GENERAL AND REGIONAL CIRCULATORY RESPONSES TO CHANGE IN BLOOD pH AND CARBON DIOXIDE TENSION *

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The pH and the carbon dioxide tension of the blood flowing through a tissue are commonly thought to be major factors in the local control of regional blood flow, for instance in the vasodilation in exercising muscle (1). They also are of recognized importance in the control of general circulatory homeostasis; for example, systemic hypertension accompanies acutely induced hypercapnia (2, 3), and hypotension the hypocapnia of hyperventilation (4). Furthermore, disorders of acid-base equilibrium occur in pathologic states with sufficient frequency to merit consideration of the role of blood pH and CO_2 tension in control of the circulation burdened by disease such as the acidosis of uremia and diabetic coma or the alkalosis of vomiting.

With these considerations in mind, the present studies were undertaken in healthy humans to determine the effects of variation in blood pH and CO_2 tension (P_{CO_2}) on cardiac output and on the flow of blood through extremity musculature. In an attempt to separate direct effects of change in pH or P_{CO_2} on blood vessels themselves from those mediated by the nervous system, sympathetic impulses to the extremity were blocked with phenoxybenzamine (Dibenzyline [1]) administered intra-arterially to the extremity under study.

METHODS

The subjects studied were healthy male volunteers and one male with essential hypertension. Their ages ranged from 22 to 46 years. Most had participated repeatedly in similar studies in the same laboratory and were, therefore, relaxed and at ease.

Acidemia was induced by intravenous infusion of 500 to 800 ml of 0.2 M lactic acid or 0.17 M ammonium chloride, and alkalosis by infusion of 500 to 600 ml of 0.5 M sodium bicarbonate. The duration of the NH_4Cl or lactic acid infusions ranged from 3 to 4 hours. Bicarbonate infusion duration varied from 45 minutes to 2.5 hours. Experiments in which arterial pH changed less than 0.05 U were excluded from the results. Normal saline, 500 to 600 ml, was administered to control subjects to observe the effects of infusion of similar volumes without pH change. In 8 subjects, 5 to 10 ml of 0.5 M $NaHCO_3$ (pH measured as 8.8) was infused directly into a brachial artery. In the same subjects similar volumes of normal saline or of 0.5 M NaCl were injected intra-arterially as control determinations.

Hypercapnia was induced by inhalation of 5 or 7 per cent carbon dioxide in air for periods of 5 to 15 minutes, and hypocapnia by vigorous voluntary hyperventilation of room air. In experiments designed to ascertain the changes in cardiac output induced by vigorous respiratory movements without change in arterial P_{CO_2}, the CO_2 concentration of expired air was continuously monitored with a Liston-Becker infrared CO_2 analyzer. During voluntary hyperventilation, carbon dioxide was added to inspired air at a rate adjusted to keep end-expiratory CO_2 concentration constant at the level present during normal breathing. As will be shown, use of this technic enabled maintenance of nearly constant arterial CO_2 tension during both quiet breathing and vigorous hyperventilation.

Forearm or calf blood flow was estimated by venous-occlusion plethysmography as described by Wise (5), with plethysmograph temperature 34° C (6), using a Statham P97 low-pressure strain gage as transducer and a Sanborn Polyviso recorder. The control and experimental estimates of extremity blood flow used for every subject were each the average of 10 or more consecutive individual flow determinations made at 30-second intervals.

Cardiac output was estimated by the indicator-dilution technic of Stewart (7) and Hamilton, Moore, Kinsman and Spurling (8). Evans blue dye, 40 mg, or indocyanine green dye, 10 mg, was injected into an antecubital vein and immediately followed by 20 ml of saline to propel the bolus of dye rapidly into the central venous circulation. Intermittent samples of blood were collected from a brachial artery at 2-second intervals through a no. 15 needle and a 5 inch piece of PE 240 polyethylene tubing. Dye concentrations in successive plasma samples were measured in a Coleman Junior spectrophotometer. Calculations were made as described by Doyle, Wilson, Lépine and Warren (9).

Sympathetic blockade of the forearm was induced by

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injection of phenoxybenzamine into the brachial artery in the upper third of the bicipital groove. Phenoxybenzamine was injected at a rate of 1 to 2 mg in 1 minute. Injections were repeated until maximal increase in forearm flow occurred. Maximal flow was attained in 10 to 15 minutes, averaged about 3 times the control value, and was maintained as long as any recordings were made—about 4 hours. The total dose of phenoxybenzamine ranged from 6 to 12 mg, a dose which did not produce any change in blood pressure, respiratory rate or heart rate, or any subjective symptoms. Effectiveness of adrenergic blockade was suggested by observations in 8 subjects that vasocontriction produced in the intact forearm by intra-arterial epinephrine and norepinephrine was absent when these substances were injected intra-arterially after phenoxybenzamine injection.

Blood pressure and pulse rate were recorded from an intra-arterial needle with Statham strain gages. The pH of arterial blood was measured with a Cambridge model R pH meter with appropriate corrections to body temperature (10). Arterial carbon dioxide content was measured by the manometric technic of Peters and Van Slyke (11), and P_{CO_2} was estimated directly by the method of Riley, Proemmel and Franke (12) or calculated from pH, CO_2 content and hematocrit by means of the nomogram of Singer and Hastings (13). In experiments on hyperventilation and CO_2 inhalation, the volume of expired air was measured, using a Tissot spirometer.

Results were evaluated statistically by calculating the standard error of the difference between control and experimental means. The 0.95 confidence limits include the difference between means ± 2.04 times the standard error of the difference, and indicate the limits in which the difference between the means of the control and experimental groups will fall 95 times out of 100 (14). Thus, when the confidence limits do not overlap zero, there is high likelihood that the difference between means is significantly different from zero. The p value expresses the probability that the control and experimental means are not significantly different, and was calculated using the Fisher *t* test (14).

