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RESPIRATORY RESPONSES TO CARBON DIOXIDE "TRANSIENTS" IN NORMAL VOLUNTEERS

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THE RESPIRATORY responses of man to carbon dioxide have been studied under various conditions by many investigators and methods. The primary aim of most of these studies has been to determine the influence of diseases, drugs, or environmental changes upon respiration in terms of variations from the normal relationships between the carbon dioxide stimulus and the ventilatory response (1–12).

Recently, the complexities of ventilatory regulation and carbon dioxide homeostasis in relation to anesthesia have become more thoroughly recognized and defined (13–25). In order to provide ultimately a means for studying quantitatively by controlled methods the influence of various anesthetic agents upon respiratory responses to carbon dioxide in man, the present investigation was instituted. A technique applicable to both conscious and anesthetized individuals was devised, and with it "normal" stimulus-response relationships were determined in conscious volunteer subjects. The purposes of this report are to describe the method in detail and to present control values for reference in subsequent reports which will consider the influence of various anesthetic agents upon the "normal" respiratory responses to carbon dioxide described herein.

METHOD

Selection and Preparation of Subjects.—Ten "normal" men, medical student volunteers, were selected as experimental subjects. Each was considered to be normal on the basis of having no history of cardiorespiratory disease and a timed vital capacity and electrocardiogram within normal range. The experimental procedure was explained, and each candidate selected for study was instructed to take nothing by

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mouth after midnight preceding the morning of the experiment and to report in the operating room at 7:30 a.m.

Upon arrival for study, each subject rested supine on the operating table while being prepared for the experiment. Contact electrodes were applied to the scalp for bipolar left frontal to left occipital electroencephalography and to the limbs for standard lead electrocardiography. A pneumatic cuff and stethoscope were applied to the left arm for blood pressure determinations by sphygmomanometry and auscultation, and an intravenous infusion of 5 per cent glucose in water was started. Atropine sulfate (0.4 mg.) was administered via the infusion tubing to inhibit salivation so that breathing through a mouthpiece would be more tolerable and less frequently interrupted by swallowing, to inhibit undesirable vagal reflexes which might occur during or sub-

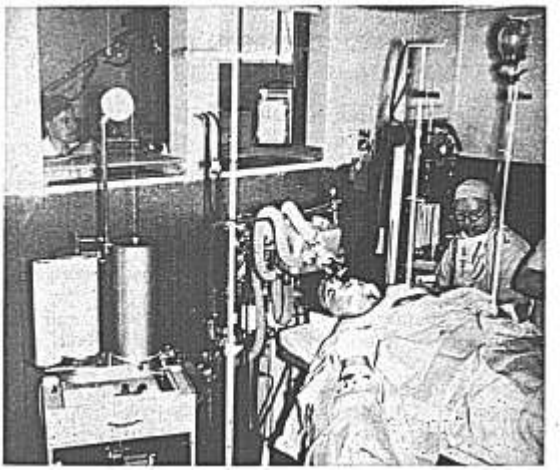

FIG. 1. Respiratory apparatus in use during a typical experiment. Subject (right foreground) breathes from Collins respirometer (left foreground) during nitrogen wash-out period. Breathing tubes, valves, respiratory stopcocks, rubber breathing bag, Liston-Becker carbon dioxide analyzer, and soda-lime canisters of anesthesia machine are visible together with water manometer connected to mouthpiece for monitoring resistance (middle foreground). Right brachial artery and left internal jugular vein needles are in place for simultaneous blood sampling. Technician records blood pressure, regulates oxygen flow, and manages intravenous infusion. Electrocardiographic and electroencephalographic leads are not visible, but wires leading to electronic recording devices may be seen passing through partition between windows separating operating room from instrumentation room. Among wires are those for intercommunication system. Television camera (far background, left window) transmits by closed circuit electrocardiographic and electroencephalographic images from Grass recorder (not visible in instrumentation room) to the operating room for constant visualization by research team. Esterline-Angus recorder for monitoring respired carbon dioxide concentrations is in direct vision (far background, right window).

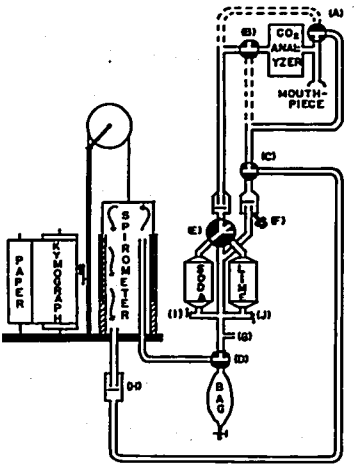

FIG. 2. Schematic diagram of closed circle spirometric system designed and used for this study during "on" and "off" transients of rebreathing carbon dioxide. Respiratory stopcocks (A) and (B) are depicted in proper positions for passing expiratory gases through Liston-Becker carbon dioxide analyzer while inspiratory gases by-pass analyzer. When these stopcocks are turned simultaneously to their alternative positions, inspiratory gases pass through analyzer and expiratory gases by-pass it through alternate channels depicted by broken lines. Respiratory stopcock (C) provides direct connection of inspiratory limb of spirometric system to spirometer to insure a completely unidirectional circuit and thorough mixing of expiratory gases in spirometer. Respiratory stopcock (D), in position depicted, eliminates semi-closed rubber breathing bag from expiratory limb of spirometric system, but when turned simultaneously with respiratory stopcock (C) a conventional circle anesthesia system is provided for emergency use. Valve (E), together with valves (I) and (J), can be turned to shunt expiratory gases through either soda lime canister for carbon dioxide absorption or through channel by-passing soda lime for carbon dioxide rebreathing. Inlet (F), for introducing oxygen and anesthesia gases from anesthesia machine to conventional anesthesia circle, is occluded and replaced by inlet (G) so that oxygen can be introduced to system from anesthesia machine even when inspiratory limb of conventional anesthesia circle is by-passed by respiratory stopcock (C). Respiratory valve (H), inserted in inspiratory limb of spirometric system, and conventional expiratory valve of anesthesia circle provide unidirectional circle between subject and spirometer.

sequent to induced hypercarbia, and to provide in these control subjects the same basal experimental conditions as those planned for subsequent comparative studies in anesthetized patients.

