Renal Response to Hypercapnia.* (20527)

EDWARD G. DOWDS,† EUGENE W. BRICKNER,† AND EWALD E. SELKURT.
From the Department of Physiology, Western Reserve University School of Medicine, Cleveland, O.

The role of the kidney in aiding in the readjustment of disturbances in acid-base balance created by respiratory acidosis has until recently received little attention(1-3). In diffusion respiration, characterized by progressive increase in blood CO_2 concentration and decreased blood pH, significant and sometimes profound alterations in renal function occur. Among these are oliguria and decreased urinary pH(4-8). Hypercapnia also induces a decrease in sodium, chloride, bicarbonate, and potassium excretion with simultaneous increase in the excretion of ammonia and phosphate(1-4,9).

The inference has been made that the oliguria results from direct or indirect action of CO_2 on the renal vasculature, presumably causing reduction of glomerular filtration rate(5,9,10). The question, therefore, arises as to whether the alterations in electrolyte excretion are due to direct tubular action or are actually due to changes in glomerular filtration rate which may accompany respiratory acidosis. It therefore appeared expedient to investigate the renal circulatory changes which occurred under conditions of progressive hypercapnia. This was done with the use of standard renal clearance procedures in dogs. Concomitant observations were made on blood CO_2 content, urinary pH, urinary volume, and excretion of sodium and potassium.

Methods. Experiments were conducted under sodium pentobarbital anesthesia (30 mg/kg, given intravenously). Following necessary surgical procedures, an intravenous sustaining solution containing creatinine, PAH, and mannitol, the last as a 10% solution, was delivered at a rate of 1.2 to 2 ml/min. Suitable priming doses were given initially. Urine was collected for 2 consecutive 10-minute periods during a control stage, 4 stages during rebreathing, and 2 recovery stages. A 20-minute discard period preceded each stage. Arterial blood samples were collected at 30-minute intervals throughout the experiment beginning in the first urine collection period. Plasma concentrations used were obtained by interpolation of the plotted data. In order to produce a progressive hypercapnia, the dogs were rebreathed from a segment spirometer (11) which had been flushed with pure O_2 to prevent hypoxia. This was attached to a tracheal cannula immediately following the second control urine collection. The animal respired from the spirometer for 20 minutes before the experimental urine samples were collected. With continued rebreathing the CO_2 content of the spirometer gas was progressively elevated during the 4 stages of hypercapnia. The spirometer was then disconnected and the animal allowed to breathe room air for 20 minutes before the recovery stages were observed. Six consecutive analyses of CO_2 and O_2 were made on spirometer gas during the rebreathing, using a Henderson-Morris apparatus(12). The CO_2 content of the arterial blood was determined in 6 of the experiments with the Van Slyke apparatus(13) on samples drawn during the control, second, fourth, and recovery stages. Hematocrit determinations were made on alternate blood samples. Urine and plasma sodium and potassium were measured with an internal standard flame photometer. Urine pH was determined on each sample with a Leeds and Northrup pH meter. The alkaline picrate method was used to analyze the plasma sodium tungstate filtrates and the urine for creatinine. The method of Smith(14) was used for the PAH analysis of urine and the plasma cadium sulfate filtrates.

Results. The results were obtained on 8 animals, but for technical reasons all measurements were not made in every experiment.

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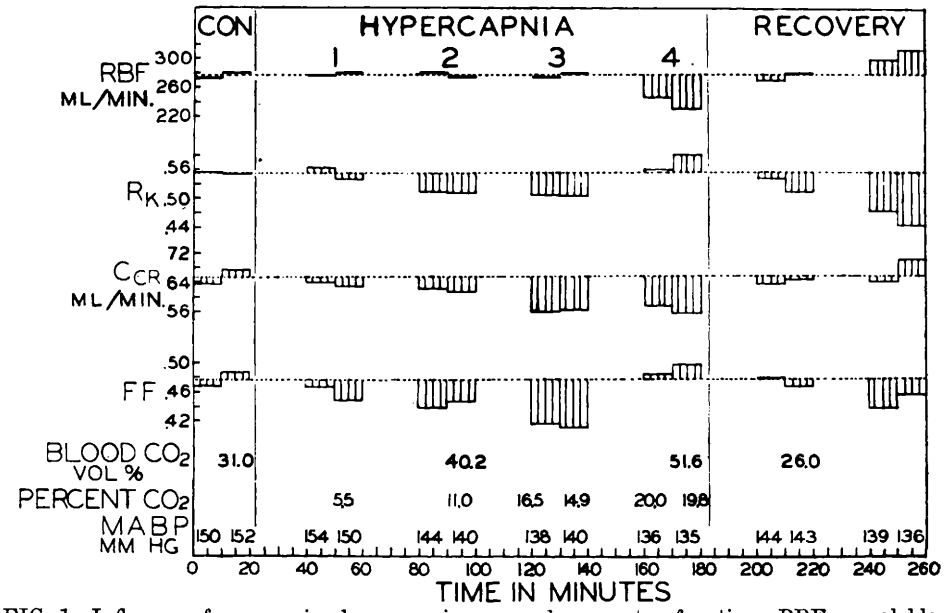