RESULTS

Acid and base infusions

Changes in blood gases and pH. Following both acid and base infusions, mean pH was significantly altered ($p < 0.01$) from the control value (Tables I, II and III). Sodium bicarbonate infusions were accompanied by a significant increase in arterial P_{CO_2} and CO_2 content in all experiments. Acid infusions were associated with moderate reduction in CO_2 content and insignificant changes in CO_2 tension.

General circulatory effects. As shown in Table I, alkalosis was accompanied by a 32 per cent increase in mean cardiac output ($p < 0.01$). Individual values for cardiac index (Figure 1) rose following $NaHCO_3$ infusion in 9 of 12 determinations and were unchanged in 3. Average total peripheral resistance decreased 22 per cent ($p < 0.05$) following bicarbonate infusion. In general, larger pH changes were associated with greater increases in cardiac output. With induced acidosis (Table I), no significant change in mean cardiac output occurred. Total peripheral resistance likewise was unchanged following reduction in blood pH. Figure 1 demonstrates the changes in cardiac index observed in individual subjects following acid and $NaHCO_3$ infusions. Infusions of 500 to 600 ml of 0.16 M NaCl produced no significant change in arterial pH or in cardiac output in any of five individuals. Heart rate and mean arterial pressure showed little change following acid or base infusions. Depth of respiration usually increased after acid infusion, but respiratory rate was not changed. Sodium bicarbonate infusions did not noticeably affect respiratory rate or depth.

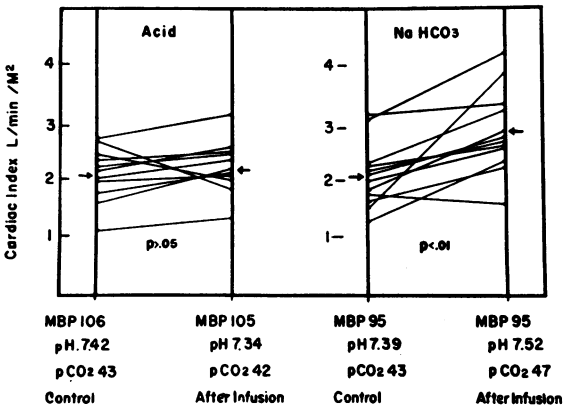

FIG. 1. CHANGE IN CARDIAC INDEX ASSOCIATED WITH INFUSIONS OF $NaHCO_3$ OR OF NH_4Cl OR LACTIC ACID. Arrows point to the mean values in each group; MPB = mean arterial blood pressure.

Changes in extremity flow. Neither induced acidosis nor alkalosis produced significant change in blood flow in the intact forearm (Table II). Average values for forearm flow were identical before and after $NaHCO_3$ infusion despite significant ($p < 0.01$) change in arterial pH. Following acid infusion, average forearm flow increased, but the change was not statistically significant. Forearm flow increased in four of six experiments in which pH was significantly reduced by acid in-

TABLE I

Effects of change in blood pH on general circulation

		Control mean, N = 12	Experimental mean,* N = 12	Difference between means	0.95 Confidence limit	p
A. $NaHCO_3$ infusion						
Arterial pH	Units	7.39	7.52	+ 0.13	+0.10– + 0.16	<0.01
Art. P_{CO_2}	mm Hg	43.1	48.4	+ 5.3	+3.1 – + 7.5	<0.01
Art. CO_2 content	mmoles/L	22.8	33.4	+10.6	+7.8 – +13.4	<0.01
Cardiac index	L/min/m²	3.8	5.0	+ 1.2	+0.6 – + 1.8	<0.01
Peripheral resistance	mm Hg/ L/min	13.8	10.7	− 3.1	−5.2 – − 1.0	<0.05
Heart rate		78.1	84.3	+ 6.2	+1.0 – +11.4	<0.05
B. Acid infusion		N = 10	N = 10			
Arterial pH	units	7.42	7.34	− 0.08	−0.10– − 0.06	<0.01
Art. P_{CO_2}	mm Hg	41.7	39.8	− 1.9	−7.2 – + 3.4	>0.1
Art. CO_2 content	mmoles/L	23.6	18.7	− 4.9	−8.0 – − 1.8	<0.01
Cardiac index	L/min/m²	3.6	3.8	+ 0.2	−0.4 – + 0.8	>0.1
Peripheral resistance	mm Hg/ L/min	16.0	14.9	− 1.1	−3.8 – + 1.6	>0.1
Heart rate		77.0	73.0	− 4.0	−8.9 – + 0.9	>0.1

* During intravenous infusion of 0.5 M $NaHCO_3$, 0.2 M lactic acid, or 0.17 M NH_4Cl, see Methods.

TABLE II

Effects of change in blood pH on blood flow in intact forearm

		Control mean, N = 6	Experimental mean,* N = 6	Difference between means	0.95 Confidence limit	p
A. $NaHCO_3$ infusion						
Arterial pH	units	7.40	7.49	+0.09	+0.08– +0.10	<0.01
Art. P_{CO_2}	mm Hg	40.7	45.0	+4.3	+2.0 – +6.6	<0.05
Art. CO_2 content	mmoles/L	20.8	26.0	+5.2	+2.6 – +7.8	<0.01
Forearm flow	ml/100 g/ min	4.4	4.4	+0.01	−0.34– +0.36	>0.1
Forearm resistance	mm Hg/ ml/100 g/ min	23.5	25.5	+2.0	−0.7 – +4.7	>0.1
B. Acid infusion		N = 6	N = 6			
Arterial pH	units	7.42	7.35	−0.07	−0.12– −0.02	<0.05
Art. P_{CO_2}	mm Hg	38.0	42.7	+4.7	−0.4 – +9.8	>0.1
Art. CO_2 content	mmoles	20.5	19.8	−0.7	−3.4 – +2.0	>0.1
Forearm flow	ml/100 g/ min	4.4	5.9	+1.5	−0.1 – +3.1	>0.1
Forearm resistance	mm Hg/ ml/100 g/ min	22.0	17.7	−4.3	−9.4 – +0.8	>0.1

* During intravenous infusion of 0.5 M $NaHCO_3$, 0.2 M lactic acid, or 0.17 M NH_4Cl; see Methods.

