Lack of dependence of urine $P_{\text{CO}_2}$ upon reduction of glomerular filtration rate in alkalotic dogs

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(Received 14 June 1976; accepted 24 August 1976)

Summary

1. The $P_{\text{CO}_2}$ gradient between alkaline urine and arterial blood (U–B $P_{\text{CO}_2}$) is thought to depend primarily on distal hydrogen ion secretion. However, other variables affecting the U–B $P_{\text{CO}_2}$ include the urine flow rate, the urinary bicarbonate and phosphate excretion rates and the glomerular filtration rate.

2. In order to evaluate the effects of acute changes in these factors on the U–B $P_{\text{CO}_2}$, bicarbonate-loaded dogs with maximal U–B $P_{\text{CO}_2}$ values were subjected to either acute unilateral elevations of ureteral pressure or hypotension caused by nitroprusside infusion. The results demonstrate that acute reduction in the glomerular filtration rate does not cause a decrease in the U–B $P_{\text{CO}_2}$ as long as the urinary concentrations of phosphate and bicarbonate do not decline.

3. Urinary concentrations of phosphate and bicarbonate appeared more important than their excretion rates in the maintenance of elevated U–B $P_{\text{CO}_2}$ values.

Key words: alkalosis, carbon dioxide, glomerular filtration rate, $P_{\text{CO}_2}$.

Introduction

The ability to increase the urine carbon dioxide tension above the arterial blood value (U–B $P_{\text{CO}_2}$) during bicarbonate infusion has been proposed to represent distal nephron hydrogen ion secretory function (Halperin, Goldstein, Haig, Johnson & Stinebaugh, 1974). However, the U–B $P_{\text{CO}_2}$ is also dependent on distal bicarbonate delivery, buffer excretion and urinary volume (Kennedy, Orloff & Berliner, 1952; Portwood, Seldin, Rector & Cade, 1959; Reid & Hills, 1965). Since alterations in glomerular filtration rate profoundly affect these variables, the present studies were designed to examine the relations between the glomerular filtration rate and the U–B $P_{\text{CO}_2}$. Our results indicate that acute changes in the glomerular filtration rate do not alter the magnitude of the U–B $P_{\text{CO}_2}$.

Methods

Mongrel dogs of either sex were anaesthetized with pentobarbital (30 mg/kg) and given supplemental doses as needed throughout the experiment. Ventilation was maintained with a large-animal respirator after tracheal intubation. Both femoral arteries and veins were cannulated through groin incisions to facilitate constant infusion, measurement of arterial pressure and blood sampling. The ureters were cannulated via a suprapubic incision and urine was collected under oil. Mean arterial blood pressure was monitored on a direct-writing recorder (Techni-Rite Electronics) via a pressure transducer. After surgery and collection of base-line blood samples, all animals received inulin (50 mg/kg), followed by a sustaining infusion of 50 mg h$^{-1}$ kg$^{-1}$. Two groups of animals were
studied. In the first series, six animals were infused with sodium bicarbonate (0·15 mol/l). When the serum bicarbonate had reached 30 mmol/l and the urine flow was stable, mid-period blood samples were collected over four control periods each of 15 min. Sodium nitroprusside (reagent grade, Eastman Kodak Co., Rochester, New York, U.S.A.), 65 mg dissolved in 250 ml of sodium chloride solution (150 mmol/l), was then infused at a rate sufficient to lower the arterial pressure by 30–50 mmHg and four to six additional collections were obtained.

In the second group of studies, five dogs were infused with sodium bicarbonate solution (0·7 mol/l) until the serum bicarbonate stabilized above 30 mmol/l, and blood samples from three control periods were obtained. Urine was then collected from each ureter separately while the pressure in the left ureter was increased to 55 cm water by elevation of the catheter tip. This degree of ureteral pressure elevation was chosen because it was found to decrease the glomerular filtration rate uniformly. After stabilization of pressure in the left ureter, five urine and blood specimens were obtained.

Inulin was determined in protein-free filtrates of urine and plasma on the Auto-Analyzer. Sodium and potassium were measured by flame photometry, and phosphate by the stannous chloride/hydrazine colorimetric method with the Auto-Analyzer. Blood and urine were collected anaerobically and the pH and CO₂ concentration was calculated from the pH and the pCO₂ meter (model 123) within 5 min of sampling. Blood bicarbonate was measured on an Instrumentation Laboratory pH and pCO₂ meter (model 123) within 5 min of sampling. Blood bicarbonate was measured similarly except that pK was corrected for ionic strength (Sendroy, Seeling & Van Slyke, 1934). Statistical analysis was performed with Student's t-test. All results are expressed as the mean ± SEM.

Results

Nitroprusside studies

The effect of nitroprusside infusion on the glomerular filtration rate, urine volume, bicarbonate concentration and U–B pCO₂ are shown in Table 1. The glomerular filtration rate fell in each experiment. Similarly, urine flow rate decreased and the bicarbonate excretion rate declined, from 803 ± 163 μmol/min to 371 ± 99 μmol/min (P<0·005). However, despite these decreases in glomerular filtration rate, urine flow rate and bicarbonate excretion rate, the U–B pCO₂ did not change.

Elevation of ureteral pressure

Elevating ureteral pressure also caused a fall in glomerular filtration rate, urine flow rate and the urinary bicarbonate excretion rate (Fig. 1). The glomerular filtration rate declined from 35·0 ± 1·0 ml/min during the control period to 22·0 ± 2·0 ml/min during ureteral pressure (P<0·02), urine flow rate from 1·72 ± 0·02 ml/min to 0·75 ± 0·05 ml/min (P<0·01), and bicarbonate excretion rate from 317 ± 15 μmol/min to 183 ± 18 μmol/min (P<0·005). The urinary excretion rate of phosphate also declined significantly from 13·5 ± 1·9 μmol/min to 8·5 ± 1·3 μmol/min (P<0·05). In this group, as in the nitroprusside studies, there was no significant difference in the U–B pCO₂ between the control and experimental periods: average 47 ± 2 mmHg before, and 50 ± 2 after, elevation of ureteral pressure (P<0·2).