Resting Minute Volume Period.—Following the preliminary preparation, each subject breathed through the mouthpiece of a spirometric system * with his nostrils occluded (figs. 1 and 2). Exhaled carbon dioxide was absorbed by a standard brand of high moisture soda lime

* The spirometer incorporated in this system was a modified balanced and compensated continuous recording 9-liter calibrated Collins respirometer with a spring wound kymograph. Resistance of the entire spirometric system, as monitored with a manometer connected to the mouthpiece, ranged from ± 1.5 cm. of water during quiet breathing to ± 5.0 cm. of water during the peak flow rates of hyperventilation.

contained in a circle filter (Foregger model C.F. II), and oxygen was added from an anesthesia machine at the rate of 4 liters per minute for twenty minutes with the system semiclosed in order to wash out nitrogen (26) and to establish a high oxygen atmosphere (27). During this twenty minute wash-out period the entire spirometric system was included in the unidirectional breathing circuit. The tail of the 5-liter breathing bag was partially opened in order to permit escape of nitrogen with the excess oxygen, and the spirometer bell was weighed and immobilized in order to minimize the total volume of the system. Gas samples collected from the petcock of the spirometer and analyzed for oxygen, carbon dioxide, and nitrogen content after the method of Scholander (28) revealed concentrations below 10 volumes per cent for nitrogen and above 90 volumes per cent for oxygen at the end of the wash-out period. Insignificant concentrations of carbon dioxide were present (less than 0.5 volumes per cent). Upon completion of the wash-out period, the gas mixture in the breathing bag was expressed into the spirometer, and the semiclosed breathing bag then was excluded from the spirometric system by turning a respiratory stopcock to close the limb leading to the bag. With the spirometric system thus converted from semiclosed to closed, the spirometric kymograph was started and the oxygen flow rate from the anesthesia machine was adjusted to metabolic requirements so as to maintain the spirogram excursions within a level range. If the spirogram excursions continued to remain in a level range except for a single step-like shift coincident with removal of the weight from the lid of the spirometer bell, the closed spirometric system was assumed to be free of leaks and ready for recording the subject's resting minute volume.

An Esterline-Angus recorder connected to a Liston-Becker carbon dioxide analyzer was started at a given signal together with a Grass 2-channel recorder for simultaneous electroencephalography and electrocardiography.† These recorders, each calibrated immediately preceding the experiment, were started at a given time marked upon the spirogram and were kept running at a constant known speed along with the spirogram so that all records could be coordinated subsequently for synchronous minute-to-minute analysis. With this synchronized multiple recording system in operation, the subject's respiratory excursions were recorded for approximately ten minutes and a section of this record representative of two or more successive minutes of relaxed breathing was selected for determination of the resting minute volume and associated ventilatory data. While the resting minute volume was being recorded, first inspired gases and then expired gases were channelled alternately through the Liston-Becker carbon dioxide analyzer for the first and second halves of each minute, respectively, by simultaneously turning two appropriate respiratory stopcocks every thirty

† Esterline-Angus Recorder, Model AW, 5 M.A., rapid response, Liston-Becker CO_2 Analyzer Model 16, low resistance cell, and Grass 2-channel recorder, Model III-DSW, with one power amplifier modified for electrocardiography.

seconds first to the "inspiratory" and then to the "expiratory" position (fig. 2). Alternate unidirectional sampling of inspiratory and expiratory gases was designed to avoid the two main disadvantages of to-and-fro sampling, namely, increased dead space and inadequate speed of instrumental response during rapid breathing.

"On" and "Off" Transients of Rebreathing.—After the subject's resting minute volume was recorded, the spirometric system was disconnected. A Cournand needle was inserted into his right brachial artery, and another needle was introduced into his left internal jugular vein. The method described by Gibbs (29) was followed for inserting the needle into the internal jugular vein in order to obtain blood draining only from the brain. When both needles were in place and the carbon dioxide analyzer recalibrated, the spirometric system was reconnected to the subject in the same manner as previously. After another twenty-minute wash-out period, the spirometric system was converted from semiclosed to closed and the multiple recording system was started synchronously as before.

During quiet breathing, a control set of arterial and internal jugular venous blood samples was collected simultaneously, and the time marked on the spirogram. Without interruption, the "on" transient of rebreathing carbon dioxide then was started by turning the valve on the circle filter to by-pass the soda lime canister, and the time was noted. By observing the calibrated meter of the Esterline-Angus recorder, the gradual accumulation of the subject's endogenous carbon dioxide was monitored while inspiratory and expiratory gases again were passed through the Liston-Becker carbon dioxide analyzer during alternate thirty-second periods. A second set of arterial and internal jugular venous blood samples was collected simultaneously when the inspiratory carbon dioxide concentration approached 5 volumes per cent, and a third set was drawn when the inspiratory carbon dioxide concentration rose above 5 volumes per cent and concomitant elevation of the end-expiratory carbon dioxide concentration indicated that compensatory hyperventilation had become incapable of maintaining carbon dioxide homeostasis. The end of the "on" transient for each subject was reached within approximately ten minutes of rebreathing carbon dioxide.

The "off" transient of rebreathing carbon dioxide was initiated without interruption of the experiment by turning the valve on the circle filter to return the soda lime canister to the spirometric system. Subsequently, three ‡ additional sets of simultaneous arterial and internal jugular venous blood samples were collected at successive intervals while the subject's ventilatory activity and respiratory carbon dioxide concentrations returned to ranges approximating those of the control period. The end of the "off" transient was reached within

‡ In some of the subjects, a fourth set of simultaneous arterial and internal jugular venous blood samples was collected, but since this provided no additional significant information, it was omitted for the sake of uniformity in tabulating the data.

approximately ten minutes of carbon dioxide absorption in each subject, and the duration of the entire carbon dioxide stimulus-response test, including both the "on" and "off" transients, therefore, lasted approximately twenty minutes. Sections from the kymographic records of a typical experiment are shown in figure 3.

Analysis of Data and Calculations of Values.—VENTILATION: Minute-to-minute values for ventilatory activity were determined from the respiratory excursions recorded on the continuous spirogram. Rate was determined by counting the number of excursions per minute. Minute volume was calculated from the sum of the measured heights of all inspiratory excursions during each minute.§ Tidal volume was determined as the average tidal volume during each minute by dividing the minute volume by the rate. Alveolar ventilation ratio was estimated for each minute by correcting minute volume for dead space and then expressing the resulting value for minute alveolar ventilation as either a fraction or a multiple of the resting minute alveolar ventilation value.‖

INSPIRATORY AND END-EXPIRATORY pCO_2: From the continuous tracing of the Esterline-Angus recorder the inspiratory and end-expiratory carbon dioxide concentrations were determined for each minute by applying an individual calibration scale prepared as part of each experiment. The ends of alternate thirty-second periods representing inspiratory and end-expiratory carbon dioxide concentrations, respectively, were measured to achieve uniformity at the expense of creating a half-minute time lag between corresponding inspiratory and end-expiratory carbon dioxide values. These values were measured from the kymogram at points of deflection representing the lowest value on the inspiratory tracing and the highest value on the expiratory tracing of the excursion being measured.¶ In order to express respired carbon dioxide values in terms analogous to those used for blood gas tensions, concentrations measured in volumes per cent were converted to partial pressures.#

§ Minute volume (l.) = Total height of inspiratory excursions per minute (mm.) × Calibration factor (21 cc./mm.) × Conversion factor (spirometer to BTPS) × 1/1000.