TABLE III

Effects of change in blood pH on blood flow in forearm after phenoxybenzamine

		Control mean, N = 8	Experimental mean,* N = 8	Difference between means	0.95 Confidence limits	p
A. $NaHCO_3$ infusion						
Arterial pH	units	7.39	7.54	+ 0.15	+0.10– + 0.20	<0.01
Art. P_{CO_2}	mm Hg	40.6	49.9	+ 9.3	+6.8 – +11.8	<0.01
Art. CO_2 content	mmoles/L	21.4	34.0	+12.6	+9.8 – +15.4	<0.01
Forearm flow	ml/100 g/ min	13.5	19.8	+ 6.3	+2.9 – + 9.7	<0.01
Forearm resistance	mm Hg/ ml/100 g/ min	7.5	5.1	– 2.4	−4.5 – – 0.3	<0.05
B. Acid infusion		N = 8	N = 8			
Arterial pH	units	7.42	7.33	– 0.09	−0.06– – 0.12	<0.01
Art. P_{CO_2}	mm Hg	42.9	38.5	– 4.4	−9.2 – + 0.4	>0.1
Art. CO_2 content	mmoles/L	23.3	17.8	– 5.5	−7.4 – – 3.6	<0.01
Forearm flow	ml/100 g/ min	13.8	17.9	+ 4.1	+0.4 – + 7.8	<0.05
Forearm resistance	mm Hg/ ml/100 g/ min	10.0	8.5	– 1.5	−0.5 – – 2.5	<0.05

* During intravenous infusion of $NaHCO_3$ or NH_4Cl, following intra-arterial administration of phenoxybenzamine (Dibenzyline).

fusion, was unchanged in one, and decreased slightly in the sixth.

Following blockade of sympathetic impulses to the forearm with intra-arterial phenoxybenzamine, significant increases in blood flow occurred as arterial pH was shifted in either direction from control values (Table III, Figure 2). Increase in pH associated with intravenous $NaHCO_3$ infusion was accompanied by a 47 per cent increase ($p < 0.01$) in mean forearm flow with individual increases ranging from 15 to 160 per cent. Decreased arterial pH following NH_4Cl infusions was associated with a 28 per cent ($p < 0.05$) increase in average forearm flow. Individual values increased in six of eight experiments with NH_4Cl and decreased slightly in two. Since blood pressure was unchanged, forearm resistance decreased significantly following acid and base infusions.

When 0.5 M $NaHCO_3$ was injected directly into the brachial artery, large (three- to sevenfold) increases in forearm flow occurred in each of eight subjects studied. Intra-arterial injection of similar volumes of normal saline or hypertonic (0.5 M) NaCl produced no change in forearm flow in the same eight subjects.

Other effects. Infusions of sodium bicarbonate produced no symptoms. Ammonium chloride infusions were accompanied by nausea and vomiting and by local pain at the site of injection if the

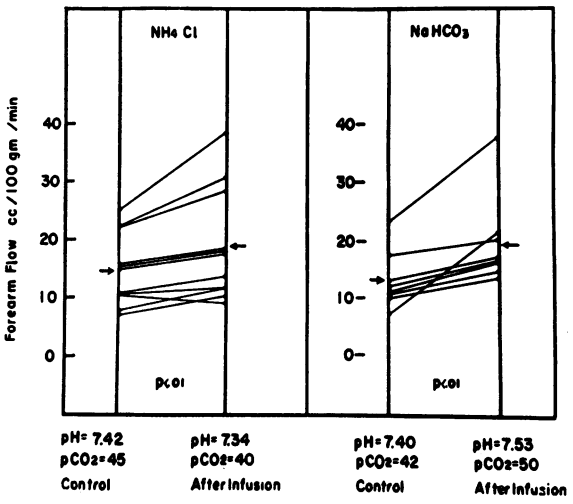

FIG. 2. CHANGES, ASSOCIATED WITH INTRAVENOUS NH_4Cl OR $NaHCO_3$ ADMINISTRATION, IN BLOOD FLOW THROUGH THE FOREARM DEPRIVED OF ITS SYMPATHETIC INNERVATION BY PREVIOUS INTRA-ARTERIAL INFUSION OF PHENOXYBENZAMINE (DIBENZYLINE). Arrows indicate mean values.

TABLE IV

Effects of hypercapnia on blood flow in the intact extremity

		Control mean, N = 11	Experimental mean,* N = 11	Difference between means	0.95 Confidence limit	p
Arterial pH	units	7.39	7.31	− 0.08	−0.10– − 0.06	<0.01
Art. P_{CO_2}	mm Hg	40.4	52.5	+12.1	+ 8.8– +15.4	<0.01
Art. CO_2 content	mmoles/L	20.6	23.5	+ 2.9	+ 1.9– + 3.9	<0.01
Limb blood flow	ml/100 ml/min	7.0	7.9	+ 0.9	−0.2 – + 2.0	>0.05
Limb. vasc. resistance	mm Hg/ ml/100 ml/min	14.2	14.0	− 0.2	−2.4 – + 2.0	>0.05
Heart rate	beats/min	87.5	95.3	+ 7.8	+2.3 – +13.3	<0.05

* Five or 7 per cent CO_2, breathed for 5 to 10 minutes.

rate of infusion exceeded 350 ml per hour. Lactic acid infusions produced pain at the site of venipuncture if the rate of administration exceeded 250 ml per hour. No systemic symptoms were noted following lactic acid infusion, but in one subject (F. S.) hemoglobinuria developed immediately following the infusion and persisted for several hours. No oliguria or azotemia resulted. Tenderness and induration of the vein into which lactic acid had been infused, with erythema of the overlying skin, developed in three of five subjects given lactic acid.

