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Research Article

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Mechanism and Pattern of Human Cerebrovascular Regulation after Rapid Changes in Blood CO_2 Tension *

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Little is known of the mechanism and pattern of cerebrovascular regulation after relatively rapid repeated alterations in blood CO_2 tension as might occur in various environmental or disease states. Quantitative measurements of change in the cerebral circulation have largely been limited to prolonged steady state conditions because the most accepted technique for measuring cerebral blood flow (CBF) and metabolism requires long periods for equilibration, i.e., the nitrous oxide method of Kety and Schmidt (1). Recently, certain radioisotope techniques capable of repetitive determinations at 1-minute intervals have been utilized in studies of CBF in the control state (2) and in response to a single alteration in blood CO_2 tension in a small number of studies (3). Analysis of the assumptions upon which these techniques are based and reasons for questioning their adequacy in following rapid changes in flow have recently been detailed by Zierler (4).

The purpose of these studies was to measure, by means of an appropriate technique, the pattern of change in CBF during a series of alterations in blood CO_2 tension to obtain information concerning the mechanism of control of the cerebral circulation during such interventions. The data demonstrate the existence of hysteresis between arterial CO_2 tension and CBF during stepwise elevations and depressions of this tension above the control in contrast to an essentially linear correlation of CBF with the simultaneously obtained jugular venous CO_2 tension. Hysteresis between arterial CO_2 tension and CBF was not observed during reductions and elevations of the CO_2 tension in the hypocapnic range.

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Methods

The technique employed for the quantitation of change in CBF from the control value was that of continuously or intermittently determining cerebral arteriovenous oxygen differences (5). The Fick principle may be utilized for estimation of blood flow if the arterial and venous concentrations of a substance (in this case oxygen) are constant, and if blood flow and the rate of tissue uptake of the substance in question are also constant (6, 7). If those conditions are satisfied, then the blood flow is directly proportional to the reciprocal of the arteriovenous difference for oxygen, $1/(a\text{-}v)_{O_2}$. If a change in CBF is induced, the ratio of the experimental and control values for $1/(a\text{-}v)_{O_2}$ multiplied by 100 will provide the per cent of change in blood flow. In view of the stability of the cerebral metabolic rate for oxygen (1, 5, 8), the arterial-internal jugular bulb oxygen difference may be used to estimate relative changes in blood flow under many circumstances and has been considered at least as precise as the nitrous oxide method by some workers (8, 9). Since alterations in blood CO_2 to the extent produced during the present experiments do not result in significant changes in cerebral oxygen uptake (1, 5, 8), this technique, allowing nearly continuous estimates of relative changes in CBF, was utilized. Comparisons of steady state data obtained by the $1/(a\text{-}v)_{O_2}$ technique with those obtained by the nitrous oxide method have shown close agreement (8, 10).

A further requirement for accuracy of this technique in states where complete equilibration of flow may not be present would be that the transit time of O_2 be short enough to keep pace with the changes in flow (6). Evidence supporting this likelihood has been found in the considerable data indicating that the cerebral O_2 pool is small, cerebral circulation time in normals is short, and O_2 transit through many tissues appears to be unusually rapid (11). Furthermore, different direct and indirect techniques reported by others in primates (12) and man (2) show temporal patterns of change in response to CO_2 inhalation similar to those obtained with the $1/(a\text{-}v)_{O_2}$ method (11) used in the present investigation.

The oximetric methods, modes of analysis and calibration, and the equipment referred to below were similar to those discussed in detail by Wood (13) and have been found satisfactory by us (8, 11). Due to technical or physiological factors or both, CBF during room air breathing as determined by this method of measurement varied 3.4 ± 5.2% above the control (11), a figure that compared favorably with other techniques proposed for minute-to-minute determinations (2).

Subjects

Thirty-seven separate studies were performed on 13 normal male volunteers whose mean age was 34 years; the range was 27 to 54 years. All studies were done in the forenoon with the subjects in the supine position.

Procedure

In all studies, indwelling needles were placed percutaneously in the brachial artery and right internal jugular bulb with local anesthesia. Brachial arterial pressure was recorded with a Statham P23-Db pressure transducer between arterial sampling times. In six studies intermittent arterial and venous blood samples were obtained.

In the remaining studies, internal jugular venous oxygen saturations were continuously determined oximetrically by drawing blood through an oximeter cuvette [1] with a syringe pump [2] at a flow of 3.8 ml per minute. The red and infrared values were recorded continuously by means of optical galvanometers and an 18-inch slit camera [1] with a 2-meter light path. Arterial oxygen saturation was continuously monitored by similarly recording red and infrared values obtained from a Waters ear oximeter. In some experiments intermittent arterial oxygen saturation values were derived from the oxygen-hemoglobin dissociation curves and arterial blood oxygen tensions determined by the equilibration technique of Riley, Proemmel, and Franke (14) or with an oxygen electrode [3] (15). Arterial blood pH was determined by a Metrohm electrode attached to the Epsco instrument at 37.5° C. Arterial CO_2 tensions were estimated by the equilibration or electrode techniques.