‖ Alveolar ventilation ratio = Minute volume less dead space minute volume/Resting minute volume less dead space minute volume. A value of 150 cc. was chosen arbitrarily as an approximate correction factor for anatomical dead space with full realization of its probable inaccuracy in comparison with values for true ventilatory dead space as defined by Rossier and Bühlmann (30).

¶ Transitory upward deviations of the tracing which occurred between inspirations through the analyzer were interpreted as manifestations of slight diffusion of carbon dioxide into the cell as the expired gas mixture by-passed it. Transitory downward deviations of the tracing which occurred between expirations through the analyzer were interpreted as manifestations of the initial passage through the cell of dead-space gas with relatively low carbon dioxide concentration. These transitory upward and downward deviations were disregarded except to be recognized for what they appeared to represent.

The partial pressures were calculated by multiplying 760 mm. of mercury by the measured volumes per cent and are not precisely accurate since ambient pressure during each experiment was not exactly 760 mm. of mercury. However, since the mean barometric pressure during the experiments being reported was 754.3 (Standard Deviation ± 6.20), the maximum error incurred by the employed method of calculations could be no greater than approximately

ARTERIAL AND INTERNAL JUGULAR VENOUS *p*H AND GAS VALUES: All blood samples were collected by a modification of the anaerobic technique of Roughton and Scholander (31) in labeled syringes which previously had been flushed out with a solution of Treburon ** and distilled water (1:3), and they were kept on ice until analyzed. Hydrogen ion

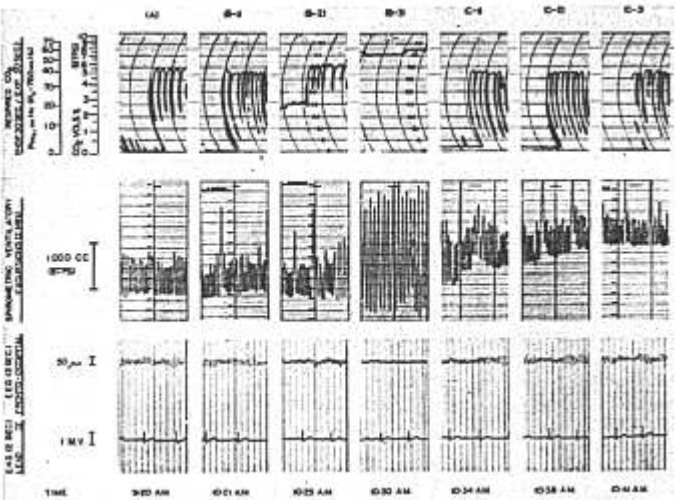

FIG. 3. Clippings of simultaneous periods of continuous kymographic records from a typical experiment. Tracing representative of pretest period and of blood-sampling periods during "on" and "off" transients of rebreathing in a "normal" conscious volunteer (subject 4). Top: carbon dioxide concentrations of, first, inspiratory and, then, expiratory gases passed through Liston-Becker carbon dioxide analyzer for thirty seconds each. Middle: spirometric ventilatory excursions for two minutes. Bottom: bipolar left frontal to left occipital electroencephalogram, above, and lead II electrocardiogram, below, for two seconds. From left to right, the periods of the experiment represented by these clippings are: (A) recording of resting minute volume; (B-1), (B-2) and (B-3) arterial and internal jugular venous blood sampling during the "on" transient of rebreathing carbon dioxide; and (C-1), (C-2), and (C-3) arterial and internal jugular venous blood sampling during the "off" transient of rebreathing carbon dioxide.

concentrations were measured anaerobically at 38 C. by means of a Beckman *p*H meter within six hours. Oxygen and carbon dioxide contents were estimated in duplicate from one-cubic-centimeter samples of blood by the method of Van Slyke and Neill (32). Oxygen capacity was determined by the technique of Sendroy (33) and the degree of oxygen

1.5 mm. of mercury even for 10 per cent carbon dioxide, a concentration exceeding any of those reached in these experiments. In relation to the ranges of partial pressures being considered this degree of error appears insignificant and within the limits of experimental accuracy.

** Treburon anticoagulant was obtained from Hoffmann-La Roche, Inc.

saturation was calculated. Volume percentages were corrected to standard temperature and pressure values (0 C. and 760 mm. of mercury), and the oxygen figures were corrected for physically dissolved gas as recommended by Comroe (34). The partial pressure of carbon dioxide was derived from the *p*H and the carbon dioxide content of plasma converted from that of whole blood according to the nomograms of Van Slyke and Sendroy (35).

Circulatory and Electroencephalographic Data: Circulatory responses during the "on" and "off" transients of rebreathing carbon dioxide were noted only in respect to gross changes in blood pressure, as determined frequently by sphygmomanometry and auscultation, and in pulse rate and electrical activity of the heart, as determined from continuous electrocardiography using a standard lead (usually lead II).

Bipolar left frontal to left occipital electroencephalographic activity was recorded continuously, and the gross variations were noted.

Results

The results presented are those obtained from 6 subjects each of whom yielded a set of data suitably complete for analysis of respiratory stimulus-response relationships during both "on" and "off" transients of rebreathing carbon dioxide. Data for the other 4 subjects studied lacked completeness owing to technical failure in some part of the experimental procedure, and though the fragmentary data obtained were in essential agreement with the results being presented, they were omitted in order to present comparable data for all subjects included in the analysis.

Respiratory Responses. Rate (table 1): The mean rate in the resting minute volume period was 13 per minute. The pattern of rate responses during the "on" and "off" transients of rebreathing varied among individuals, but the mean rate did not change significantly during either the "on" or "off" transient of rebreathing and remained between 13 and 16 per minute.

Tidal Volume (table 2): The mean tidal volume in the resting minute volume period was 738 cc. Each individual exhibited a progressive increase in tidal volume in response to rebreathing carbon dioxide during the "on" transient (669 cc. to 1,684 cc. in mean values). The highest mean tidal volume (1,737 cc.) was observed during the first minute of the "off" transient. After this the mean tidal volume declined progressively toward control values.