Effects of CO_2 inhalation and hyperventilation on extremity blood flow

Changes in blood gases and pH. Following CO_2 inhalation there was marked elevation in arterial P_{CO_2} and reduction in pH (Tables IV and V). With the subjects breathing room air, the arterial P_{CO_2} averaged 40 mm Hg, whereas during CO_2 inhalation arterial P_{CO_2} rose to 56 mm Hg, a significant increase of 35 per cent. Arterial pH fell from a mean of 7.38 while the patients were breathing room air to 7.30 during inhalation of CO_2, this change being statistically significant. Similar magnitudes of change in pH, P_{CO_2}, and CO_2 content occurred in both the control and phenoxybenzamine groups. Inhalation of 7 per cent CO_2 raised average arterial P_{CO_2} more (average increase in P_{CO_2}, 17 mm Hg) than did 5 per cent CO_2 (average rise 12 mm Hg), but there was considerable individual variability in response of arterial P_{CO_2} to these two concentrations of inspired gas.

During voluntary hyperventilation, changes in pH and P_{CO_2} were achieved which were slightly

TABLE V

Effects of hypercapnia on extremity after phenoxylbenzamine

		Control mean, N = 8	Experimental mean,* N = 8	Difference between means	0.95 Confidence limit	p
Arterial pH	units	7.38	7.29	− 0.09	− 0.13– − 0.05	<0.01
Art. P_{CO_2}	mm Hg	40.1	54.9	+14.8	+10.9 – +18.7	<0.01
Art. CO_2 content	mmoles/L	20.3	23.3	+ 3.0	+ 1.4 – + 4.0	<0.01
Limb blood flow	ml/100 ml/min	14.4	23.7	+ 9.3	+ 3.7 – +14.9	<0.02
Limb vasc. resistance	mm Hg/ ml/100 ml/min	6.4	4.6	− 1.8	− 2.7 – − 0.9	<0.01
Heart rate	beats/min	94.1	112.9	+18.8	+ 9.2 – +28.4	<0.01

* Five to 7 per cent CO_2, breathed for 5 to 10 minutes.

TABLE VI

Effects of voluntary hyperventilation on blood flow in intact forearm

		Control mean, N = 11	Experimental mean,* N = 11	Difference between means	0.95 Confidence limits	p
Arterial pH	units	7.39	7.57	+ 0.18	+ 0.15– + 0.21	<0.01
Art. P_{CO_2}	mm Hg	42.0	25.6	−16.4	−17.6 – −15.2	<0.01
Art. CO_2 content	mmoles/L	21.5	19.0	− 2.5	− 4.9 – − 0.1	<0.10
Blood flow	ml/100 ml/min	4.2	5.1	+ 0.9	+ 0.3 – + 1.5	<0.05
Vascular resistance	mm Hg/ ml/100 ml/min	24.1	20.2	− 3.9	− 7.3 – − 0.5	<0.05
Heart rate	beats/min	77.2	88.8	+11.6	+ 6.0 – +17.2	<0.01
Ventilation	L/min	7.8	36.5	+28.7	+19.6 – +37.8	<0.01

* Vigorous voluntary hyperventilation for 5 to 7 minutes.

greater in magnitude and, of course, opposite in direction to those occurring during induced hypercapnia, as shown in Table VI. Arterial pH rose from an average of 7.40 during normal breathing to 7.54 during hyperventilation, while CO_2 tension fell from a control average of 42 to 28 mm Hg, accompanying two- to sixfold increases in ventilation. Correlation between increase in ventilation and fall in arterial P_{CO_2} was fair ($R = 0.5$, $p < 0.05$).

Changes in extremity blood flow. In the intact extremity, hypercapnia produced slight and inconsistent changes in blood flow despite marked change in P_{CO_2} and pH (Table I). Figure 3 shows similar inconsistent changes in extremity resistance accompanying hypercapnia. After phenoxybenzamine, comparable elevation in arterial P_{CO_2} was accompanied by large increase in extremity flow (40 per cent; $p < 0.02$) and decrease in extremity vascular resistance. As demonstrated in Figure 3, extremity resistance decreased 29 per cent ($p < 0.01$). Individual changes in blood flow correlated well with degree of reduction in pH (Figure 4).

Hypocapnia was accompanied by moderate increases in blood flow in the intact forearm (Table

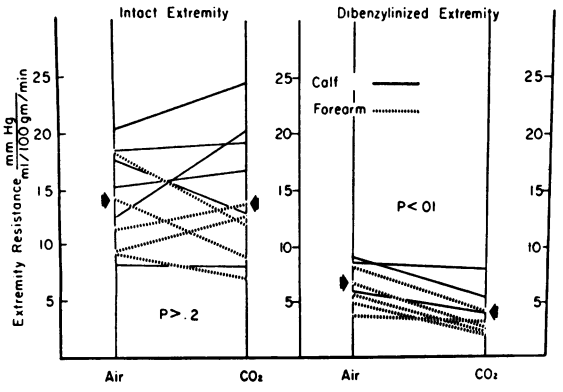

FIG. 3. INHALATION OF 5 OR 7 PER CENT CARBON DIOXIDE PRODUCED NO CHANGE IN RESISTANCE TO BLOOD FLOW IN THE INTACT EXTREMITY BUT WAS ACCOMPANIED BY 29 PER CENT DECREASE IN VASCULAR RESISTANCE IN THE EXTREMITY DEPRIVED OF SYMPATHETIC STIMULI BY INTRA-ARTERIAL INJECTION OF PHENOXYBENZAMINE. Arrows point to the mean of each vertical volume. The horizontal lines connect determinations of resistance in the same subject before and during CO_2 inhalation.