FIG. 1. Influence of progressive hypercapnia on renal vasomotor function. RBF: renal blood flow based on PAH clearance; R_K: renal vascular resistance; C_{CR}: creatinine clearance, a measure of glomerular filtration rate; FF: ratio of C_{CR}/C_{PAH}.

Rebreathing caused the CO_2 content of the spirometer gas to increase progressively to an average of 16.8% (range 13.5-19.9) during Stage 4. Paralleling the increase in the CO_2 concentration of the inspired air was a marked increase in respiratory rate and respiratory minute volume, and a decrease in heart rate. Hyperventilation was observed to continue for a time after the return to room air; then respiration gradually became slow and shallow during the later recovery periods.

Mild hypercapnia appeared to have little effect on blood pressure; however, as hypercapnia became more severe, it decreased to a level approximately 10% below the control average of 149 mm Hg (range, 138-162). During recovery, blood pressure increased slightly but, like heart rate, did not reach control level.

To simplify the presentation of the effects of hypercapnia on renal hemodynamics, a typical experiment has been chosen for detailed consideration as representative of the over-all data (Fig. 1). At the beginning of the experiment, blood pressure was 150 mm Hg of mercury; it decreased during the second stage, when it averaged 142 mm; then finally declined to 135 mm during maximal hypercapnia. Blood pressure was restored to 144 mm on return to room air. Very little change in renal blood flow occurred until the later stages of hypercapnia; during Stage 4 it decreased from 275 ml/min. to 230 ml/min. Levels at or slightly above control values were reached during recovery. Renal resistance tended to remain constant during the first stage of hypercapnia, but decreased slightly during Stages 2 and 3. During Stage 4 there was a trend toward increased resistance which did not, however, persist during the subsequent recovery periods.

Glomerular filtration rate, as measured by creatinine clearance, exhibited a progressive slight tendency to decrease. During recovery it returned to near control levels. The filtration fraction in this experiment showed a decrease in the Stages 1, 2, and 3. However, during Stage 3, when renal resistance increased, the filtration fraction also increased.

The data on renal hemodynamics for all 8 dogs are shown in Fig. 2. The values, as ratios to the control average, are related to CO_2 content of the inspired air. The over-all effect on renal blood flow, in the range of CO_2 content of inspired air observed, did not appear to be significant.

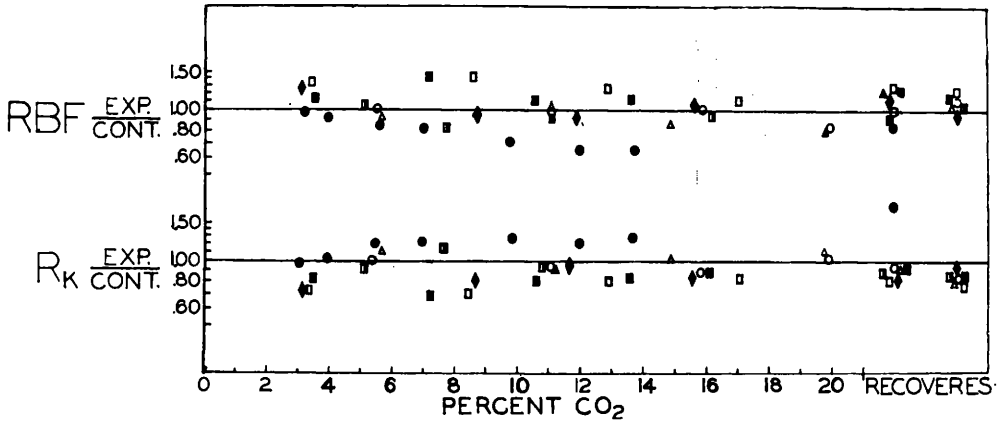

FIG. 2. Summary of RBF and R_K changes given as percentage of control, and related to the CO_2 content of the inspired air.