After an occluding noseclip was clamped in place, each subject breathed through a mouthpiece into which room air or various carbon dioxide in air mixtures could be supplied. End-tidal CO_2 concentration was continuously monitored with an infrared CO_2 analyzer [4] by sampling from the mouthpiece through the microcatheter cell of the analyzer. Arterial pressure and end-tidal CO_2 tension were recorded on a multichannel oscilloscopic recorder,[5] which allowed visual monitoring of these parameters. An electrical marker simultaneously noted arterial sampling on the paper in the oscilloscopic recorder and that in the optical slit camera. Corrections were later made for time parallax from internal jugular bulb to oximeter cuvette.

[1] Waters Corp., Rochester, Minn.
[2] Harvard Apparatus Co., Dover, Mass.
[3] Epsco, Inc., Cambridge, Mass.
[4] Beckman Instruments, Inc., Fullerton, Calif.
[5] Electronics for Medicine, Inc., White Plains, N. Y.

Experimental design

A) Six studies on five subjects were carried out to correlate changes in jugular venous CO_2 tension with arterial CO_2 tension and CBF changes during stepwise increase of blood CO_2 tension and during its return to control values. In order to accomplish this, intermittent withdrawal of blood through the needle in the jugular bulb and the brachial artery was carried out 100 seconds after the onset of breathing each of the following gas mixtures *in seriatim:* 21% O_2 in N_2; 3, 4, 5, 7, 5, 4, and 3% CO_2 in 21% O_2 in N_2; and then 21% O_2 in N_2. In three studies the 4% CO_2 mixture was not administered. Stability in arterial or end-tidal P_{CO_2} may be expected at the stated sampling intervals (11) (see Figure 6).

B) In 21 studies on six subjects one of the following three protocols was followed during continuous withdrawal of jugular venous blood through the oximeter system described above, which precluded analysis of this venous blood for anything other than O_2 saturation.

1) After control records and samples were obtained, the subject breathed *in seriatim* 21% oxygen in nitrogen mixtures containing 3.50, 4.83, and 6.88% CO_2. When the visually monitored end-tidal CO_2 concentration became stable during inhalation of each CO_2 mixture, arterial blood samples were drawn for analysis of blood gas tensions and pH. After arterial sampling while the subject breathed the highest CO_2 mixture, decreasing concentrations of this gas were administered in stepwise fashion (3.5, 1.75% CO_2 and room air) in an attempt to retrace the previously noted plateaus of end-tidal CO_2 concentration. Arterial gas tension analysis and cerebral blood flow values could then be determined at a comparable series of points during the series of increasing and then decreasing levels of CO_2 inhalation.

2) Similar sequential determinations were made during voluntary hyperventilation, which was altered by asking the subject to overbreathe mildly, moderately, and severely. Stability at each level was estimated in the same manner as before. After severe hyperventilation, stepwise decreases in the intensity of hyperventilation allowed the subject to return to each hypocapnic plateau of end-tidal CO_2 tension.

3) In a few instances, it was possible to carry a subject through procedures 1 and 2 without interruption (see Figures 3 and 4).

C) In ten experiments on five subjects, a single breath of 28.5% CO_2 in 21% oxygen and 50.5% nitrogen was administered. Control arterial blood samples were obtained, and after the gas inhalation they were obtained via a syringe manifold system as rapidly as possible for the first minute, every 10 to 15 seconds for the second and third minutes, and at 30-second intervals during the subsequent 2 minutes. Jugular venous and arterial oxygen saturations were measured continuously as described above. Arterial pressure was obtained in two of these ten studies. On several occasions, two studies were performed on the same subject with a 30-minute rest period between studies.

Graphs were constructed relating change in arterial

or end-tidal CO_2, or both, and, where available, jugular venous CO_2 tension to changes in CBF, as calculated from changes in cerebral arteriovenous oxygen difference, and cerebral vascular resistance (mean arterial pressure/CBF expressed as per cent of the control value). Statistical analyses were carried out with the aid of a digital computer by accepted methods (16).

Results

The experiments were well tolerated by all subjects. On one occasion a right facial palsy was discovered at the conclusion of the procedure, and 4 weeks was required for complete recovery.