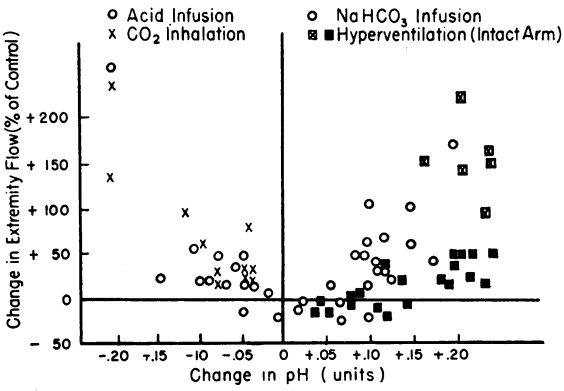

FIG. 4. RELATION BETWEEN CHANGE IN PH AND ALTERATION IN EXTREMITY BLOOD FLOW. All data refer to the extremity following phenoxybenzamine injection except the data regarding voluntary hyperventilation, which denote changes in the intact arm. Boxed crosses represent data of Burnum, Hickam and McIntosh (4); see Discussion.

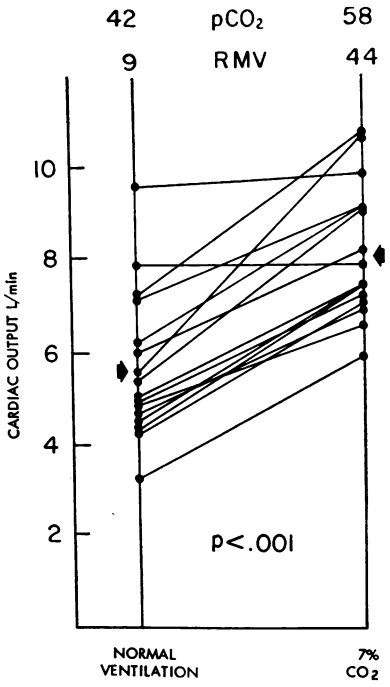

FIG. 5. THE EFFECT OF INHALATION OF 7 PER CENT CARBON DIOXIDE ON CARDIAC OUTPUT. RMV = respiratory minute volume in liters per minute, and P_{CO_2} = arterial CO_2 tension in millimeters of mercury.

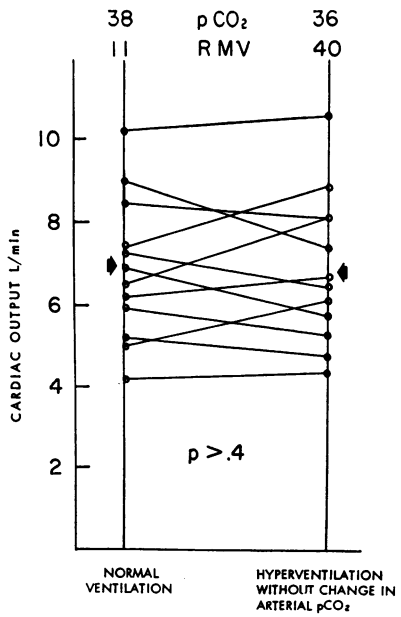

FIG. 6. THE EFFECT ON CARDIAC OUTPUT OF VIGOROUS VOLUNTARY HYPERVENTILATION DURING WHICH ARTERIAL CO_2 TENSION WAS MAINTAINED AT LEVELS PRESENT DURING NORMAL BREATHING. Abbreviations as in Figure 5.

VI). Average flow increased 20 per cent ($p < 0.05$), and individual changes in forearm flow correlated reasonably well with changes in pH, as shown in Figure 4.

In these experiments, blood pressure and heart rate rose significantly ($p < 0.01$) during CO_2 inhalation (Table IV and V), blood pressure increasing in 17 of 18 individual experiments and heart rate in 15 of 18. Hypocapnia, on the other hand, produced no significant change in blood pressure (see Table VI) or in heart rate, despite changes in P_{CO_2} of comparable magnitude. Average blood pressure was 8 mm Hg lower ($0.05 < p < 0.02$) and heart rate was slightly higher after phenoxybenzamine administration, during both air and CO_2 breathing.

Effects of CO_2 inhalation on the general circulation

The circulatory effects of breathing 7 per cent CO_2 are shown in Figure 5 and Table VII. Accompanying the rise in respiratory minute volume from 9 to 44 L per minute and in arterial CO_2

TABLE VII

Circulatory effects of induced hypercapnia

		Control mean, N = 16	Experimental mean,* N = 16	Difference between means	0.95 Confidence limits	p
Arterial pH	units	7.38	7.25	− 0.13	− 0.11 − − 0.15	<0.01
Art. P_{CO_2}	mm Hg	42.0	58.5	+16.5	+13.3 − +19.7	<0.01
Cardiac index	L/min/m²	2.9	4.2	+ 1.3	+ 1.0 − + 1.6	<0.01
Peripheral resistance	mm Hg/ L/min	16.8	13.1	− 3.7	− 2.3 − − 5.1	<0.01
Heart rate	beats/min	70.6	88.3	+17.7	+12.4 − +23.0	<0.01
Ventilation	L/min	9	44	+34.9	+27.5 − +42.3	<0.01

* Seven per cent CO_2, breathed for 7 minutes.