Urinary concentrations

Neither nitroprusside infusion nor ureteral pressure elevation diminished the urinary concentration of bicarbonate. In the nitroprusside studies, the urinary bicarbonate concentration was 178 ± 17 mmol/l during control periods and 181 ± 20 mmol/ml during infusion (P>0·7). After elevation of ureteral pressure, urine bicarbonate concentration increased from 186 ± 9 mmol/l (P<0·05) to 229 ± 14 (P<0·05), and urine phosphate concentration rose from 8·0 ± 1·1 mmol/l to 11·0 ± 1·2 mmol/l (P>0·1).

Discussion

The rationale for using the U–B pCO₂ as an index of distal hydrogen ion secretion is shown in Fig. 2. Hydrogen ions are secreted by cells of the distal nephron and react with bicarbonate in the tubular lumen to form H₂CO₃. As there is no luminal carbonic anhydrase in this segment of the nephron, the H₂CO₃ does not undergo dehydration until it reaches the collecting system, which is relatively impermeable to
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<th>HCO₃⁻ (mmol/l)</th>
<th>Pco₂ (mmHg)</th>
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\[ P < 0-005 \quad < 0-05 \quad > 0-6 \quad > 0-8 \quad > 0-7 \quad > 0-7 \quad > 0-8 \quad > 0-5 \]
FIG. 1. Effect of elevation of ureteral pressure on (a) glomerular filtration rate (GFR), (b) urine flow \((U_f)\), (c) \(U_{\text{HCO}_3} V\), (d) \(U_{\text{PO}_4} V\) and (e) \(U-B P_{\text{CO}_2}\). As in the nitroprusside experiments, there was no decline in the \(U-B P_{\text{CO}_2}\) despite significant depression of the GFR, \(V\), \(U_{\text{HCO}_3} V\), and \(U_{\text{PO}_4} V\).

FIG. 2. Origin of the urinary \(\text{CO}_2\). Secreted \(\text{H}^+\) reacts with \(\text{HCO}_3^-\) to form \(\text{H}_2\text{CO}_3\). The dehydration of \(\text{H}_2\text{CO}_3\) is not instantaneous and a portion dehydrates in the pelvis, elevating the urine pH. The rise in urine pH causes the release of \(\text{H}^+\) from buffers, which reacts with \(\text{HCO}_3^-\) to form additional \(\text{H}_2\text{CO}_3\). Therefore the urine \(\text{CO}_2\) is derived from two sources: (1) \(\text{CO}_2\) which was delivered as such from the collecting duct, and (2) \(\text{CO}_2\) formed in the renal pelvis as a result of delayed dehydration. Since the arterial blood \(P_{\text{CO}_2}\) approximates to the medullary \(P_{\text{CO}_2}\), the \(U-B P_{\text{CO}_2}\) measures the urine \(\text{CO}_2\) resulting from the delayed dehydration of \(\text{H}_2\text{CO}_3\) formed as a result of distal \(\text{H}^+\) secretion.

(1) During bicarbonate infusion, medullary \(P_{\text{CO}_2}\) = blood \(P_{\text{CO}_2}\)
(2) \(U-B P_{\text{CO}_2}\) = \(P_{\text{CO}_2}\) elevation due to post-papillary dehydration of \(\text{H}_2\text{CO}_3\)
(3) \(U-B P_{\text{CO}_2} = \text{H}^+\) secretion in the distal nephron
CO₂. Thus the magnitude of the post-papillary rise of the urine Pco₂ is a function of the hydrogen ion secretory capacity of the distal nephron (Halperin et al., 1974).

The U–B Pco₂ is dependent on distal bicarbonate delivery, buffer excretion and urinary volume, in addition to hydrogen ion secretory capacity (Kennedy et al., 1952; Portwood et al., 1959; Reid & Hills, 1965). Since changes in the glomerular filtration rate profoundly alter these variables, we have examined the influence of acute alterations in the glomerular filtration rate on the U–B Pco₂. Neither the reduction of the glomerular filtration rate by administration of nitroprusside nor its reduction by elevation of ureteral pressure in bicarbonate-loaded dogs caused any change in the U–B Pco₂, despite significant decrements in the urinary flow rate and urinary bicarbonate and phosphate excretion rates. Similar results were obtained when the glomerular filtration rate was lowered by balloon constriction of the aorta of dogs receiving a bicarbonate infusion (Thompson & Barrett, 1954). Thus acute reduction of glomerular filtration rate does not alter the U–B Pco₂ in the absence of a concomitant decline in the urinary concentrations of bicarbonate and phosphate.

We conclude that a reduction in the U–B Pco₂ can be viewed as evidence of a decrease in distal hydrogen ion secretion despite the occurrence of acute changes in the glomerular filtration rate, provided that the urinary phosphate and bicarbonate concentrations do not decline.

Acknowledgments

This investigation was presented to the Southern Society for Clinical Investigation on 24 January 1976, and appeared in abstract form in Clinical Research (1976) 24, 57A. Support for the investigation was supplied by research grant no. AM 16943 and training grant no. HL 05963 (R.A.P.). The technical assistance of Ms Diane Rouse and the secretarial support of Ms Connie Hansen and Ms Kay Reider is gratefully acknowledged.

References