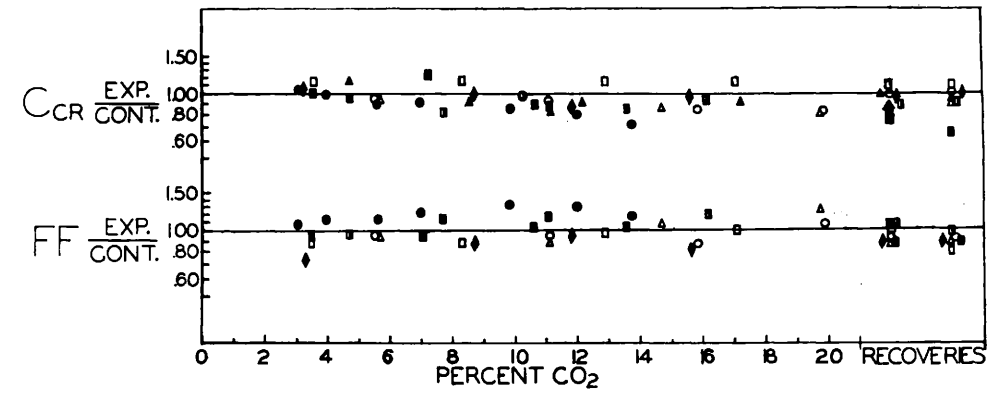

FIG. 3. Filtration rate and FF changes as related to CO_2 content of the inspired air.

The over-all trend of filtration rate is shown in Fig. 3. It can be seen that there existed a small downward trend. The filtration fraction, considering the group as a whole, revealed no consistent change.

Urinary pH declined steadily during hypercapnia to an average of 6.2 (range, 5.75-6.7) during Stage 4 from a control average of 7.3. This decrease was related to a progressive increase in arterial blood CO_2 content from 35 volume % during the control period to an average of 52.8 at the peak effect, then to 32.2 volume % during the recovery stages at which time urinary pH rose to 7.50. Plasma sodium concentration increased slightly (7.4 mEq/L) above the control average of 137 mEq/L, and plasma potassium increased 1.27 mEq/L (control average, 3.53 mEq/L) during hypercapnia.

Changes in electrolyte excretion are presented in Fig. 4 as deviations from the control average. The average control value for sodium excretion was 0.174 mEq/min. (range, 0.016 to 0.369), and for potassium 0.056 mEq/min. (range, 0.036 to 0.108). A downward course in sodium excretion is apparent in these experiments, with an average ratio to control of 0.355 in Stage 4. An interesting finding was an increase in the excretion during the recovery periods to values as high as 4.7 times the control rate in one experiment and averaging 1.12 in all experiments. It is evident from the figure that potassium excretion exhibited a similar trend. In Stage 4, excretion averaged 0.70 of control and rose to 1.94 during recovery.‡

The urine volume increased and remained consistently above the control volume throughout hypercapnia. During recovery the urine volume tended to increase to an even higher level. However, no significance can be attached to this observation since

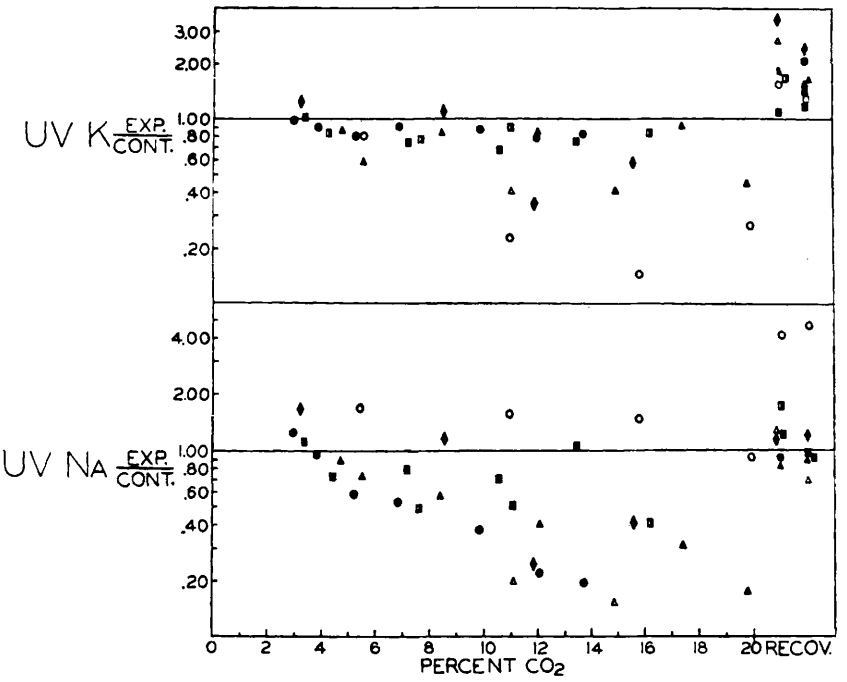

FIG. 4. Changes in electrolyte excretion resulting from hypercapnia, given as percentage of control related to % CO_2 in the inspired air.

mannitol, acting as an osmotic diuretic, was constantly infused. Its action would tend to interfere with any alterations in water reabsorption due to hypercapnia; therefore, no further consideration of the changes in urine volume can be made.

