THE CHANGES IN CEREBRAL VASCULAR RESISTANCE OF MAN IN EXPERIMENTAL ALKALOSIS AND ACIDOSIS [1]

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Available evidence suggests that cerebral vascular resistance in man is primarily under chemical control. Past studies indicate that neurogenic stimuli, hormonal influences and most drugs have little ability to dilate cerebral vessels significantly. The potent chemical regulators which dilate cerebral vessels have been shown to be: *1*) anoxia and *2*) either CO_2 retention or decrease in the pH of arterial blood (1, 2). Using the nitrous oxide technique, Kety found increased cerebral blood flow (CBF) in subjects breathing 10 per cent O_2. He also showed that the increased CBF of respiratory acidosis produced by breathing 5 per cent or 7 per cent CO_2 was associated with increased CO_2 content and a lowered pH of arterial blood and decreased CBF of respiratory alkalosis following hyperventilation with a lowered CO_2 content and elevated pH.

Because of a tendency to an increase in CBF in late stages of diabetic acidosis, it was suggested originally by Kety, Polis, Nadler, and Schmidt (3) that the pH level might be more important than the CO_2 content in regulation of cerebral vascular tone. This viewpoint has been stated by others (4, 5). Some doubt about this interpretation is suggested by earlier findings of Bronk and Gesell (6). In 1927, they found that intravenous injection of sodium carbonate and sodium bicarbonate increased blood flow in the femoral and the carotid arteries of dogs under anesthesia.

The present study attempts to separate the effect on cerebral vessels of changes in pH and CO_2 content. By infusing $NaHCO_3$ and NH_4Cl intravenously, metabolic alkalosis and acidosis, respectively, were produced in man. The changes which occurred in CBF and cerebral vascular resistance were noted and compared to the changes previously reported after respiratory acidosis and alkalosis.

METHOD

The subjects studied were patients on the Medical Service of Duke Hospital. They were convalescing from a variety of illnesses and cannot be considered as a group of normal people. Six subjects were patients at Butner State Hospital. These patients were ill with schizophrenia and presented no physical illnesses. Metabolic alkalosis was produced by intravenous infusion of 1000 ml. of 3 per cent $NaHCO_3$ or 1000 ml. of 1.2 per cent $NaHCO_3$ over a period of sixty minutes. Metabolic acidosis was established by slower infusion of approximately 350 cc. of 0.8 per cent NH_4Cl intravenously over a period of 60 to 90 minutes. NH_4Cl caused slight hyperpnea, and nausea occurred if the speed of the infusion was increased. Changes in pulse rate and blood pressure did not occur if the drip rate was kept below the nausea threshold.

The effect of changes in blood volume was determined by administering 1000 ml. of 0.85 per cent NaCl solution intravenously over a period of one hour. The effects of both volume change and hypertonicity on the cerebral circulation were observed after the intravenous administration of 1000 ml. of 2 per cent NaCl solution over a period of one hour.

Cerebral blood flow (CBF) was measured, using the nitrous oxide technique described by Kety and Schmidt (7) and modified by Scheinberg and Stead (8). Oxygen differences in volume per cent ($A\text{-}VO_2$) were determined by the method of Hickam and Frayser (9) on the integrated arterial and cerebral venous blood specimens, respectively, or on the arterial and venous blood samples obtained immediately before and after the patient breathed N_2O. Cerebral metabolic rate of oxygen consumption ($CMRO_2$) in cubic centimeters of oxygen used per minute, per 100-grams of brain, was calculated by multiplying the rate of CBF in cc./min./100 gms. of brain by the $A\text{-}VO_2$ differences in volumes per cent. Arterial blood pH changes were determined anaerobically by a glass electrode, using a Beckman pH meter, and the readings were corrected to 37° C. Arterial blood hemoglobin levels were measured, using spectrophotometric methods. Blood pressure readings were made by the auscultatory method, using a sphygmomanometer with the arm held at heart

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TABLE I

Effect of a 60-minute intravenous infusion of 1000 ml. of isotonic NaCl (0.9%) in six subjects

	Control	*S.D.	†S.E.	Experiment	S.D.	S.E.	p Value
CBF ml./min./100-grams brain	60	±17	±7	60	±14	±6	n.s.
A−VO_2 Difference vols. %	6.5	±1.3	±.5	6.2	±.9	±.4	n.s.
$CMRO_2$ ml. O_2 used/min./100-grams brain	3.7	±.5	±.2	3.7	±.6	±.2	n.s.
CVR (mean arterial BP/CBF)	1.7	±1	±.6	1.6	±.8	±.5	n.s.
Arterial pH units	7.36	±.01	±.005	7.35	±.01	±.005	n.s.
Arterial Hemoglobin grams %	14.0	±1.1	±.5	12.7	±1	±.5	.05

* Standard Deviation $= S = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{N}}{N-1}}$ † Standard Error $= \frac{S}{\sqrt{N}}$

level. The mean arterial blood pressure was calculated by adding one-third of the pulse pressure to the diastolic blood pressure.