Minute Volume (table 3): The mean minute volume in the resting minute volume period was 9.31 liters. As a function of tidal volume and despite variations in the patterns of rate responses among individuals, the minute volume progressively increased in each subject during the "on" transient (9.09 l. to 23.07 l. in mean values). The highest mean minute volume (24.37 l.) was observed during the first minute of the "off" transient. After this the mean minute volume declined progressively toward control values.

TABLE 1

RESPIRATORY RATES (PER MINUTE) DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Pretest	Control	Minutes of Rebreathing									Minutes of Recovery									
			1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11
1	10	10	17	18	17	18	16	18	17	16	17*	15	18	18	17	10	18	10	18	17	14	17
2	10	15	12	15	17	18	19	16	10	18	19	18	16	15	14	16	16	14	13	16	16	17*
3	12	12	13	12	12	14	14	15	16	10	17	17	15	16	15	15	16	15	14	11	15	15
4	12	14	14	12	14	11	7	8	8	7	8	9	10	13	14	16	14	14	17	16	15	17
5	11	11	14	11	11	10	10	11	12	12	13	14	14	14	13	12	12	13	11	13	12	11
6	10	13	13	10	14	12	8	12	11	11*	12*	12	13	15	15	15	13	14	13	13	13*	14*
Mean	13	14	13	13	14	14	12	13	14	13	14	14	14	15	15	10	15	15	14	14	14	15

* Estimated by applying to the preceding minute value for this subject the ratio (average value in this minute/average value in preceding minute) as derived from subjects having both values.

TABLE 2

RESPIRATORY TIDAL VOLUMES (CUBIC CENTIMETERS) DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Pretest	Control	Minutes of Rebreathing									Minutes of Recovery									
			1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11
1	657	663	642	585	698	705	1098	1100	1449	1560	1689*	1780	1439	880	760	728	661	628	607	598	731	706
2	648	630	560	572	622	640	738	887	970	1217	1437	2135	1804	1553	1071	706	673	641	641	633	924	863*
3	739	685	790	771	671	850	1011	1081	1118	1369	1446	1488	956	804	776	704	683	743	859	790	747	790
4	720	710	584	780	747	891	1458	1540	2075	2355	2433	2245	1362	802	721	640	606	771	584	603	643	532
5	831	751	846	819	872	938	941	1030	1090	1031	1150	1161	1200	974	912	828	736	714	708	716	846	744
6	828	606	685	674	738	919	1812	1193	1606	1801*	1950*	1616	1134	854	835	756	752	848	533	720	839*	784*
Mean	738	669	686	700	708	840	1176	1139	1387	1656	1684	1737	1317	989	846	727	700	724	670	677	788	737

* Estimated by applying to the preceding minute value for this subject the ratio (average value in this minute/average value in preceding minute) as derived from subjects having both values.

ALVEOLAR VENTILATION RATIO (table 4): The alveolar ventilation ratios, which were unity by definition in each subject's resting minute volume period, progressively increased during the "on" transient (0.95 to 2.83 in mean values). The highest mean alveolar ventilation ratio (3.02) was observed during the first minute of the "off" transient. After this the mean alveolar ventilation ratio declined progressively toward control values. Since alveolar ventilation ratios express relative minute volume values corrected for dead space and since dead space becomes less of a factor when minute volume is increased as a function primarily of tidal volume, the alveolar ventilation ratios in this case manifest an even greater progressive increase in response to rebreathing carbon dioxide than do the minute volume values (a three fold compared to a two and one-half fold increase in mean values).

Respiratory "Stimuli".—INSPIRATORY pCO_2 (table 5): The mean inspiratory carbon dioxide tension in the resting minute volume period was 0.1 mm. of mercury (0.01 volumes per cent). During the "on" transient, the mean inspiratory carbon dioxide tension progressively rose from 0.1 mm. of mercury (0.01 volumes per cent) in the control period to 54 mm. of mercury (7.1 volumes per cent) at the height of rebreathing. During the "off" transient, the mean inspiratory carbon dioxide tension fell precipitously during the first two minutes and then continued to fall more gradually in the form of an exponential decay curve until it returned to a negligible value approximating that of the control period. Changes were qualitatively similar in all subjects.

END-EXPIRATORY pCO_2 (table 6). The mean end-expiratory carbon dioxide tension in the resting minute volume period was 41.8 mm. of mercury (5.5 volumes per cent). During the "on" transient the mean end-expiratory carbon dioxide tension progressively rose from 40.2 mm. of mercury (5.3 volumes per cent) in the control period to 58.6 mm. of mercury (7.7 volumes per cent) at the height of rebreathing. During the "off" transient the mean end-expiratory carbon dioxide tension promptly fell to a value approximating that of the control value and then continued to fall further to 36.9 mm. of mercury (4.9 volumes per cent) before stabilizing slightly below the control value. Changes were qualitatively similar in all subjects.

ARTERIAL AND INTERNAL JUGULAR VENOUS *p*H AND GAS VALUES (table 7): The arterial and internal jugular venous blood *p*H and gas values during the "on" and "off" transients of rebreathing are presented in tabular form together with the ventilation values corresponding to the time of blood sampling. As would be expected, the arterial blood samples exhibited lower carbon dioxide values and higher *p*H and oxygen values than corresponding internal jugular venous blood samples. During the "on" transient of rebreathing, the carbon dioxide values rose and the *p*H values fell progressively in both the arterial and the internal jugular venous blood. The oxygen values did not change appreciably in the arterial blood, but the internal jugular venous blood oxygen values increased at the height of rebreathing. This resulted

TABLE 3

RESPIRATORY MINUTE VOLUMES (LITERS) DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Pretest	Control	Minutes of Rebreathing									Minutes of Recovery									
			1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11
1	10.45	10.67	10.90	10.52	11.88	14.32	17.58	19.80	24.63	24.93	29.60*	26.79	25.92	16.00	12.89	13.84	11.90	11.94	10.93	10.18	10.43	11.99
2	10.38	9.84	6.84	8.59	8.88	11.51	14.02	14.20	18.60	21.88	27.25	38.40	28.85	23.32	15.00	11.30	10.76	8.96	8.33	10.13	14.79	14.66*
3	8.87	8.34	10.28	9.25	8.06	11.99	13.84	10.21	17.87	21.90	24.59	25.28	14.33	12.85	11.64	10.56	10.91	11.14	12.01	8.69	11.20	11.83
4	8.71	10.06	8.18	9.36	10.44	9.81	10.20	12.32	16.60	16.48	19.47	20.21	13.62	11.20	10.10	10.23	9.76	10.80	9.93	9.66	9.03	9.06
5	9.15	8.27	9.31	8.19	9.60	9.38	9.41	11.32	13.16	12.38	14.95	10.13	10.92	13.63	11.87	9.95	8.81	9.28	9.78	9.31	10.16	8.19
6	8.28	7.37	8.90	6.74	10.32	11.03	14.49	14.32	17.67	18.97*	22.53*	19.39	14.75	12.81	12.51	11.33	9.78	11.88	8.92	9.36	10.97*	10.87*
Mean	9.31	9.09	9.07	8.78	9.86	11.34	13.26	14.70	18.09	19.42	23.07	24.37	19.07	14.97	12.34	11.20	10.33	10.07	9.82	9.56	11.20	11.10

* Estimated by applying to the preceding minute value for this subject the ratio (average value in this minute/average value in preceding minute) as derived from subjects having both values.