Discussion. Fig. 3 reveals that there is a tendency for filtration rate to decrease during the period of hypercapnia in all dogs but one. Although the magnitude of the decrease is too small to claim significance in individual animals, the consistency of the trend strongly suggests that the alteration is real and worthy of consideration. In this connection it has been conclusively demonstrated that small reductions in glomerular filtration rate, resulting in minimal decreases in load, can cause electrolyte excretion to diminish(15,16). Apparently, with a decreased load, sodium and potassium excretion are reduced because of more efficient reabsorption of the filtered electrolyte. One must therefore be cautious of accepting the present data as proving that the reduced electrolyte excretion is solely the result of altered renal tubular mechanisms. Nevertheless, certain of the experiments do suggest that hypercapnia has an additional direct effect upon the tubular cells which influence their reabsorptive and secretory functions. An example is presented in Table I. During hypercapnia the percentage of load reabsorbed is increased and excretion diminished in periods 8, 9, and 10 despite no decrease in load. Note that potassium excretion diminishes during periods 7 to 10 despite actual increases in load.

In another experiment (solid squares in Fig. 3 and 4) the filtration rate increased 19% at 7.2% CO_2, but the sodium excretion decreased 21%. In this experiment potassium excretion was also diminished somewhat. These findings show that in respiratory acidosis increased sodium reabsorption may be stimulated as a part of a base conserving mechanism by the kidneys, as demonstrated

‡ One experiment was atypical with regard to effects on electrolyte excretion, and was therefore not included in Fig. 4. The excretion of sodium and potassium increased in this animal and did not show a characteristic decline during hypercapnia. Perhaps bearing on this effect was the fact that filtration rate increased to 15% above the control level and remained elevated throughout the course of the experiment.

TABLE 1. A Representative Experiment Showing Influence of Hypercapnia on Electrolyte Excretion.

Period	CO_2 inspired air, vol/%	Arterial CO_2, vol/%	Urinary pH	P, mEq/ml	GFR, ml/min.	Load, mEq/min.	U, mEq/ml	V, mEq/min.	UV, mEq/min.	Amt reabsorbed	% reabsorbed
					Sodium						
Control											
1		33.7	7.55	.123	41.4	5.08	.026	1.5	.039	5.04	99.3
2	.0		7.50	.124	44.3	5.50	.037	1.6	.059	5.44	98.7
Hypercapnia											
3			7.10	.127	49.3	6.26	.034	2.4	.082	6.18	98.6
4	3.3		7.22	.125	45.1	5.64	.036	2.4	.087	5.55	98.5
5			6.95	.128	45.5	5.82	.030	2.3	.069	5.75	98.7
6	8.62	43.2	6.85	.131	40.9	5.35	.023	1.9	.044	5.31	99.3
7			6.25	.132	35.7	4.72	.013	1.0	.013	4.71	99.6
8	11.93		6.14	.132	38.6	5.08	.011	1.1	.012	5.07	99.7
9			6.14	.133	42.2	5.62	.012	1.4	.017	5.60	99.7
10	15.62	55.2	6.25	.133	41.4	5.50	.016	1.5	.024	5.48	99.7
Recovery											
11		37.1	7.55	.130	47.0	6.12	.026	2.3	.060	6.06	99.2
12	.0		7.59	.130	41.0	5.32	.030	2.2	.066	5.25	98.7
13			7.70	.150	38.7	5.80	.032	1.7	.054	5.75	98.9
14	.0		7.70	.156	38.0	5.81	.037	1.7	.063	5.75	98.8
					Potassium						
Control											
1		33.7	7.55	.0040		.166	.029		.043		
2	.0		7.50	.0040		.179	.028		.044		
Hypercapnia											
3			7.10	.0041		.202	.024		.056		
4	3.3		7.22	.0042		.192	.024		.057		
5			6.95	.0048		.217	.024		.055		
6	8.62	43.2	6.85	.0050		.204	.024		.045		
7			6.25	.0054		.193	.015		.015		
8	11.93		6.14	.0054		.208	.015		.016		
9			6.14	.0057		.242	.016		.023		
10	15.62	55.2	6.25	.0060		.247	.018		.026		
Recovery											
11		37.1	7.55	.0059		.276	.070		.162		
12	.0		7.59	.0057		.233	.065		.144		
13			7.70	.0055		.212	.066		.111		
14	.0		7.70	.0055		.208	.059		.101		

for metabolic acidosis(17,18).