Correlation of arterial and jugular venous CO_2 tension with CBF during 100-second exposures to serial CO_2 mixtures. Figure 1 depicts simultaneous data for arterial and jugular venous CO_2 tension and CBF from two of the six studies described in Methods (section A under Experimental design; *vide supra*). The plot relating arterial CO_2 tension and CBF reveals a hysteresis-like pattern, i.e., the CBF was lower with rising arterial CO_2 tension than it was later with decreasing arterial CO_2 tensions. In contrast, the jugular

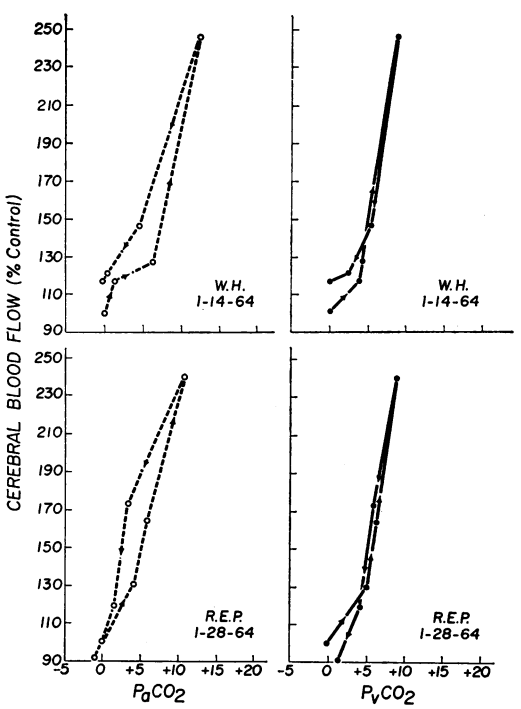

FIG. 1. COMPARISON OF RELATIONSHIP OF SIMULTANEOUS ARTERIAL AND JUGULAR VENOUS CO_2 TENSIONS TO CEREBRAL BLOOD FLOW IN TWO STUDIES. See text for discussion. $Paco_2$ = arterial CO_2 tension; $Pvco_2$ = jugular venous CO_2 tension.

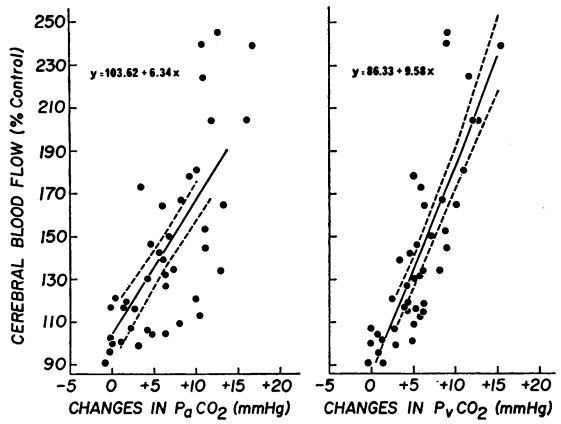

FIG. 2. COMPARISON OF RELATIONSHIPS OF ALL DATA FOR SIMULTANEOUS ARTERIAL AND JUGULAR VENOUS CO_2 TENSIONS TO CEREBRAL BLOOD FLOW FROM THE SIX EXPERIMENTS IN WHICH BOTH VENOUS AND ARTERIAL CO_2 TENSIONS WERE OBTAINED. Correlation coefficient for $Pvco_2$ vs. cerebral blood flow (CBF) was better ($r = .83$) than for $Paco_2$ vs. CBF ($r = 0.72$). Solid lines are the regression lines; the dotted lines indicate the 95% confidence limits.

venous CO_2 tensions and CBF showed an almost linear correlation in which no clear differences between ascending and descending values could be discerned. Figure 2 contrasts the relationship of all values for arterial CO_2 tension and CBF with that for all values of jugular venous CO_2 tension and CBF from these six studies. The data were subjected to linear regression analysis. Analyses of variance revealed both regressions to be highly significant ($p < 0.0005$) as might be expected. The F value for CBF and jugular venous CO_2 tension was higher than that for CBF and arterial CO_2 tension (86.3 vs. 42.1) reflecting an even better linear relationship under the conditions of the study. The correlation coefficient for jugular venous CO_2 tension vs. CBF was also better ($r = .83$) than that for arterial CO_2 tension vs. CBF ($r = 0.72$).

Further studies of arterial CO_2 tension and CBF during serial exposure to CO_2 mixtures. Ten of 13 experiments in which only arterial (or end-tidal) values for Pco_2 were obtained demonstrated a loop pattern when the tensions were plotted against CBF (Figures 3 and 4). Analysis of jugular venous blood for Pco_2 was not possible in this series because the blood had been continuously withdrawn through the whole blood oximeter system. Repeated studies of an individual at inter-