TABLE VIII

Effect of hyperventilation without change in arterial CO_2 tension on the circulation

		Control mean, N = 12	Experimental mean,* N = 12	Difference between means	0.95 Confidence limits	p
Arterial pH	units	7.37	7.38	+ 0.01	− 0.01 − + 0.03	>0.1
Art. P_{CO_2}	mm Hg	37.7	36.1	− 1.6	− 4.7 − + 1.5	>0.1
Cardiac index	L/min/m²	3.6	3.6	0	− 0.4 − + 0.4	>0.1
Peripheral resistance	mm Hg/ L/min	14.2	15.0	+ 0.8	− 0.6 − + 2.2	>0.1
Heart rate	beats/min	69.5	74.7	+ 5.2	+ 1.1 − + 9.3	<0.05
Ventilation	L/min	11.8	39.6	+27.8	+21.9 − +33.7	<0.01

* Vigorous voluntary hyperventilation of CO_2 in low concentration; see Methods.

tension from 42 to 52 mm Hg during the CO_2 inhalation, cardiac output rose in every subject and attained a mean of 8.2 L per minute, a value 45 per cent greater than the control mean of 5.7 L per minute. The mean arterial pressure of the group rose from an average of 89 to 105 mm Hg, and heart rate increased from 70 to 87 beats per minute. Stroke volume increased by 20 per cent, while calculated total peripheral resistance fell by 23 per cent. Changes in cardiac output, blood pressure, heart rate, stroke volume and peripheral resistance were significant at the $p < 0.01$ level.

When two control observations were performed, before and after the experimental observations in 12 experiments, good reproducibility of the cardiac output measurement was demonstrated. Cardiac output averaged 6.2 L per minute in the first and 5.9 L per minute in the second control determinations.

Similar degrees of hyperventilation, with maintenance of a constant arterial CO_2 tension, produced insignificant changes in circulatory dynamics (Figure 6 and Table VIII). Despite increase in respiratory minute volume from 14 to 38 L per minute, cardiac output did not change significantly from its control value of 6.9 L per minute during quiet breathing. Blood pressure, heart rate, and the derived measurements of stroke volume and peripheral resistance also remained unchanged.

DISCUSSION

I. Acid and bicarbonate infusions

A. Extremity circulation. In the forearm, pretreated with intra-arterial phenoxybenzamine, blood flow increased during change of pH in either direction from control values, suggesting that such change in the pH of perfusing blood exerts a direct vasodilator effect in this region. In the intact forearm this dilation probably is prevented by competitive sympathetic vasoconstrictor impulses, initiated by pH change in blood perfusing some other area, perhaps the carotid and aortic chemoreceptors (15).

Deal and Green (16) have shown in dogs that if arteries directly supplying extremity muscle are infused with acid or alkaline solutions, there is an associated increase in muscle blood flow. Similarly, our experiments show large increases in forearm flow following infusion of 0.5 M $NaHCO_3$ directly into the brachial artery, but not after similar intra-arterial infusions of 0.5 M NaCl. It is therefore evident that change in pH of the blood immediately supplying extremity musculature results in increased flow through the extremity.

In man, the effects of change in pH of blood perfusing the carotid and aortic chemoreceptors and the vasomotor center have not been studied for obvious technical reasons. In the dog, perfusion of both carotid bodies with blood acidified by lactic acid (2 ml of 0.1 N lactic acid added to 6 ml of blood) was followed by vasoconstriction in the circulation supplied by the axillary artery, and this vasoconstriction was abolished by sympathectomy. Perfusion of the carotid bodies by blood to which 0.12 M $NaHCO_3$ had been added resulted in little change in foreleg blood flow (17). To the extent to which these findings in the anesthetized dog can be applied to the intact human, they lend credence to the view presented above

that the local vasodilating effect of reduction in pH of perfusing blood is opposed in the intact forearm by sympathetic nervous impulses originating in the carotid chemoreceptors. Similarly, the most probable explanation for absence of vasodilation in the intact extremity in response to intravenous $NaHCO_3$ infusion is an opposing neurogenic vasoconstrictor mechanism, since infusion of $NaHCO_3$ directly into the artery produces vasodilation. Since the chemoreceptors of the dog fail to respond to intracarotid $NaHCO_3$ infusion by inducing extremity vasoconstriction (17), it is necessary to invoke species difference in chemoreceptor responsiveness to explain the results observed in man, or to postulate another mechanism —possibly baroreceptor-induced vasoconstriction in response to a tendency to lowered blood pressure accompanying the decrease in total peripheral resistance observed during bicarbonate infusion.

B. General circulatory effects. Increase in cardiac output following $NaHCO_3$ infusions, with little change in cardiac output after acid infusions, may be explained by the assumption that both reduction and elevation in blood pH exert a direct vasodilator effect on a large portion of the total vascular bed. In the case of acid infusion a competitive influence is introduced by central chemoreceptors to cause concomitant stimulation of vasoconstrictor centers in the central nervous system. On the other hand, as shown by Bernthal (17), addition of $NaHCO_3$ to blood perfusing the carotid chemoreceptor produces little stimulation of the medullary vasomotor center. The direct vasodilation produced by alkalosis is therefore unopposed by sympathetic vasoconstrictor impulses, and can bring about reduction in total peripheral resistance and secondary increase in cardiac output.

Since bicarbonate infusion produced increase in cardiac output without change in blood flow through the intact forearm, a question is raised as to the possible vascular beds to which the increased cardiac output is distributed. Increase in pH produced by bicarbonate infusion increases cerebral blood flow and decreases cerebrovascular resistance (18). Data relative to other areas of the circulation are not available, so that the question cannot be satisfactorily answered at present.

It should be noted that ammonium chloride infusions generally required a longer time for their completion than did the bicarbonate infusions because of the nausea produced by rapid NH_4Cl infusion. Furthermore, changes in pH were generally less marked in the group of acid experiments than in the bicarbonate studies. In addition, the toxic potentialities of NH_4Cl prevented infusion of equimolar concentrations of acid and $NaHCO_3$ solutions. The observed differences in response of cardiac output to acid as opposed to $NaHCO_3$ infusions may be attributable, at least in part, to these differences in experimental conditions.