In each study, the CBF was measured by the N_2O technique, both before and during infusions of $NaHCO_3$, NaCl, and NH_4Cl. In five instances after infusion of $NaHCO_3$, and in one instance after infusion of NH_4Cl, the patient breathed 5 per cent CO_2 for four minutes. In these six instances, the changing A-VO_2 difference before and during CO_2 inhalation was measured. From the change in A-VO_2 difference, a third cerebral blood flow was estimated utilizing the fact that during 5 per cent CO_2 inhalation, $CMRO_2$ remains constant (2).

RESULTS

Control studies with saline

The results recorded in Table I show that intravenous infusion of 1000 ml. of isotonic (0.9 per cent) saline over sixty minutes has no effect on CBF, or $CMRO_2$, A-VO_3 difference, or pH of arterial blood. Significant decreases in hemoglobin values occur, indicating a measurable degree of hemodilution. Table II shows the results in six patients after infusion of 1000 ml. of 2 per cent NaCl. This is approximately isotonic with a 3 per cent solution of $NaHCO_3$. There is a 10 per cent, but statistically insignificant, increase in CBF. A significant narrowing in A-VO_2 difference does occur. This, combined with the directional change in cerebral blood flow, suggests that hypertonic saline solution does increase cerebral blood flow. We have no ready explanation for this effect. Hemodilution of approximately the same magnitude occurred with both isotonic and hypertonic saline, and neither changed pH significantly.

Metabolic alkalosis

Tables III and IV show the effect of intravenous infusions of approximately 1000 ml. of isotonic (1.2 per cent) and hypertonic (3 per cent $NaHCO_3$), respectively. Similar results occur in both instances, but the changes are greater after 3 per cent $NaHCO_3$, suggesting a quantitative action of the bicarbonate ion. The increase in blood flow with hypertonic $NaHCO_3$ solution is greater than that produced by hypertonic NaCl solution. The sharp increase in CBF after 3 per cent $NaHCO_3$ is comparable to that found after inhalation of 5 per cent CO_2. The increased CBF after bicarbonate infusion is associated with an increased pH of arterial blood. The increased CBF after CO_2 inhalation is associated with decreased pH of arterial blood.

Although CO_2 tensions were not measured in the $NaHCO_3$ infusion experiments reported here, other studies (10–12) suggest that after $NaHCO_3$ infusion, the CO_2 tension changes are minimal, while changes in the bicarbonate ion content are great. The absence of visible changes in respiratory rate and depth after $NaHCO_3$ infusion also suggests little change in CO_2 tension.

TABLE II

Effect of a 60-minute intravenous infusion of 1000 ml. of hypertonic NaCl (2.0%) in seven subjects

	Control	S.D.	S.E.	Experiment	S.D.	S.E.	p Value
CBF ml./min./100-grams brain	59	±12	±5	66	±16	±6	n.s.
A−VO_2 Difference vols. %	6.2	±.95	±.4	5.0	±.5	±.2	.01
$CMRO_2$ ml. O_2 used/min./100-grams brain	3.6	±.5	±.2	3.3	±.8	±.3	n.s.
CVR (mean arterial BP/CBF)	1.5	±.4	±.1	1.4	±.4	±.2	n.s.
Arterial pH units	7.35	±.01	±.007	7.33	±.02	±.01	n.s.
Arterial Hemoglobin grams %	13.0	±1.4	±.6	11.5	±1	±.4	.05

TABLE III

Effects of a 60-minute intravenous infusion of 1000 ml. of isotonic $NaHCO_3$ (1.2%) in six subjects

	Control	S.D.	S.E.	Experiment	S.D.	S.E.	p Value
CBF ml./min./100-grams brain	60	±12	±5	78	±18	±7	.1 to .05
A−VO_2 Difference vols. %	6.1	±.8	±.3	5.1	±.7	±.3	.02
$CMRO_2$ ml. O_2 used/min./100-grams brain	3.6	±.6	±.2	3.9	±.5	±.2	n.s.
CVR (mean arterial BP/CBF)	1.6	±.3	±.05	1.2	±.2	±.04	.05
Arterial pH units	7.39	±.01	±.004	7.48	±.01	±.005	.01
Arterial Hemoglobin grams %	12.3	±.8	±.3	11.3	±1.7	±.7	n.s.