Concomitant with the reduction in urinary sodium and potassium excretion there is increased hydrogen ion secretion. Presumptive proof of this is the decreasing urinary pH during hypercapnia. Hydrogen ions are secreted in the tubular lumen in increased amounts because of the elevated concentration of H^+ in the blood and tubular cells. Simultaneously, the tubular cells reabsorb sodium more efficiently. The fact that potassium excretion is reduced suggests that H^+ secretion proceeds in preference to K^+ secretion in the ion exchange mechanism(19).

The increased plasma potassium concentration during hypercapnia may be the result of mobilization of this ion from intracellular compartments. Renal retention of potassium is another possibility. The slight increase in plasma sodium concentration can probably be accounted for on similar bases.

After return to room air the dogs continued to hyperventilate and apparently went into a mild degree of respiratory alkalosis. Evidence of this was the reduction of blood CO_2 to 32.2 volumes % and the increase of urinary pH to 7.5 during the recovery stages. Apparently, this reversed the processes of electrolyte excretion, for now both sodium and potassium were excreted at a more rapid rate than normally.

No final answer can be given in explanation of the oliguria observed during hypercapnia with diffusion respiration(4-8). Oliguria did not occur, and only slight reduction in glomerular filtration rate was observed during hypercapnia in the present experiments. Perhaps the phenomenon was masked by the osmotic diuretic action of the mannitol.

Summary. An average increase of 17.9 volume % in arterial blood CO_2 concentration was produced in dogs by rebreathing from a spirometer. No evidence of significant renal vasomotor alteration was noted. However, urinary pH decreased, and sodium excretion progressively decreased to an average of 35% of control. Thus, elevated H^+ concentration of the blood had in some manner enhanced the tubular reabsorption of sodium. Potassium excretion also diminished, presumably due to depressed tubular secretion by the predominance of H^+ made increasingly available for exchange with sodium. Plasma concentration of potassium increased during hypercapnia, due to renal retention or mobilization from the intracellular compartment. Plasma sodium showed a similar trend. Hyperventilation occurred for a time on return to room air. This phase manifested a decrease in blood CO_2, increase in urinary pH, and increase in the excretion of potassium and sodium beyond control averages.

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1. Brazeau, P., and Gilman, A., *Fed. Proc.*, 1953, v12, 19.

2. Darman, P. J., and Sullivan, W. J., *Fed. Proc.*, 1953, v12, 34.

3. Elkington, J. R., Singer, R. B., Barker, E. S., and Clark, J. K., *Fed. Proc.*, 1953, v12, 38.

4. Draper, W. B., and Whitehead, R. W., *Anesth. and Analg.*, 1949, v28, 307.

5. Kopecky, F. A., Rayburn, C. J., Whitehead, R. W., and Draper, W. B., *Am. J. Physiol.*, 1952, v168, 131.

6. Shires, T., and Eyer, S. W., *J. Aviation Med.*, 1951, v22, 22.

7. Whitehead, R. W., Spencer, J. N., Parry, T. M., and Draper, W. B., *Anesthesiology*, 1949, v10, 54.

8. Draper, W. B., and Whitehead, R. W., *Anesthesiology*, 1944, v5, 262.

9. Brassfield, C. R., and Behrmann, V. G., *Am. J. Physiol.*, 1941, v132, 272.

10. Adolph, E. F., *Am. J. Physiol.*, 1935, v111, 64.

11. Burlage, S. R., and Wiggers, C. J., *Am. J. Physiol.*, 1925, v72, 192.

12. Henderson, Y., and Morriss, W. H., *J. Biol. Chem.*, 1917, v31, 217.

13. Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, v61, 523.

14. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B., and Graber, M., *J. Clin. Invest.*, 1945, v24, 388.

15. Selkurt, E. E., Hall, P. W., and Spencer, M. P., *Am. J. Physiol.*, 1949, v159, 369.

16. Selkurt, E. E., Third Conference on Renal Function, Josiah Macy, Jr. Foundation, 1952.

17. Pitts, R. F., *Am. J. Med.*, 1950, v9, 356.

18. Pitts, R. F., and Alexander, R. S., *Am. J. Physiol.*, 1945, v144, 239.

19. Berliner, R. W., Kennedy, T. J., Jr., and Hilton, J. G., *Am. J. Physiol.*, 1950, v162, 348.

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