II. Hypercapnia and hypocapnia

A. Extremity circulation. The fact that hypercapnia dilates extremity blood vessels after phenoxybenzamine administration, but does not modify blood flow in the intact extremity, leads to the conclusion that hypercapnia acts directly to dilate calf and forearm vasculature, and that this direct vasodilation is antagonized in the intact organism by sympathetic vasoconstrictor impulses which also result from hypercapnia, presumably from its effect on the central nervous system. In conditions in which hypercapnia occurs throughout the body, competition exists between local direct vasodilator and sympathetic vasoconstrictor effects of high CO_2. These results suggest the existence of a mechanism whereby local tissue needs for vasodilation can take precedence when there is but slight change in the general blood level of CO_2—e.g., in reactive hyperemia. On the other hand, this mechanism allows general body needs for circulatory homeostasis to have preference over local needs; for example, in the maintenance of blood pressure during general hypercapnia.

Figure 4 demonstrates information available from two sources regarding the effects of hypocapnia accompanying voluntary hyperventilation on the extremity circulation. The data of Burnum, Hickam and McIntosh (4) (shown as boxed crosses) demonstrate much larger increases in forearm blood flow for a given increase in pH than do our data. The responses to hypocapnia of their subjects differ from ours in a number of other respects, outstanding among which are the 25 per cent fall in blood pressure and the 75 per cent rise in heart rate which occurred during hypocapnia in their subjects who hyperventilated maximally

for 1 minute. Arterial P_{CO_2} fell 22 mm Hg in their group, an average decrease somewhat greater than the 14 mm Hg achieved in our patients. The more marked circulatory changes observed by Burnum and co-workers are presumably associated with the greater and more abrupt decrease in CO_2 tension induced. Despite these quantitative differences, it seems reasonable to conclude that respiratory alkalosis dilates forearm vessels, especially when it is rapidly induced and of marked degree. Available information does not permit decision as to whether this vasodilation is a direct vascular effect of hypocapnia or the result of decrease in sympathetic "tone," but the former is suggested by observations of Burnum and associates that similar increase in blood flow occurred during hypocapnia in extremities previously subjected to sympathectomy or regional nerve block.

From the data presented, it is difficult to separate the effects of pH change on extremity vasculature from those of change in CO_2 tension. Hypercapnia increases blood flow in the extremity following sympathetic blockade no matter whether pH is increased, as by $NaHCO_3$ infusion, or decreased as during 7 per cent CO_2 inhalation. Hypocapnia during voluntary hyperventilation is accompanied by vasodilation (see Figure 4) in the intact and sympathectomized forearm (4). Hypocapnia associated with primary excess of hydrogen ions dilates vessels in the "Dibenzylinized" extremity, as shown above. With regard to the intact extremity, during definite acidemia resulting from NH_4Cl infusion, there was no change in blood flow, although in our experiments, as in those of others (18), CO_2 tension was not definitely lowered during the acid infusion. It is therefore possible that vasodilation might occur in the intact extremity if arterial CO_2 pressure and pH were both reduced. These observations suggest that change in the caliber of extremity vasculature accompanies body-wide shift in acid-base balance only when fall in CO_2 tension and rise in pH occur together, namely in respiratory alkalosis, and that local change in blood pH or P_{CO_2}, in either direction from the values normally present, results in vasodilation in the extremity. The latter conclusion rests on the assumption that changes in blood flow in the extremity after phenoxybenzamine represent modifications in vascular caliber effected by the direct vascular actions of CO_2 and hydrogen ions.

In areas of the circulation other than the extremity, rapid elevation of arterial CO_2 tension produces varied effects. Cerebral vessels dilate during hypercapnia (19, 20). Sympathetic control of cerebral blood vessels is thought to be minimal (21), and in their response to hypercapnia, the cerebral vessels behave as do forearm vessels deprived of sympathetic stimuli. In their vasoconstrictive response to hypocapnia (19), on the other hand, cerebral vessels react differently from the vessels in the sympathectomized human extremity (4). Renal vasoconstriction accompanies hypercapnia in normal man, 13 per cent reduction in renal blood flow and 46 per cent increase in renal vascular resistance occurring with inhalation of 10 per cent CO_2 (22). Thus, the renal circulation reacts differently from either the cerebral or the extremity vessels. The effects of hypercapnia on splanchnic and hepatic circulation in man have not been investigated.

Phenoxybenzamine was used in these investigations as a tool for study of blockade of sympathetic impulses to the extremity. In doses of 2 to 4 mg, arterial administration of phenoxybenzamine completely blocked the constrictor response of forearm vessels to intra-arterial norepinephrine and epinephrine in eight subjects studied in this laboratory. The agent has long been known to block response of smooth muscle to sympathetic nerve stimulation and to circulating catecholamines. It does not block ganglia, or prevent contraction of smooth muscle in response to numerous other stimuli (1). Duff (23) showed that intra-arterial phenoxybenzamine increased blood flow in the hand after sympathectomy. He assumed that this indicated a direct vasodilating effect of the drug. An alternate explanation can be proposed —namely, that phenoxybenzamine blocked the constrictor response of the vessels to circulating catecholamines.

With regard to the vascular beds evaluated by forearm plethysmography, it has long been assumed that, since the forearm contains four times as much muscle as skin (24), recorded flow chiefly represents muscle blood flow. Cooper, Edholm and Mottram (25) have recently shown, using epinephrine iontophoresis, that muscle flow represents 80 per cent of total plethysmographically

recorded flow in the normal forearm, but that when total flow is increased by raising plethysmograph temperature, skin flow may represent 50 per cent of the total. In our experiments, therefore, muscle blood flow probably represents the majority of recorded flow in the intact forearm, but the relative proportions of muscle and skin flow in the forearm after phenoxybenzamine are unknown. It seems probable, however, that it is largely muscle flow which is increased in the "Dibenzylinized" forearm by induced acidosis or alkalosis. This probability is supported by the observations of Deal and Green (16) that blood flow through dog extremity muscle increases when either acid or alkaline solutions are infused directly into arteries supplying the muscle. Furthermore, uptake of radiosodium from deposits in the leg muscle of dogs pretreated with tetraethyl ammonium chloride increases with intravenous acid or alkaline infusions (26).