TABLE 4

ALVEOLAR VENTILATION RATIOS (VaR) DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Pretest	Control	Minutes of Rebreathing									Minutes of Recovery									
			1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11
1	1.00	1.03	1.04	0.98	1.16	1.45	1.80	2.13	2.75	2.80	3.36*	3.26	2.89	1.65	1.20	1.37	1.14	1.13	1.02	0.95	1.04	1.17
2	1.00	0.94	0.63	0.79	0.79	1.10	1.40	1.48	1.97	2.40	3.06	4.47	3.32	2.64	1.62	1.11	1.05	0.86	0.80	0.97	1.55	1.49*
3	1.00	0.87	1.18	1.05	0.74	1.40	1.00	1.07	2.19	2.70	3.12	3.22	1.71	1.48	1.33	1.18	1.12	1.16	1.40	1.00	1.20	1.35
4	1.00	1.15	0.88	1.00	1.21	1.18	1.32	1.01	2.23	2.24	2.04	2.73	1.76	1.34	1.16	1.13	1.11	1.20	1.07	1.05	1.07	0.94
5	1.00	0.91	1.02	0.89	1.06	1.05	1.00	1.34	1.52	1.41	1.74	1.87	1.98	1.54	1.32	1.00	0.94	0.98	0.95	0.98	1.12	0.87
6	1.00	0.81	1.03	0.77	1.21	1.36	1.06	1.85	2.30	2.67*	3.08*	2.50	1.89	1.56	1.51	1.34	1.15	1.44	1.03	1.09	1.33*	1.28*
Mean	1.00	0.95	0.96	0.93	1.03	1.26	1.55	1.73	2.17	2.30	2.83	3.02	2.26	1.70	1.37	1.20	1.09	1.14	1.05	1.01	1.23	1.18

* Estimated by applying to the preceding minute value for this subject the ratio (average value in this minute/average value in preceding minute) as derived from subjects having both values.

in a decreased arterial-venous blood oxygen difference which persisted during the initial phase of the "off" transient. Also during the initial phase of the "off" transient, the carbon dioxide values fell and the *p*H values rose promptly in the arterial blood. In the internal jugular venous blood, however, these values returned toward control levels more gradually. Furthermore, the arterial-venous blood differences for carbon dioxide and *p*H values during the initial phase of the "off" transient occasionally exceeded those not only for the control period but also for later phases of the "off" transient when greater stability had developed. The exaggerated arterial-venous blood differences for carbon dioxide and *p*H values during the initial phase of the "off" transient resulted from the more rapid fall in carbon dioxide values and the more rapid rise in *p*H values which occurred in the arterial blood as opposed to the internal jugular venous blood at this time. These changes, with few exceptions, were qualitatively similar in all subjects.

Relationships Between Respiratory Responses and Carbon Dioxide "Stimuli." In order to show graphically the quantitative relationships between the respiratory responses and the carbon dioxide "stimuli" in the resting minute-volume period and during the "on" and "off" transients of rebreathing, the minute-to-minute mean values for rates, tidal volumes, minute volumes, and alveolar ventilation ratios taken from tables 1, 2, 3 and 4, respectively, were plotted graphically against the corresponding mean values for inspiratory and end-expiratory carbon dioxide tensions taken from tables 5 and 6, respectively, and the sample-to-sample mean values for rates, tidal volumes, minute volumes, and alveolar ventilation ratios taken from table 7 were plotted in similar fashion against the corresponding mean values for arterial and internal jugular venous carbon dioxide tensions taken from the same table. The resulting stimulus-response curves are shown in figure 4. The relationship between internal jugular venous carbon dioxide tension and ventilatory activity as expressed by the alveolar ventilation ratio (V_AR) appears direct, linear, and almost identical for both the "on" and "off" transients of rebreathing. The regression equation for this relationship is:

$$V_AR = (\text{Internal Jugular Venous } pCO_2, \text{ mm. Hg})\ 0.115\text{–}6.004$$

However, the relationships between the carbon dioxide tensions of the arterial blood, the end-expiratory gas, and the inspiratory gas, respectively, and ventilatory activity as expressed by the alveolar ventilation ratios appear increasingly curvilinear for each transient and increasingly divergent between transients.

Circulatory and Electroencephalographic Observations. During the resting minute volume period and the "on" and "off" transients of rebreathing carbon dioxide no remarkable circulatory changes were noted in any of the subjects studied. Fluctuations of the blood pressure were inconstant and minor elevations only occasionally accompanied the height of rebreathing. Electrocardiographic patterns in the leads recorded remained essentially normal in all subjects. Occasionally dur-

TABLE 5

INSPIRATORY pCO_2 (MM. OF MERCURY) DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Pretest	Control	Minutes of Rebreathing									Minutes of Recovery										
			1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11
1	0.0	0.0	0.0	10.7	10.8	30.4	39.5	45.0	48.6	53.2	57.4*	54.0	3.0	1.5	0.8	0.8	0.8	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	2.3	0.9	19.0	25.8	34.2	41.8	45.0	49.4	12.2	3.8	2.3	1.5	1.5	0.0	0.0*	0.0	0.0	0.0	0.0*
3	0.0	0.0	8.4	18.2	24.3	30.4	38.0	42.6	45.6	49.4	53.2	2.3	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
4	0.0	0.0	0.0	11.4	20.5	27.4	34.2	40.3	45.6	50.1	53.0	3.8	2.3	1.5	1.5	0.8	0.8	0.8	0.0	0.0	0.0	0.0
5	0.0	0.0	0.0	11.4	19.0	25.8	34.2	40.3	46.4	50.1	54.0	50.3	12.2	4.6	2.3	2.3	1.5	1.5	1.5	1.5	0.8	0.0
6	0.8	0.8	0.8	0.8	17.5	20.6	41.8	42.0	47.9	52.2*	56.3*	21.3	4.6	3.4	1.5	1.5	0.8	0.8	0.8	0.8	0.4*	0.0*
Mean	0.1	0.1	1.5	10.1	18.5	26.6	35.6	40.0	46.0	50.1	54.0	25.5	4.6	2.2	1.3	1.2	0.7	0.5	0.4	0.4	0.2	0.0

* Estimated by applying to the preceding minute value for this subject the ratio (average value in this minute/average value in preceding minute) as derived from subjects having both values.