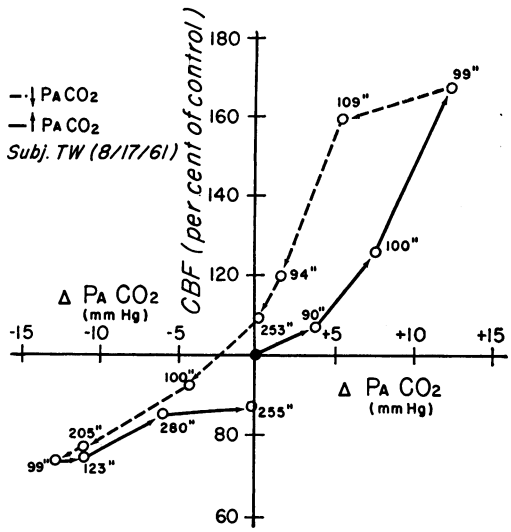

FIG. 3. RESPONSE PATTERN OF THE CEREBRAL BLOOD FLOW TO SERIAL ALTERATIONS IN ARTERIAL AND END-TIDAL CO_2 TENSION ABOVE AND BELOW THE CONTROL LEVEL. The hysteresis-like phenomenon was evident only at return to control CO_2 tension during the hypocapnic phase of this experiment. The time in seconds between the serial simultaneous determination of end-tidal and arterial CO_2 tension and per cent change in cerebral blood flow is indicated beside each point. The arrows indicate the direction of the changes in arterial CO_2 tension. Solid lines indicate rising P_{CO_2}; interrupted lines indicate decreasing end-tidal CO_2 tension (P_{ACO_2}).

vals of 6 or more weeks revealed similar but not identical responses (Figure 5). The level of cerebral blood flow on the rising limb of arterial CO_2 tension was lower than on the descending

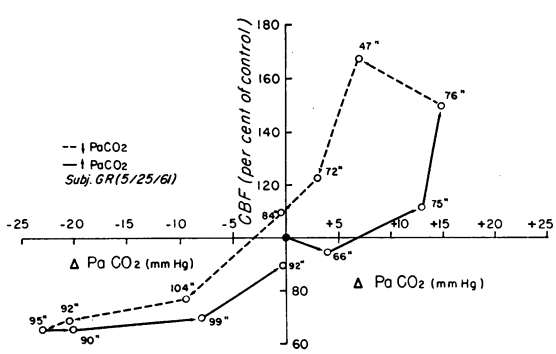

FIG. 4. RESPONSE PATTERN OF CEREBRAL BLOOD FLOW TO A CONTINUOUS SEQUENCE OF STEPWISE CHANGES IN ARTERIAL CO_2. Times in seconds between each determination are indicated and the direction of changes in arterial CO_2 shown by the arrows. Solid dot is the control point. Solid lines indicate rising P_{aCO_2}; interrupted lines indicate decreasing P_{aCO_2}.

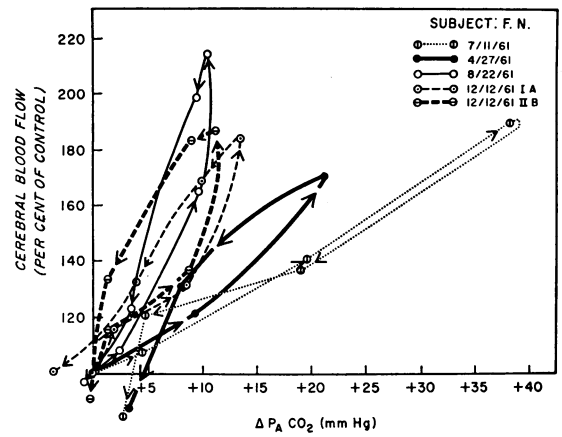

FIG. 5. RESULTS OF FIVE SEPARATE EXPERIMENTS IN ONE SUBJECT. Although quantitatively inconstant, hysteresis between arterial and end-tidal P_{CO_2} and CBF was clearly present in four studies.

limb of this tension at each level of arterial CO_2 tension measured. In seven of ten experiments exhibiting hysteresis, CBF approximated control levels when arterial CO_2 was returned to the control tension; in three it remained higher when arterial CO_2 tension was returned to control.

Analysis of the records at 10-second intervals from four of these experiments demonstrated the stability of end-tidal CO_2 tension during one to several 10-second periods before arterial sampling at each level of inspired CO_2 (Figure 6). This confirmed the judgments of stability based on observation of the oscilloscope during each study. Arterial pressures rose slightly during inhalation of the serially increasing and decreasing concentrations of CO_2 in air, but the cerebrovascular re-

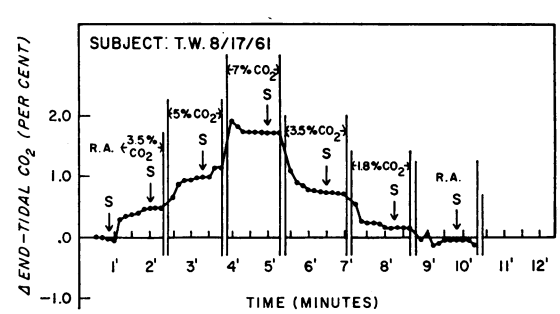

FIG. 6. PATTERN OF RISE AND FALL IN END-TIDAL CO_2 DURING CO_2 INHALATION PORTION OF EXPERIMENT DEPICTED IN FIGURE 3. Note relative stability at the various sampling times. RA = room air, and S = time of sampling for arterial CO_2 tension and determination of change in cerebral blood flow.

