effect of the hypoxic ventilatory drive at rest must be taken into consideration. As pointed out by Tenney (5), it might be expected that the diminution in anoxemia coincident with CO_2 inhalation would reduce this drive, and therefore the observed slope of the stimulus response curve might be less. As noted above, in these patients there was little or no further rise in arterial oxygen saturation with 5 per cent CO_2 inhalation as compared with 3 per cent CO_2, so that there was presumably no change in the degree of hypoxic drive between these two points on the stimulus response curve. Yet the slope of the curves between these two points did not differ from that between those determined at rest and on 3 per cent CO_2 inhalation, there being a consistent linear relationship of the three. Therefore changing hypoxic drive, such as may have occurred, did not modify the results obtained in any detectable way.

The reduction in sensitivity to the carbon dioxide-hydrogen ion stimulus found in patients with cor pulmonale secondary to emphysema might be ascribed to one or more of the following mechanisms: 1) Increased buffering capacity of the blood associated with an elevated plasma bicarbonate level or polycythemia; 2) failure of the chest bellows to respond adequately to the normal nervous stimuli; 3) the presence of congestive heart failure, chronic anoxemia, chronic acidosis, or chronic hypercapnia *per se*.

In 1920, Scott (3) suggested that the reduced ventilatory response to CO_2 inhalation which he observed in two patients with chronic emphysema might be explained on the basis of an increased buffering capacity of the blood secondary to a high bicarbonate level. This would result in a smaller increment in free hydrogen ion concentration on addition of a given amount of CO_2, and therefore a lesser ventilatory response. However, our measurements show that with CO_2 inhalation the blood hydrogen ion concentration in these patients actually increases more than in the normal group despite the presence of elevated blood bicarbonate and polycythemia. Thus the sensitivity is reduced as referred to either the CO_2 or hydrogen ion stimulus. Furthermore the absence of a reduced sensitivity in the patients with marked polycythemia associated with cyanotic congenital heart disease would argue against a specific effect of polycythemia in this regard.

The presence of mechanical ventilatory impairment did not condition the diminished sensitivity since a normal response was found in the Group II emphysema patients who suffered from com-

parable ventilatory defects. Likewise the presence of congestive heart failure *per se* does not account for the diminished sensitivity in cor pulmonale, since a reduction was also found in the Group III emphysema patients without congestive difficulty, and conversely one of the Group II emphysema patients with congestive failure on another basis had a normal response.

Since the anoxemia and acidosis of the patients with cor pulmonale were presumably of long duration, it appeared that a pertinent question in the present study was whether or not either chronic anoxemia or chronic acidosis might in themselves result in a diminished sensitivity to the carbon dioxide-hydrogen ion stimulus. Although the available evidence would indicate an increase in sensitivity to CO_2 associated with acclimatization to the anoxemia of altitude (22, 28), these observations were made over a period of days or weeks, and it was considered desirable to investigate the possibility that anoxemia of considerably longer duration might result in a diminished sensitivity. Likewise, although the observations of Peabody (19) suggested that if anything, an increased sensitivity to CO_2 was associated with renal failure, it seemed that the possible effects of known long-term acidosis should be explored. Accordingly, the patients with cyanotic congenital heart disease and slowly progressing uremia were selected to fulfill the criterion of chronicity. The absence of diminished sensitivity in either of these two patient categories has been taken as evidence that neither chronic anoxemia nor chronic acidosis in themselves condition the reduced response in patients with cor pulmonale.

The hypothesis that chronic hypercapnia itself might eventually lead to a diminished sensitivity to the carbon dioxide-hydrogen ion stimulus, although likely on the basis of exclusion, was more difficult of direct test. The hypercapnia of metabolic alkalosis seemed to offer the best clinical opportunity to explore this possibility, but long standing severe alkalosis and CO_2 retention are infrequently seen. The two patients with Cushing's syndrome therefore were chosen because of well-documented evidence of chronic metabolic alkalosis and CO_2 retention, there being no reason to believe that other metabolic derangements in these patients might condition the ventilatory response. As was the case with the emphysematous subjects, the diminution in sensitivity with reference to hydrogen ion precludes the possibility that increased buffering capacity of the blood resulted in a reduced response to CO_2. The findings are therefore taken as evidence that chronic hypercapnia *per se* leads to a diminution in sensitivity to the carbon dioxide-hydrogen ion stimulus. This thesis is further supported by the findings of Schäfer (29), who observed a reduced response to CO_2 in two normal men after four to six days residence in an atmosphere of 3 per cent CO_2.

Since both respiratory acidosis and metabolic alkalosis are associated with elevations in blood and tissue bicarbonate ion concentration as well as free carbon dioxide tension, no conclusion can be drawn from these observations as to which of these two excess quantities may lead to a reduced sensitivity, or whether both together do.