TABLE 6

END-EXPIRATORY pCO_2 (MM. OF MERCURY) DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Pretst	Control	Minutes of Rebreathing									Minutes of Recovery									
			1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	10	11
1	38.4	38.5	38.0	41.8	43.3	46.4	49.4	51.6	53.2	57.0	59.4*	44.8	38.0	36.5	35.0	36.5	37.2	36.5	38.8	38.0	39.5	38.0
2	38.0	37.0	38.8	38.0	40.3	43.3	41.8	44.8	47.1	49.4	50.0	33.4	20.0	28.0	30.4	30.4	30.4*	30.4	30.5	31.2	31.2*	30.0*
3	42.6	34.6	38.0	41.8	42.6	45.0	49.4	48.6	50.0	53.2	55.5	35.0	34.2	32.7	32.7	33.4	34.2	31.2	31.2	31.9	31.9	30.4
4	41.8	30.6	40.3	42.6	43.3	47.1	49.4	51.6	53.2	57.0	60.0	40.3	36.5	38.0	30.5	38.8	38.8	38.8	38.8	38.8	38.0	38.8
5	40.4	48.1	40.4	47.1	49.4	52.0*	53.2	55.5	57.8	60.8	63.1	60.2	47.1	43.3	41.8	41.8	42.6	42.6	43.3	44.1	43.3	44.1
6	43.4	43.2	44.1	47.1	47.1	49.4	50.0	54.0	57.0	60.3*	62.8*	44.8	44.1	41.8	41.8	43.4	41.1	41.8	42.6	44.1	44.1*	43.7*
Mean	41.8	40.2	40.0	43.1	44.3	47.5	49.0	51.0	53.2	56.3	58.6	44.1	37.8	36.0	36.0	37.4	37.4	36.9	38.5	38.0	38.0	37.7

* Estimated by applying to the preceding minute value for this subject the ratio (average value in this minute/average value in preceding minute) as derived from subjects having both values.

TABLE 7

ARTERIAL AND INTERNAL JUGULAR VENOUS BLOOD pH AND GAS VALUES AND CORRESPONDING VENTILATION VALUES DURING "ON" AND "OFF" TRANSIENTS OF REBREATHING CARBON DIOXIDE IN "NORMAL" SUBJECTS

Subject	Sample	Transient	Time (minutes)	Arterial Blood					Internal Jugular Venous Blood					Ventilation			
				pH	CO_2 Content (Vol. per cent)	pCO_2 (mm. Hg)	O_2 Content (Vol. per cent)	O_2 Saturation (per cent)	pH	CO_2 Content (Vol. per cent)	pCO_2 (mm. Hg)	O_2 Content (Vol. per cent)	O_2 Saturation (per cent)	Rate Per Minute	Tidal Volume (cc.)	Minute Volume (liters)	Alveolar Ventilation Ratio
1	1	Control	—	7.42	49.0	41.2	21.7	100	7.30	53.3	56.4	15.4	73	16	663	10.67	1.03
	2	On	5	7.48	49.9	37.5	21.4	100	7.31	52.1	53.8	16.4	78	16	1098	17.58	1.89
	3	On	8	7.38	53.6	49.3	22.0	100	7.17	55.5	76.2	17.7	84	16	1560	24.93	2.80
	4	Off	3	7.39	49.8	44.9	21.7	100	7.28	51.4	57.5	16.2	77	18	889	16.00	1.65
	5	Off	7	7.31	48.6	50.9	20.8	98	7.31	52.3	53.3	15.0	71	19	628	11.94	1.13
	6	Off	11	7.33	47.3	47.1	22.2	100	7.27	50.9	57.8	15.2	72	17	706	11.99	1.17
2	1	Control	—	7.38	46.5	41.2	20.6	100	7.32	47.2	47.3	13.8	72	15	630	9.84	0.94
	2	On	5	7.30	48.5	49.8	20.6	100	7.22	51.4	62.2	14.9	78	19	738	14.02	1.40
	3	On	10	7.26	50.5	56.3	20.8	100	7.21	53.4	66.2	16.7	87	19	1878	35.68	4.11
	4	Off	2	7.31	50.3	51.2	20.6	100	7.23	54.6	65.0	17.3	90	16	1804	28.85	3.32
	5	Off	3	7.41	43.1	36.0	20.9	100	7.27	53.7	64.1	12.0	62	15	1553	23.32	2.64
	6	Off	9	7.37	44.8	38.8	20.9	100	7.32	51.8	51.7	13.4	70	16	633	10.13	0.97
3	1	Control	—	7.33	52.6	52.4	20.7	100	7.21	47.2	62.3	15.0	78	12	695	8.34	0.87
	2	On	4-5	7.22	46.5	57.7	21.0	100	7.20	50.0	69.2	15.3	80	14	934	12.92	1.53
	3	On	8-9	7.21	51.4	65.2	21.0	100	7.14	51.1	94.0	15.2	79	17	1408	23.25	2.94
	4	Off	2-3	7.26	43.8	50.1	21.5	100	7.17	58.5	93.0	17.8	92	16	880	13.50	1.60
	5	Off	4	7.24	42.7	48.0	20.8	100	7.18	48.5	73.5	14.8	77	15	776	11.04	1.33
	6	Off	5-6	7.27	43.4	48.8	20.9	100	7.21	48.2	65.3	13.2	71	16	694	10.74	1.15
4	1	Control	—	7.30	50.2	46.5	20.1	97	7.20	56.8	64.6	12.8	61	14	719	10.06	1.15
	2	On	3-4	7.27	51.5	58.3	20.3	98	7.20	55.7	71.2	13.4	64	13	819	10.13	1.20
	3	On	8-9	7.20	53.9	68.8	20.2	97	7.18	56.0	76.0	16.4	79	8	2394	17.98	2.44
	4	Off	2-3	7.29	51.3	55.8	20.1	97	7.21	55.0	69.2	13.6	65	12	1112	12.41	1.55
	5	Off	6-7	7.30	50.6	53.8	20.3	98	7.26	55.1	63.7	12.0	58	14	734	10.28	1.10
	6	Off	10	7.38	49.8	45.2	20.3	98	7.27	52.6	59.3	12.3	59	15	643	9.65	1.07

TABLE 7 (*Continued*)