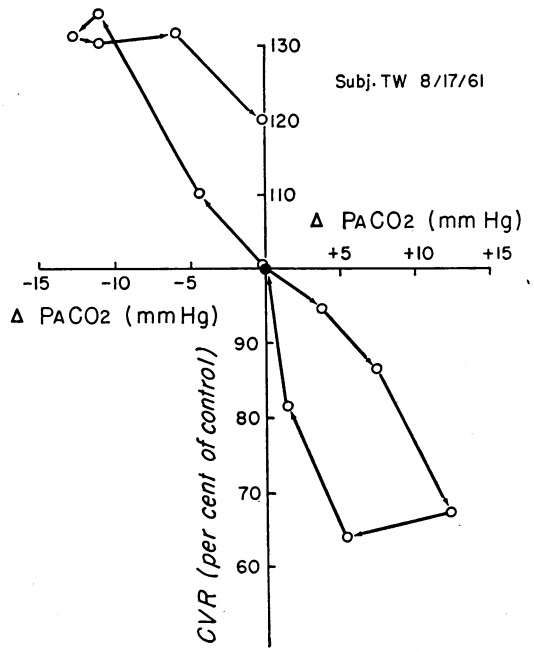

FIG. 7. CHANGES IN CEREBROVASCULAR RESISTANCE (CVR) PLOTTED AGAINST END-TIDAL CO_2 TENSION IN EXPERIMENT DEPICTED IN FIGURE 3. Arrows indicate sequence of changes starting from control (closed circle). During the period when arterial CO_2 tension was above control, a loop for this function was present. The final two points were obtained during the stepwise return of arterial CO_2 tension to the control value. Hysteresis for this function was present at this time.

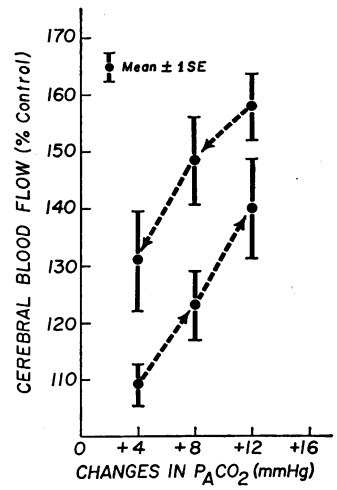

FIG. 8. MEAN VALUES FOR CEREBRAL BLOOD FLOW AT COMPARABLE POINTS DURING RISING AND FALLING END-TIDAL CO_2 TENSIONS ABOVE CONTROL FROM SEVEN EXPERIMENTS. Each mean difference was significant, $p < 0.05$. See text for discussion.

sistance formed loops when plotted against arterial or end-tidal CO_2 tension (Figure 7).

Measurements of CBF at identical points of ascending and descending arterial (or end-tidal) CO_2 tensions were present in seven studies. Analysis of the mean differences in CBF during ascent and during descent of CO_2 tension was carried out to gain a general picture of the observed

TABLE I

*Cerebral blood flow during gradual ascent and descent and during continuous ascent and descent of arterial or end-tidal CO_2 tensions**

Change in CO_2 tension		CBF during stepwise ascent and descent of $P_{A_{CO_2}}$† A	CBF during stepwise ascent and descent of $P_{A_{CO_2}}$† D	CBF during continuous ascent and descent of $P_{a_{CO_2}}$ after single breath 28.5% CO_2‡ A	CBF during continuous ascent and descent of $P_{a_{CO_2}}$ after single breath 28.5% CO_2‡ D
mm Hg		*% control*		*% control*	
+4	Mean	109.3	131.1	98.6	124.4
	SD	9.5	22.4	11.1	16.2
	SE	3.6	8.5	4.9	7.3
		$p < 0.05$		$p < 0.01$	
+8	Mean	123.3	148.7	101.8	126.6
	SD	15.5	19.3	12.9	18.7
	SE	5.9	7.3	5.8	8.4
		$p < 0.05$		$p < 0.01$	
+12	Mean	140.1	158.1	105.6	128.0
	SD	23.2	14.9	95.1	18.3
	SE	8.8	5.7	6.8	8.2
		$p < 0.05$		$p < 0.01$	

* Abbreviations: CBF = cerebral blood flow, A = ascending P_{CO_2} levels, D = descending P_{CO_2} levels, $P_{A_{CO_2}}$ = end-tidal CO_2 tension, and $P_{a_{CO_2}}$ = arterial CO_2 tension.