TABLE IV

Effect of a 60-minute intravenous infusion of 1000 ml. of hypertonic $NaHCO_3$ (3%) in ten subjects

	Control	S.D.	S.E.	Experiment	S.D.	S.E.	p Value
CBF ml./min./100-grams brain	52	±11	±3	88	±15	±5	.01
A−VO_2 Difference vols. %	6.9	±1.4	±.4	4.2	±.7	±.2	.01
$CMRO_2$ ml. O_2 used/min./100-grams brain	3.6	±1.1	±.3	3.4	±.8	±.3	n.s.
CVR (mean arterial BP/CBF)	1.8	±.4	±.1	1.1	±.3	±.1	.01
Arterial pH units	7.34	±.03	±.01	7.52	±.02	±.006	.01
Arterial Hemoglobin grams %	13.6	±1.3	±.4	12.2	±1.4	±.4	.02

TABLE V

Effect of a 60 to 90-minute intravenous infusion of 350 cc. of NH_4Cl (0.8%) in seven subjects

	Control	S.D.	S.E.	Experiment	S.D.	S.E.	p Value
CBF ml./min./100-grams brain	66	±12	±5	52	±8	±3	.05 to .02
A−VO_2 Difference vols. %	6.3	±.5	±.2	8.6	±.8	±.3	.01
$CMRO_2$ ml. O_2 used/min./100-grams brain	4.2	±.7	±.3	4.4	±.5	±.2	n.s.
CVR (mean arterial BP/CBF)	1.3	±.3	±.1	1.6	±.5	±.1	.01
Arterial pH units	7.36	±.014	±.005	7.32	±.016	±.006	.05
CO_2 content vols. %	50	±3	±1	46	±3	±1	.1 to .05
Hemoglobin grams %	13.0	±2	±.7	12.4	±2	±.6	n.s.
p CO_2 mm. Hg	48	±7	±3	47	±5	±2	n.s.

Metabolic acidosis

In Table V are recorded the effects of the slow infusion of 0.8 per cent NH_4Cl on the cerebral circulation. There is a reduction in blood flow, the A-VO_2 difference widens greatly, and no change in $CMRO_2$ occurs. There is a consistent drop in arterial pH and serum CO_2 content and very little change in CO_2 tension. Thus, metabolic acidosis, as produced by NH_4Cl is accompanied by a reduction of CBF, in contrast to respiratory acidosis in which CBF is increased. Metabolic acidosis produced in some other fashion than by HN_4Cl should be studied. It is possible that we are really measuring, in part, the effects of NH_4 ion rather than the uncomplicated effects of acidosis.

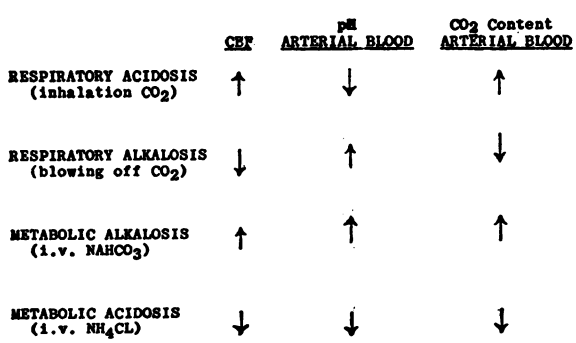

FIG. 1. THIS CHART SHOWS THE DIRECTIONAL CHANGES IN CBF ARTERIAL pH AND ARTERIAL CO_2 CONTENT AS FOUND BY KETY AND SCHMIDT IN RESPIRATORY ACIDOSIS AND ALKALOSIS AND BY THIS STUDY IN METABOLIC ALKALOSIS AND ACIDOSIS

Carbon dioxide inhalation in metabolic alkalosis and acidosis

In Figures 1 and 2 are schematically drawn the effect of CO_2 when breathed by alkalotic and acidotic subjects, respectively. When the subject who is alkalotic from $NaHCO_3$ breathes CO_2, a sharp further increase in CBF occurs while pH returns toward, but does not quite reach, pre-bicarbonate levels. Similarly demonstrated, but in a reverse fashion, are the results (Figure 2) in a metabolic acidotic subject who breathes CO_2. Here, CBF increases above pre-ammonium chloride levels while pH becomes even lower.