B. General circulatory effects. The mechanisms by which hypercapnia produces the demonstrated increase in cardiac output cannot be completely understood from the data presented. The vigorous respiratory movements accompanying elevation in blood CO_2 tension cannot be responsible, since, as shown above, comparable degrees of voluntary hyperventilation without change in arterial P_{CO_2} do not alter cardiac output. These data are not in keeping with the time-honored concept of the effectiveness of the respiratory movements of the thorax as a blood pump. Sechzer and co-workers (3) have recently demonstrated that inhalation of CO_2 in concentrations such as to raise end-expiratory CO_2 tension to 50 to 60 mm Hg was accompanied by increase in plasma concentrations of norepinephrine and epinephrine, so that these catecholamines may be responsible for the rise in heart rate, cardiac output, and blood pressure during hypercapnia.

The findings herein reported are at variance with the conclusions of Grollman (27) who studied the effect of hypercapnia on cardiac output in much the same manner 28 years ago and concluded that the changes observed after natural breathing of carbon dioxide mixtures are to be attributed to the mechanical aid which violent respiratory efforts exert on the circulation. Grollman's data included ten experiments on six individuals who breathed CO_2 and eight experiments on three individuals who voluntarily hyperventilated while breathing mixtures of CO_2 in air which maintained alveolar CO_2 concentration near control levels. In his subjects, hypercapnia produced only an 18 per cent increase in cardiac output, which was statistically insignificant. The different conclusion reached in the present study results from more extensive data, believed to be more significant.

The increased cardiac output and decreased total peripheral resistance accompanying hypercapnia indicate vasodilation, either active or passive, in some vascular beds (28). Elevation in blood CO_2 tension does not affect blood flow in the human calf or forearm (*vide supra*), areas representative of muscular circulation. Hypercapnia decreases flow through the hand (29, 30), where blood flow is largely cutaneous. In normal man, 13 per cent reduction in renal blood flow and 46 per cent increase in renal vascular resistance accompany inhalation of 10 per cent CO_2 (22). Splanchnic blood flow has not been measured in man with elevated CO_2 tension, but it increases during hypercapnia in the anesthetized, open-chest dog (31). Human brain blood flow nearly doubles during 7 per cent CO_2 inhalation, with increases averaging about 0.8 L of blood per brain per minute, a figure calculated from data of Schieve and Wilson (18), with assumed brain weight of 1,400 g. This rise in brain blood flow accounts for one-third of the increase in cardiac output observed during hypercapnia. Presumably increased splanchnic blood flow accounts for most of the remainder.

It would appear that elevation in blood CO_2 tension, rather than fall in pH, is the important factor in the rise in cardiac output accompanying hypercapnia, since it has been shown above that decrease in pH of similar magnitude, without change in arterial P_{CO_2}, during infusion of ammonium chloride or lactic acid, had no effect on cardiac output.

The effects of hypocapnia on cardiac output and arterial pressure have been summarized by Burnum and co-workers (4). They demonstrated that 50 per cent reduction in arterial P_{CO_2}, induced in normal subjects by vigorous voluntary overbreathing for 1 minute, was accompanied by rise in cardiac output from a control average of 7.5 to 10.5 L per minute, by blood pressure re-

TABLE IX

Circulatory effects of changes in arterial CO_2 tension

	7% CO_2 Increased arterial P_{CO_2}	Hyperventilation Decreased arterial P_{CO_2}*	Hyperventilation Unchanged arterial P_{CO_2}
	%	%	%
Cardiac output	+45†	+50†	−0.6
Heart rate	+24†	+63†	+4
Stroke volume	+20†	−13	+3
Blood pressure	+18†	−26†	+5
Systemic vascular resistance	−23†	−45†	+6

* Data from Burnum, Hickam and McIntosh (4).
† Statistically significant change ($p < 0.01$).

duction which averaged 23 mm Hg, and by 45 per cent decrease in systemic vascular resistance.

General circulatory responses to change in arterial carbon dioxide tension and to vigorous respiratory movements without change in arterial P_{CO_2} are summarized in Table IX.

SUMMARY

In human subjects, alkalemia produced by intravenous infusion of hypertonic sodium bicarbonate was accompanied by significant increase in cardiac output and decrease in total peripheral resistance. Acidemia produced by intravenous ammonium chloride or lactic acid solutions was not associated with significant change in cardiac output.

Neither induced alkalosis nor acidosis caused change in blood flow through the intact human forearm. With sympathetic vasoconstrictor impulses to the forearm blocked by phenoxybenzamine (Dibenzyline), both acidosis and alkalosis produced increases in forearm blood flow, the larger increase being associated with alkalosis.

In the intact extremity, blood flow did not change during inhalation of 5 to 7 per cent CO_2 for 5 to 10 minutes. Following blockade of sympathetic impulses by intra-arterial injection of phenoxybenzamine, CO_2 inhalation produced a significant increase in blood flow and decrease in vascular resistance. Hypocapnia, induced by voluntary hyperventilation, was accompanied by 20 per cent increase in blood flow in the intact forearm.

Inhalation of 7 per cent carbon dioxide in air for 7 minutes, in 16 experiments on 10 normal human subjects, produced a 45 per cent increase in cardiac output accompanied by a rise in blood pressure and heart rate. Comparable degrees of voluntary hyperventilation without change in arterial CO_2 tension caused no changes in these functions.

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