† Seven studies with determinations at +4, 8, and 12 mm Hg of end-tidal CO_2 tension during ascent and descent.

‡ Five studies with determinations at +4, 8, and 12 mm Hg of arterial CO_2 tension during ascent and descent.

hysteresis (Figure 8, Table I). In Table I it can be seen that during stepwise ascent and descent of end-tidal (and arterial) CO_2 tension, the mean differences varied from 18 to 25% at + 4, 8, and 12 mm Hg and were significant ($p < 0.05$).

Studies of arterial CO_2 tension and CBF during stepwise exposures to decreased arterial CO_2 tensions. Hysteresis between CBF and arterial CO_2 tension was present in one of the ten hyperventilation experiments (Figures 3, 4, 9). Plots of cerebrovascular resistance against arterial P_{CO_2} revealed a loop in only two of the eight studies from which these data were available.

Response to single breath inhalations of 28.5% CO_2. Figure 10 illustrates the alterations in CBF and the times in seconds in which they occurred after a single inhalation of 28.5% CO_2 in one of the ten experiments of this type. The curves obtained from different subjects and those obtained from duplicate studies in the same subject were similar but not identical in their time course and magnitude of change in CBF. The depth and rapidity of the single inhalation were variable and may have accounted for part of the inconstancy. Maximal rises of CBF occurred 10 to 32 seconds after the beginning of the inhalation and returned to control levels within 2 minutes. The time intervals required for attainment of the highest observed arterial CO_2 tension and the highest observed cerebral blood flow were identical in five studies. In the remaining five, the highest flow followed the peak arterial CO_2 tension observed by an average of 16 seconds, range 7 to 25. Continuous arterial pressure was recorded in only

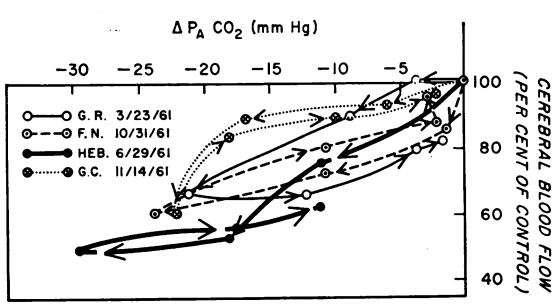

FIG. 9. TYPICAL RESULTS AFTER STEPWISE DECREASES AND SUBSEQUENT INCREASES TO CONTROL OF ARTERIAL AND END-TIDAL CO_2 TENSIONS DURING CONTROLLED LEVELS OF VOLUNTARY HYPERVENTILATION. One of these four (G.R.) shows a loop pattern. Arrows indicate the sequence of the plotted changes.

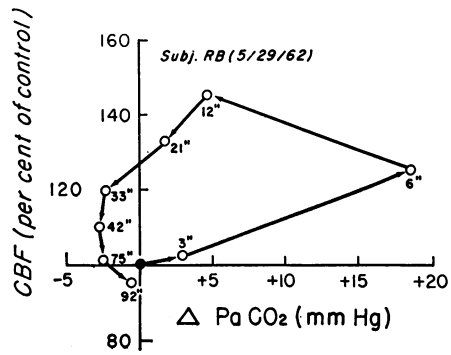

FIG. 10. TIME COURSE OF CHANGE OF ARTERIAL CO_2 TENSION AND CEREBRAL BLOOD FLOW TO A SINGLE BREATH OF 28.5% CO_2. The closed circle represents control values immediately before the inhalation. Time in seconds from the beginning of the breath is shown next to each determination. Note that at the end of 33 seconds increased alveolar ventilation had produced a slight decrease in Pa_{CO_2}, but that CBF remained 20% above control. Corrections were not made for changes in arterial blood pressure.

two of these ten studies. It was determined that the observed elevations in perfusion pressure were sufficient to account for 25 to 30% of the flow increase in these two studies and, presumably, in the eight others of this type.

A general picture of the differences in CBF during these continuous rises and falls in arterial CO_2 tension, uncorrected for the effects of blood pressure changes, may be seen in the analysis in Table I of five studies providing CBF measurements at identical CO_2 tension points during the rising and falling phases. The mean differences in CBF ranged from 23 to 26% at + 4, 8, and 12 mm Hg arterial CO_2 tension, and all were significant at the 1% level.

Discussion

The classical studies of Kety and Schmidt (1) defined the alterations in cerebral blood flow and metabolism induced by CO_2 inhalation and hyperventilation maintained for a prolonged period (15 to 30 minutes) in normal man. Subsequent studies demonstrated the threshold of the response to increase in blood CO_2 (5), the slope of the response during hypocapnia (8), the full range of responsiveness to CO_2 in primates (17), and the roles of H^+ and P_{CO_2} in cerebral circulatory control (9).