The findings in this study lend no support to the idea (30, 31) that an increased ventilatory response to CO_2 necessarily accompanies the condition of metabolic acidosis by reason of the lowered buffering capacity of the blood resulting in a greater increase in hydrogen ion concentration with the addition of a given amount of CO_2. Firstly, no increase in response to CO_2 was observed in two of the three patients with metabolic acidosis, and secondly, the patient demonstrating an increased response was found to have increased sensitivity in terms of hydrogen ion as well as CO_2. This latter observation would be consistent with the notion that an increase in sensitivity may accompany *chronic* hypocapnia, since this patient was observed to have a lowered venous serum CO_2 content on occasion for several years. On the other hand, if CO_2 acts as a respiratory stimulus only by increasing the hydrogen ion concentration in blood and tissue, then it might be expected that chronic metabolic acidosis would result in some diminution in sensitivity to the carbon dioxide-hydrogen ion stimulus as is observed with respiratory acidosis. The absence of such diminution with metabolic acidosis therefore may be construed as evidence favoring the theory that CO_2 acts as a specific stimulus.

We have interpreted the data as consistent with the hypothesis of CO_2 adaptation in prolonged hyper- and hypocapnia, and with the multiple factor theory of the chemical regulation of respiration advanced by Gray (17).

Little information is available presently as regards the degree of reversibility possible once a chronic diminution in sensitivity has become established. It is noteworthy that a diminished sensitivity was found in patient J. T. with Cushing's syndrome some four months after the venous serum CO_2 content had returned to normal.

The sequence of events in the natural history of chronic pulmonary emphysema leading to CO_2 retention is at present poorly defined. A tentative hypothesis suggested by these studies is the following: At some point in the course of the disease the ventilatory capacity becomes insufficient to eliminate the additional CO_2 produced during exertion, and transient rises in arterial CO_2 tension occur. Eventually these repeated bouts of hypercapnia result in a diminished sensitivity to the carbon dioxide—hydrogen ion stimulus, thus permitting an elevated CO_2 tension at rest though ventilatory capacity may be such that a normal CO_2 tension at an increased resting ventilation is possible. Furthermore, this elevated CO_2 tension at rest favors increased retention of bicarbonate by the kidney (32, 33) and thus a vicious cycle of increasing CO_2 retention and diminishing respiratory sensitivity is initiated.

The question of whether increasing CO_2 retention is associated with further diminution in sensitivity to the carbon dioxide-hydrogen ion stimulus cannot be answered with certainty at this time. Presumably serial observations on a number of patients would be needed. Lacking these, we have attempted to correlate the degree of sensitivity change with the amount of CO_2 retention in those patients having a reduced response to the carbon dioxide-hydrogen ion stimulus. In Figures 3 and 4 sensitivity is expressed both as the change in effective alveolar ventilation per square meter body surface area associated with 1 mm. Hg increase in arterial CO_2 tension, and as the change associated with unit increase in arterial hydrogen ion concentration. Sensitivity is plotted against the level of arterial CO_2 tension at rest. It is apparent that the sensitivity tends to diminish as the resting arterial CO_2 tension increases. No correlation between sensitivity and arterial serum CO_2 content in these same patients is demonstrable.

It is difficult to define possible therapeutic implications of these observations at this time. Nevertheless, it would seem reasonable to suppose that circumstances making for further CO_2 retention in some patients, such as acute pulmonary infection, vigorous exertion, or long continued oxygen therapy, would further accelerate a vicious cycle of diminishing sensitivity to CO_2, with resultant reduction in effective alveolar ventilation at rest, increased anoxemia and acidosis.

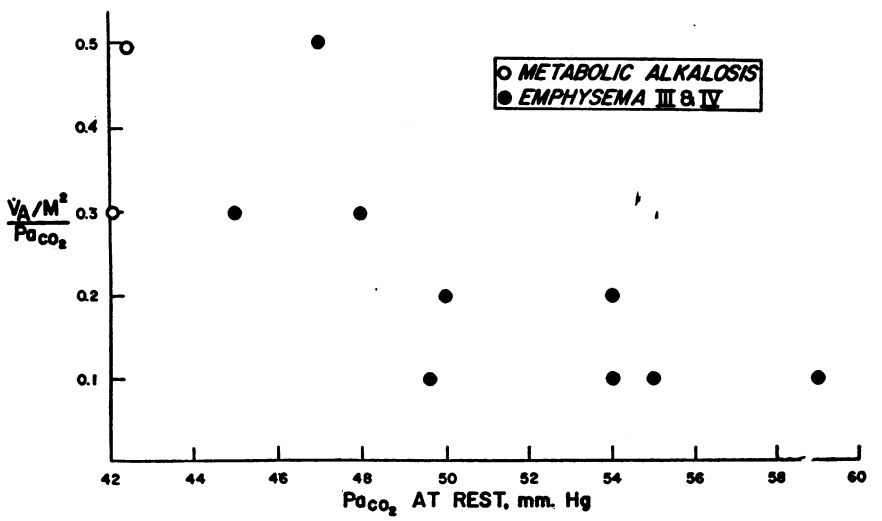

FIG. 3. SENSITIVITY TO THE CO_2 STIMULUS AS A FUNCTION OF THE DEGREE OF CARBON DIOXIDE RETENTION

Sensitivity appears on the ordinate in terms of increase in effective alveolar ventilation (liters BTPS per square meter body surface area) associated with 1 mm. Hg rise in arterial CO_2 tension. On the abscissa is plotted arterial CO_2 tension at rest.