DISCUSSION

Sodium bicarbonate increases cerebral flow by decreasing cerebral vascular resistance. NH_4Cl decreases cerebral blood flow by increasing cerebral vascular resistance. Earlier studies (2) have shown that increased and decreased amounts of carbon dioxide in the arterial blood increase and decrease CBF, respectively. The summary chart

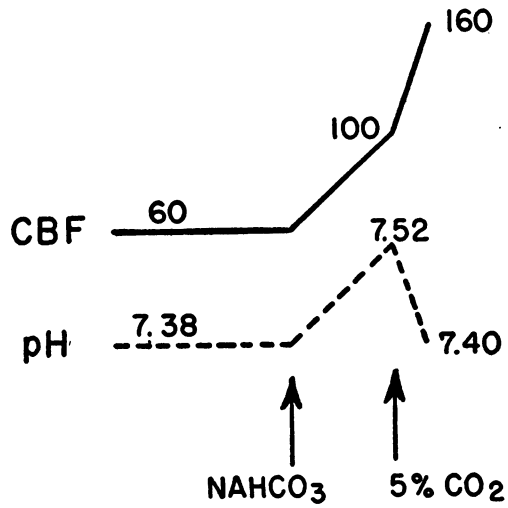

FIG. 2. SCHEMATICALLY DRAWN ARE THE CHANGES IN CBF AND pH OF ARTERIAL BLOOD BEFORE AND DURING THE ADMINISTRATION OF 1000 ML. OF 3 PER CENT $NaHCO_3$ OVER A 60-MINUTE TIME PERIOD

At the second arrow, 5 per cent CO_2 was inhaled and the changes recorded occurred after four minutes.

(Figure 3) indicates by arrow the directional changes in CBF, pH and CO_2 content which occur in respiratory acidosis and alkalosis as described by Kety, and metabolic alkalosis and acidosis as found in this study. When one compares the directional changes in arterial blood pH with cerebral blood flow changes, no correlation exists. However, when one compares the directional changes in total CO_2 content of arterial blood with those of CBF, one finds complete correlation.

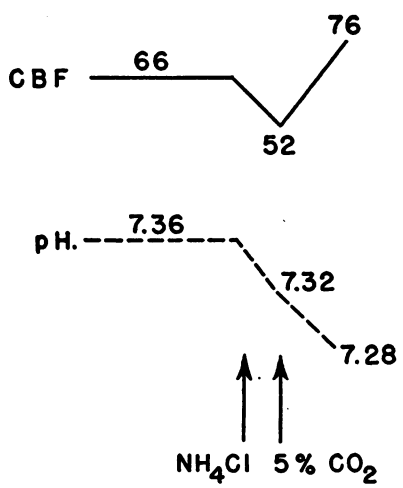

FIG. 3. SCHEMATICALLY DRAWN ARE THE CHANGES IN CBF AND pH OF ARTERIAL BLOOD BEFORE AND AFTER INTRAVENOUS INFUSION OF 0.8 PER CENT NH_4Cl OVER A PERIOD OF 60 TO 90 MINUTES

At the second arrow 5 per cent CO_2 was inhaled and the changes recorded occurred after four minutes.

CONCLUSIONS

1. Metabolic alkalosis, as produced by giving 3 per cent $NaHCO_3$ solution intravenously, increases CBF 65 per cent above resting normal values; isotonic bicarbonate solution (1.2 per cent) causes a 30 per cent increase.

2. The increase in CBF after $NaHCO_3$ is not primarily due to changes in intravascular volume because an equivalent degree of hemodilution produced by the infusion of isotonic NaCl solution does not cause an increase in CBF.

3. Infusion of 2 per cent NaCl solution does cause a demonstrable increase in CBF. It is not of the order of magnitude produced by the infusion of an equally hypertonic solution of $NaHCO_3$.

4. Intravenous infusion of 0.8 per cent NH_4Cl solution reduced CBF approximately 20 to 25 per cent.

5. These studies, when coupled with previous studies of Kety, show that—in the absence of anoxia—cerebral vascular tone is more closely related to total CO_2 content of arterial blood rather than arterial pH levels.

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