The present study is the first to provide continuous or rapidly repeated measurements of CBF

and blood CO_2 tensions during serial stepwise progressive increases and decreases in blood CO_2 tension above and below the normal resting blood Pco_2 range in normal man. These studies provide insight into the mechanism of cerebral circulatory control during rapid alterations in arterial CO_2 tension. Steady state experiments would be expected to obliterate any temporally dependent differences in the relationships between arterial CO_2 tension, jugular venous CO_2 tension, and CBF. Observations immediately following a single increase in inspired CO_2 concentration are available. As early as 1935, Gibbs, Gibbs, and Lennox (18) demonstrated rapid cerebral circulatory responses to CO_2 inhalation and hypoxia, but their data were qualitative. Lewis and colleagues (3) devised a radioisotope technique for minute-to-minute measurements of CBF and reported continuous rises in CBF during CO_2 inhalation and progressive decreases in CBF during voluntary hyperventilation in a limited number of studies. We have reported (11) plateaus for arterial CO_2 tension, jugular venous CO_2 tension, and CBF to be reached within 1 to several minutes after the onset of a given change in inspired CO_2. Generally, cerebral blood flow became stable at a finite interval after arterial Pco_2, and jugular venous Pco_2 correlated as well or better than arterial Pco_2 with the corresponding changes in CBF. Repeated studies in the same normal subjects performed on separate occasions resulted in similar but not identical responses, and the range of CBF rise with given alterations in blood CO_2 tension was wide.

Despite repeated attempts (2, 3, 18), technical problems have prevented a complete description of the instantaneous responsiveness of the cerebral circulation. The technique of estimating changes in CBF from the reciprocal of arteriovenous oxygen differences across the brain can be applied in those situations in which the cerebral O_2 consumption is known to be constant and absolute values for flow are not required as detailed in Methods and elsewhere (11), providing the other conditions for application of the Fick principle are satisfied (6). The accuracy of the techniques employed in this study has been repeatedly tested (5, 8, 10, 13) and found satisfactory.

The present study demonstrates hysteresis between the CBF and arterial Pco_2 during a sequence of exposures to increasing and then decreasing arterial CO_2 tensions above the control range. This was not seen in correlations of the simultaneously obtained jugular venous CO_2 tension and CBF, nor was it regularly present during voluntary hyperventilation. Although a wide variety of mammalian tissues, including arteries, possess nonlinear stress-strain characteristics explicable in terms of the intrinsic physicochemical properties of the tissue walls (19–25), Peterson (26), on the basis of his studies, considers a hysteresis-like pattern in arterial dilatation and constriction *in vivo* very unlikely. The present data may be interpreted to show that the intra-arterial CO_2 tension is not the effective stimulus for cerebral vasodilatation in these experiments. In view of the better correlation of jugular venous CO_2 tension with the associated changes in CBF, one might speculate that "tissue" CO_2 tension (if jugular venous Pco_2 is assumed to be equivalent to tissue Pco_2) is the effective stimulus. Studies of human cerebral blood flow and arterial and jugular venous CO_2 tensions during the first 5 to 8 minutes of inhalation of a given concentration of carbon dioxide have led to similar conclusions (11). Observations in cats have shown that cortical vascular tone can be markedly influenced by alterations in cortical tissue O_2 and CO_2 tensions (27). Inconsistency in the correlation of CBF with arterial CO_2 tension would not be observed in prolonged steady state experiments in which temporally dependent relationships would be obliterated. Indeed, an excellent correlation between arterial CO_2 tensions and simultaneous determinations of CBF was found in the data reported herein. The present and previously obtained (11) data substantially agree with observations on the stimulus to vasodilatation in the forearm during and after CO_2 inhalation that also appears to be the tissue rather than the arterial CO_2 tension (28, 29).

The present data may be explained by assuming that a finite time is required for the achievement of an equilibrium between arterial and tissue CO_2 tensions that would not be evident in steady state studies but was apparent in the first several minutes after a single elevation in the concentration of inspired CO_2 (11). As the arterial Pco_2 is progressively increased in stepwise fashion for periods too short to allow full equili-

bration, the tissue tension should lag behind the arterial while arterial CO_2 tension is rising, and during the period of descending arterial CO_2 tension it should exceed arterial Pco_2. Thus, the hysteresis between arterial Pco_2 and CBF would be present because the actual determinant of cerebrovascular resistance (i.e., tissue Pco_2) was overestimated on the ascending limb and underestimated on the descending limb. Strong evidence favoring this hypothesis is contained in the six studies in which simultaneous jugular venous and arterial Pco_2 values were obtained and is depicted in Figures 1 and 2. Inspection of individual studies reveals the venous values to show a straight-line relationship to CBF, whereas the arterial CO_2 tension plots yield counterclockwise loops in five of the six studies and during the highest flows in the sixth. Whereas regression analysis confirms the good correlation with CBF expected of both of these closely related parameters, the F value for the venous CO_2 tension was much higher than that for the arterial. These studies should also rule out the possibility that random scatter of data or systematic errors produced the loops, since no clockwise loops were recorded, and whereas arterial CO_2 consistently showed the phenomenon, the simultaneously obtained jugular venous Pco_2 did not.