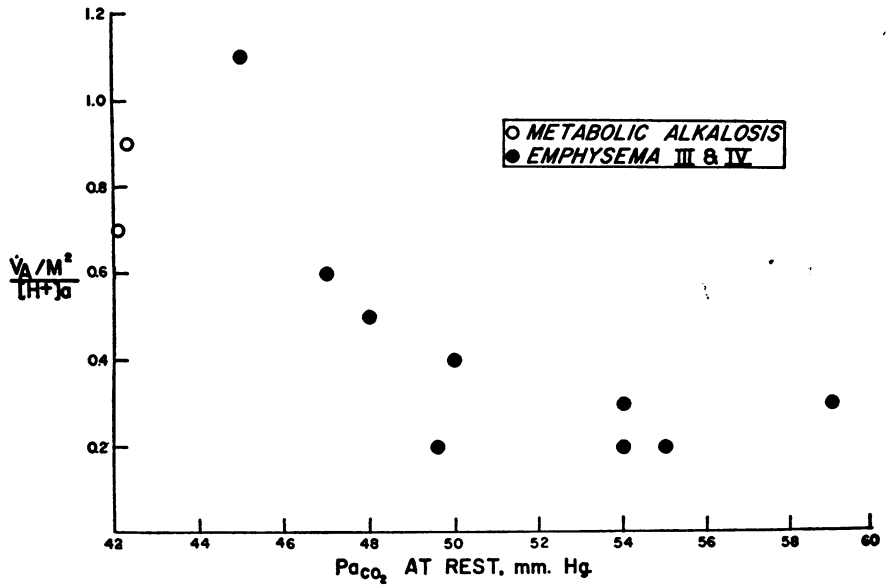

FIG. 4. SENSITIVITY TO THE HYDROGEN ION STIMULUS AS A FUNCTION OF THE DEGREE OF CARBON DIOXIDE RETENTION

Sensitivity appears on the ordinate in terms of increase in effective alveolar ventilation (liters BTPS per square meter body surface area) associated with unit rise in arterial hydrogen ion concentration (billionths of moles per liter). On the abscissa is plotted arterial CO_2 tension at rest.

SUMMARY AND CONCLUSIONS

1. In 12 normal subjects and 21 patients, sensitivity of the respiratory nervous regulatory mechanism to the carbon dioxide-hydrogen ion stimulus has been determined by relating effective alveolar ventilation to changes in arterial CO_2 tension and hydrogen ion concentration induced by CO_2 inhalation.

2. Six patients with chronic pulmonary emphysema and cor pulmonale were found to have a markedly reduced sensitivity to the carbon dioxide-hydrogen ion stimulus as compared with the normal.

3. Several mechanisms of possible importance in conditioning the reduced ventilatory response to CO_2 in the patients with cor pulmonale have been explored. They are: (a) increased buffering capacity of the blood associated with an elevated plasma bicarbonate level or polycythemia; (b) failure of the chest bellows to respond adequately to the normal nervous stimuli; (c) the presence of congestive heart failure, chronic anoxemia, chronic acidosis, or chronic hypercapnia *per se*.

4. The diminished response to CO_2 in the patients with cor pulmonale could not be accounted for on the basis of increased blood buffering capacity since the sensitivity was found to be reduced relative to the hydrogen ion as well as to the CO_2 stimulus.

5. Four patients without CO_2 retention but having chronic pulmonary emphysema and a mechanical ventilatory defect similar to that of the cor pulmonale group were found to have normal sensitivity to the carbon dioxide-hydrogen ion stimulus.

6. The diminished sensitivity in patients with cor pulmonale was not dependent upon the presence of congestive heart failure since three patients without congestive difficulty but having emphysema and CO_2 retention were found to have a reduced sensitivity.

7. No reduction in sensitivity was found in three patients with chronic anoxemia secondary to cyanotic congenital heart disease, nor in three patients with chronic metabolic acidosis associated with renal failure.

8. In two patients with chronic metabolic alkalosis and CO_2 retention, a diminished sensitivity was demonstrated.

9. It is concluded that chronic hypercapnia *per se* results in a diminished sensitivity to the CO_2 inhalation stimulus, which is associated with a rise

in both arterial CO_2 tension and hydrogen ion concentration.

10. Implications of these results are discussed in terms of the specificity of CO_2 as a respiratory stimulus and the development of reduced sensitivity in emphysematous subjects.

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