Subject	Sample	Transient	Time (minutes)	Arterial Blood					Internal Jugular Venous Blood					Ventilation			
				pH	CO_2 Content (Vol. per cent)	pCO_2 (mm. Hg)	O_2 Content (Vol. per cent)	O_2 Saturation (per cent)	pH	CO_2 Content (Vol. per cent)	pCO_2 (mm. Hg)	O_2 Content (Vol. per cent)	O_2 Saturation (per cent)	Rate Per Minute	Tidal Volume (cc.)	Minute Volume (liters)	Alveolar Ventilation Ratio
5	1	Control	—	7.31	51.9	55.0	22.8	100	7.20	58.6	65.1	15.8	70	11	751	8.27	0.91
	2	On	0	7.26	53.9	63.8	23.0	100	7.27	57.1	65.7	16.6	74	11	1030	11.32	1.34
	3	On	0	7.22	59.3	75.8	23.1	100	7.21	58.9	76.1	18.7	84	13	1150	14.95	1.74
	4	Off	2–3	7.39	54.1	49.3	23.1	100	7.23	60.5	75.5	19.2	86	14	1092	15.28	1.76
	5	Off	4–5	7.31	49.8	52.2	23.1	100	7.25	59.3	70.0	15.1	68	13	870	10.91	1.21
	6	Off	7	7.32	51.3	54.0	23.1	100	7.27	58.4	67.2	13.6	61	13	714	9.28	0.98
6	1	Control	—	7.33	53.8	53.6	22.5	100	7.23	51.2	61.9	15.0	75	13	566	7.37	0.81
	2	On	4–5	7.27	53.9	60.3	22.6	100	7.21	53.4	67.3	15.2	76	10	1366	12.76	1.66
	3	On	6–7	7.22	53.2	66.0	22.5	100	7.10	54.5	71.9	16.8	85	12	1400	16.00	2.11
	4	Off	1–2	7.20	53.2	57.8	22.3	100	7.21	53.4	66.0	17.2	86	13	1375	17.07	2.24
	5	Off	4–5	7.32	51.4	53.0	22.1	100	7.22	54.6	67.3	14.1	71	15	796	11.92	1.43
	6	Off	6–7	7.32	51.4	53.0	22.3	100	7.26	54.7	63.0	14.3	72	14	800	10.83	1.30
MEAN	1	Control	—	7.36	50.7	48.3	21.4	100	7.27	52.4	59.6	14.6	72	14	669	9.09	0.95
	2	On	5	7.30	50.7	54.5	21.5	100	7.24	53.3	64.9	15.3	75	14	998	13.12	1.50
	3	On	8	7.25	53.7	63.6	21.6	100	7.18	54.9	76.6	16.9	83	14	1632	22.13	2.69
	4	Off	2	7.32	50.4	51.5	21.6	100	7.22	55.6	71.0	16.9	83	15	1192	17.20	2.02
	5	Off	5	7.32	47.7	49.0	21.3	99	7.25	53.9	65.3	13.8	68	15	893	13.34	1.49
	6	Off	8	7.33	48.0	47.8	21.6	100	7.27	52.8	60.7	13.7	68	15	698	10.44	1.11

ing the initial phase of the "off" transient the heart rate accelerated transiently but only to a slight degree. No pathological arrhythmias appeared at any time.

Bipolar left frontal to left occipital electroencephalographic activity remained essentially normal in most of the subjects studied. In a few, decreased alpha activity was apparent during the height of rebreathing, but this was an inconstant finding and difficult to differentiate from artefacts which resulted occasionally when the subject failed to keep his eyes closed. No subject lost consciousness or reported any significant subjective sensorial change.

Discussion

The method developed and employed for this study proved satisfactory as applied to "normal" conscious volunteers, and appears equally applicable for comparative studies upon anesthetized subjects. Though studies of the stimulus-response relationships conducted by others generally have been based on methods providing "steady" states of breathing various fixed concentrations of carbon dioxide, the technical difficulties and explosion hazards inherent in such methods applied to studies during general anesthesia with flammable agents seem prohibitive. The method herein described minimizes these disadvantages and provides a feasible means of more safely studying stimulus-response relationships under the conditions of anesthesia. However, it does necessitate studying these relationships during "transient" rather than "steady" states.

Grodins *et al.* (15) have suggested that discrepancies between the results of various studies conducted during the "steady" state in "normal" subjects may be owing to failure in obtaining a truly "steady" state and that the "steady" state would not be essential to determining the true stimulus-response relationships if the carbon dioxide stimulus could be measured at its site of stimulatory activity, that is, in the respiratory center rather than in the arterial blood or in the respired gas mixture. Both a "lag" of respiratory response to abrupt carbon dioxide administration before the "steady" state is achieved and an "overshoot" of respiratory response following abrupt termination of the "steady" state by carbon dioxide withdrawal have been observed and studied by Padget (3) in humans and by Hesser (36) in dogs. Hesser, assuming the opinion ". . . that the changes in pCO_2 of the center lag behind those of the arterial blood in consequence of saturation and desaturation processes," postulated that ". . . the changes in pCO_2 and pH of the venous blood coming from the center would be smaller than those of the arterial blood."

Grodins *et al.* (15) have suggested that the physiological system controlling ventilation is a biological feed-back regulator and that if the carbon dioxide concentration in the respiratory center itself were considered the stimulus, no "lag" or "overshoot" might appear in the ventilatory response to abrupt changes in this stimulus. The report of Lambertsen *et al.* (7) regarding the hyperventilatory effect in man of

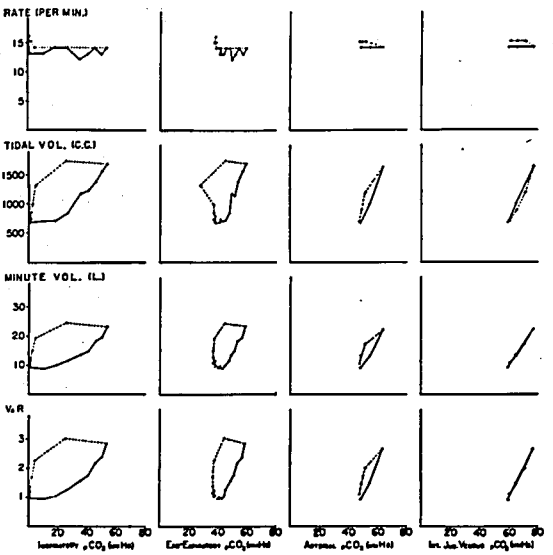

FIG. 4. Stimulus-response relationships during "on" and "off" transients of rebreathing carbon dioxide ("normal" subjects). Points plotted represent mean values obtained from tables 1–7. The "on" and "off" transients of rebreathing carbon dioxide are represented by solid and broken lines, respectively.