Absence of manifest hysteresis between arterial CO_2 tension and CBF in the hyperventilation experiments may in part have been due to the smaller range available for the response. CBF may increase 200 to 300% when arterial CO_2 tension is elevated but will decrease only to 50 to 60% of the control value when this tension is lowered by maximal voluntary hyperventilation in conscious man (1, 8, 17). It may be that the continuous oximetric technique, probably insufficiently sensitive to detect accurately CBF changes of much less than 5% (11), did not clearly reveal narrow loops that might have been present. It is evident in Figure 9 that the greatest decrease in CBF possible in conscious man was regularly achieved with maximal hyperventilation efforts reducing arterial (or end-tidal) CO_2 tension 23 to 30 mm Hg below control. The counter influence provided by tissue CO_2 production that would be enhanced during periods of reduced flow may also have smoothed out the response.

The single breath experiments represent observations in an almost continuously changing state. Perhaps one-fourth to one-third of the increase in flow may have been due to elevated perfusion pressures, but sufficient pressure data for definitive analysis are not available. The arteriovenous oxygen difference method has its greatest potential limitation in studies such as these and could, theoretically, have resulted in underestimation of actual flow on the ascending portion of the curve followed by overestimation of flow during the descending portion of the curve. Considering the rapidity of O_2 transit, the lack of change in cerebral O_2 consumption, and the similarity in shape to the "slow" loops, such errors may not be great. If this is so, these observations may reflect the speed of progression of dilatation of small vessels after a maximal dilator stimulus administered as a square wave, i.e., the observed pattern could be due to lags in the exposure to CO_2 of arterioles in areas of more sluggish flow in this vascular bed. The data indicate cerebral vasodilatation not to be an instantaneous phenomenon, and its maximum may require as long as 32 seconds after inhalation of a single potent stimulus and up to 25 seconds after a peak in arterial CO_2 tension is achieved. Dilatation of a progressively increasing number of arteries may be visualized as the cause of the vertical rise in flow over a 30-second period in the experiment depicted in Figure 11 while the arterial CO_2 tension hovered at a level of 20 mm Hg above control. Expansion of such studies, confirmed by a direct technique, might well lead to a method of evaluating the adequacy of cerebrovascular reactivity.

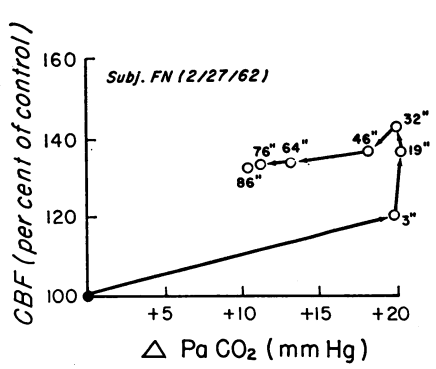

FIG. 11. RESPONSE OF ARTERIAL CO_2 TENSION AND CEREBRAL BLOOD FLOW TO A SINGLE BREATH OF 28.5% CO_2. See text for discussion.

Summary

The relationships between cerebral blood flow and blood CO_2 tension after rapid alterations in inspired CO_2 were explored in 37 separate studies on 13 normal male volunteers. During progressive stepwise increases and decreases in arterial CO_2 tension above the control level, jugular venous CO_2 tension correlated more exactly with cerebral blood flow than did the arterial CO_2 tension. In 16 of 19 experiments arterial CO_2 tension described a counterclockwise loop when plotted against the corresponding values for cerebral blood flow. This distinct hysteresis between arterial CO_2 tension and cerebral blood flow was evident in only one of ten experiments during stepwise reductions and return to control in the hypocapnic range, which was accomplished by variable levels of hyperventilation.

On ten occasions cerebral blood flow and arterial CO_2 tension were measured as rapidly as possible after a single breath of 28.5% CO_2. These studies provided further evidence that a finite interval is required for the cerebral vessels to respond to a given elevation in arterial CO_2 tension.

The data are interpreted to suggest that the tissue tension of CO_2 may be the effective regulator of cerebrovascular resistance rather than the intra-arterial tension of this gas. Thus, measurements restricted to arterial CO_2 tension during ascent of arterial CO_2 tension may overestimate and, during descent of this tension, underestimate the actual determinant of cerebrovascular resistance when these measurements are made in the rapidly or continuously changing state.

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