breathing 100 per cent oxygen at 3 atmospheres of pressure, suggests that the responsible degree of carbon dioxide accumulation in the respiratory center under these conditions is reflected more closely by the internal jugular venous pCO_2 than by the arterial pCO_2. The results of the present study likewise support the view that the degree of carbon dioxide stimulus effecting a given ventilatory response via the respiratory center is more accurately estimated by measuring the carbon dioxide tension in the internal jugular venous blood as it leaves the brain than by measuring the carbon dioxide tension in any other medium. Theoretically, it would be ideal to measure the carbon dioxide tension in the respiratory center itself, but there is no known direct method of accomplishing this. However, since the tensions of gases in the venous blood leaving a given tissue generally are considered to reflect closely their tensions in that tissue at any given moment, measurements of the carbon dioxide tension in blood obtained from the internal jugular vein as it drains from the brain should furnish indirectly a close approximation of the carbon dioxide tension in the respiratory center even during "transient" states. Certainly this approximation should be closer than one based upon the measurement of the carbon dioxide tension in

either arterial blood or the respired gas mixture. The results of the present study appear to support this assumption, for the stimulus-response relationships between internal jugular venous blood carbon dioxide tension and ventilatory activity during both the "on" and the "off" transients of rebreathing carbon dioxide were essentially linear and almost identical while these relationships showed progressively less direct correlation when arterial, end-expiratory, and inspiratory carbon dioxide tensions, respectively, were considered as "stimuli." The regression equation for the relationship between alveolar ventilation ratio and internal jugular venous blood carbon dioxide tension was found to be: V_AR = (Internal Jugular Venous pCO_2, mm. Hg) 0.115–6.004.

The differences in the stimulus-response relationships which were demonstrated for the various carbon dioxide media by considering, in turn, internal jugular venous, arterial, end-expiratory, and inspiratory carbon dioxide tensions as "stimuli" were more apparent during the "off" transient than during the "on" transient in this study. The reason for this is most probably the fact that the rate at which the biological feed-back regulator could adjust to changing carbon dioxide tensions was exceeded to a greater extent during the more abrupt "off" transient than during the more gradual "on" transient.

The stimulus-response relationships described represent those based upon mean values for the experimental group as a whole. Although the

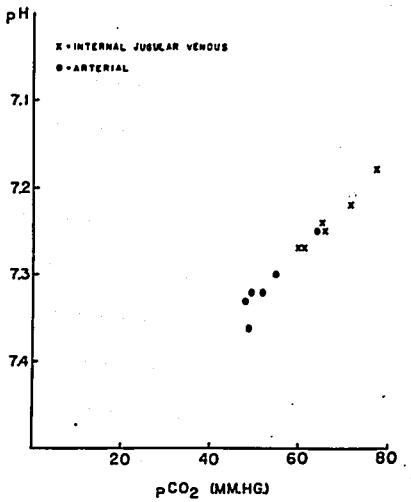

FIG. 5. pH and pCO_2 relationships during "on" and "off" transients of rebreathing carbon dioxide. Points plotted represent mean values for arterial and internal jugular venous pH and pCO_2, taken from table 7.

stimulus-response relationships showed quantitative variations among the individuals studied, qualitatively these relationships were essentially similar in all subjects.

It is realized that carbon dioxide is not the only stimulus which may influence ventilatory activity and that other factors such as oxygen lack, metabolic acidosis, exercise, and psychogenic as well as physical stimuli, may be involved in accordance with Gray's multiple factor theory of respiratory regulation (14). Also, changes in *p*H which occur in the internal jugular venous blood as well as in the arterial blood in reciprocal relationship to imposed changes in pCO_2 must be recognized (fig. 5), and the role of the hydrogen ion as a partial stimulus to the respiratory responses evoked by carbon dioxide must be considered in relation to the existing status of the acid-base balance of the body. However, by eliminating or controlling influencing factors to the greatest extent possible and by making allowances for any uncontrollable variables which still may exist, the use of carbon dioxide as a tool in conducting respiratory stimulus-response studies seems justifiable. Furthermore, from the data presented, it appears that the "true" stimulus-response relationship can be defined *even during "transient" states* provided that the specific stimulus is considered to be the carbon dioxide tension which exists in the respiratory center itself, as estimated from the pCO_2 of internal jugular venous blood draining from the brain. The carbon dioxide tension which at any moment exists elsewhere, such as in the arterial blood or in the respired gas mixture, must be regarded as the effect rather than the cause of the coincident ventilatory activity.

Limited observations regarding associated effects of rebreathing carbon dioxide upon the circulatory system and the brain under the conditions of these experiments revealed no significant influence either upon cardiac rate or rhythm or upon blood pressure, but electroencephalographic changes suggestive of alpha activity depression of the brain at the height of rebreathing carbon dioxide appeared in a few of the subjects. It has been reported (37) that increased carbon dioxide concentrations do exert a depressant influence upon cortical activity similar to that which occasionally appeared to accompany hypercapnia in these experiments. The augmenting influence of carbon dioxide upon cerebral blood flow, as reported by others (38), appeared to be manifested in this study by the decreased arterial-venous blood oxygen difference which usually accompanied hypercapnia. This effect of carbon dioxide probably was because of its direct vasodilating action upon cerebral blood vessels. However, increased cardiac output or decreased brain metabolism secondary to hypercapnia also might have played a role in producing this effect.

Summary

A method for quantitatively studying respiratory responses of man to carbon dioxide during transient states of rebreathing has been described.

Control values for stimulus-response relationships obtained in "normal" conscious volunteers by this method have been presented and analyzed.

The respiratory response in terms of alveolar ventilation ratio (V_aR) varies with the carbon dioxide stimulus in terms of pCO_2 of the internal jugular venous blood directly and almost identically during both "on" and "off" transients of rebreathing according to the equation: V_aR = (Internal Jugular Venous pCO_2, mm. Hg) 0.115–6.004. The relationship of the ventilatory response to the carbon dioxide stimulus becomes progressively less linear in each transient and more dissimilar between transients when the carbon dioxide stimulus is considered in terms of pCO_2 of arterial blood, end-expiratory gas, and inspiratory gas, respectively. This decreasing correlation appears related to "on" transient "lag" and "off" transient "overshoot" of the ventilatory response in relation to changing carbon dioxide tensions in media which do not reflect the degree of stimulus in the respiratory center.

Reasons for interpreting internal jugular venous carbon dioxide tension as the value most closely reflecting the "true" respiratory stimulus under the conditions of these experiments have been discussed.

Limited observations regarding associated effects of rebreathing carbon dioxide upon the circulatory system and the brain have been described.

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