The acute effects of respiratory and metabolic acidosis on renal function in the dog

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Summary

1. Effective renal plasma flow, glomerular filtration rate and cardiac output were measured in osmotically loaded dogs before and during comparable acute respiratory and metabolic acidosis.

2. Urine output increased in control dogs and in animals with metabolic acidosis, but declined with respiratory acidosis. Effective renal plasma flow and glomerular filtration rate declined with respiratory and metabolic acidosis.

3. When respiratory acidosis was buffered with sodium bicarbonate, urine volume increased and glomerular filtration rate and effective renal plasma flow were unchanged; with trihydroxymethylaminomethane, urine volume increased but glomerular filtration rate and effective renal plasma flow fell.

4. When metabolic acidosis was buffered with sodium bicarbonate, urine volume increased; with trihydroxymethylaminomethane, urine volume increased but glomerular filtration rate fell. Cardiac output declined only during metabolic acidosis, both buffered and unbuffered.

5. These studies demonstrate that, even with osmotic loading: (1) respiratory acidosis causes a decrease in glomerular filtration rate, effective renal plasma flow and urine volume; (2) metabolic acidosis depresses glomerular filtration rate and effective renal plasma flow but does not change urine volume even though cardiac output falls; (3) sodium bicarbonate is more effective than trihydroxymethylaminomethane in preserving renal function during respiratory and metabolic acidosis.

Key words: acidosis, renal function.

Introduction

Studies in animals have demonstrated marked falls in urine flow, glomerular filtration rate and effective renal plasma flow when acute acidosis is produced by hypercapnia (Bersentes & Simmons, 1967; Kopecky, Rayburn & Whitehead, 1952; Stone, Wells & Draper, 1958). In a parallel fashion, hypercapnic acidosis in man has been shown to have a similar effect on renal function when acute hypercapnia is superimposed upon chronic hypercapnia (Kilburn & Dowell, 1971). The role of hydrogen ion as opposed to any other effect(s) of hypercapnia in producing these changes in renal function is ill-defined.

This study was carried out to investigate the effects of acute respiratory acidosis and of acute metabolic acidosis on renal function in dogs both with and without exogenous buffering. We intended to differentiate between the effects produced by an increase in hydrogen ion concentration ([H+] alone, and effects produced by an increase in carbon dioxide tension (Pco2).

Methods

Forty-four female mongrel dogs, weighing between 14 and 23 kg, were anaesthetized with pentobarbital (20 μmol/kg) and mechanically ventilated with a Harvard pump respirator. Dogs were not conditioned and had free access to food and water before study. There were forty-four separate experiments divided into seven groups.

Group 1 (n = 5): 0.55 mol/l sodium chloride (1020 mosmol/kg).
Group II (n = 8): 13% CO₂ in 18.2% O₂ plus 0.55 mol/l sodium chloride.

Group III (n = 6): 13% CO₂ + 0.6 mol/l sodium bicarbonate (1010 mosmol/kg).

Group IV (n = 5): 13% CO₂ + 1.0 mol/l trihydroxymethylaminomethane in distilled water (1020 mosmol/kg).

Group V (n = 6): 0.5 mol/l hydrochloric acid (1000 mosmol/kg) plus 0.55 mol/l sodium chloride.

Group VI (n = 5): 0.5 mol/l hydrochloric acid plus 0.6 mol/l sodium bicarbonate.

Group VII (n = 9): 0.5 mol/l hydrochloric acid plus 1 mol/l Tham₁ buffer.

Samples for measurements of arterial blood gas tensions as well as inulin, p-aminohippurate, Indocyanine Green and sodium concentration were collected from a cannula in the femoral artery. A Swan-Ganz catheter was placed in the pulmonary artery for determination of cardiac index (Indocyanine Green), and a contralateral femoral vein was used for infusions of hypertonic solutions, which were given at a rate of 7 ml/min. A Foley catheter was inserted in the bladder for all urine collections.

In groups V, VI and VII, 0.5 mol/l hydrochloric acid was infused at 1 ml/min and the additional solution at 6 ml/min. The various gas and acid mixtures were always started together at zero time. All animals received 35 ml/kg of 155 mmol/l sodium chloride intravenously over a 1.5 h period before the base-line values were obtained in order to establish a urine flow of at least 2.0 ml/min at zero time. Inulin and p-aminohippurate were administered in 155 mmol/l sodium chloride at 2.0 ml/min by constant infusion into the femoral vein. Priming and infusion doses were calculated to keep plasma inulin concentration at 25 mg/100 ml and plasma p-aminohippurate at 1.2 mg/100 ml. Three 15 min clearance periods, starting at 45 min after the priming dose, were averaged to determine renal function at zero time. Renal clearances were continued during each experimental infusion and determined at 30 min intervals to 60 min.

Inulin and p-aminohippurate in plasma and urine were analysed by an AutoAnalyzer technique (Krees, Bukal & Wolff, 1967). Blood gas tensions were measured by an I.L. model 313. Urine and plasma osmolalities (Pₐₒₘ) were measured by an international osmometer. Indocyanine Green dye-dilution curves and mean blood pressure were recorded.

Significance of differences was assessed by unpaired t-test. Packed cell volume was determined during base-line measurements and at the end of each experimental infusion. GFR, ERPF and cardiac index were all corrected for body surface area (Altman & Dittmer, 1964; Mountcastle, 1968).

Results (Tables 1 and 2)

Group I

Control group (osmotic loading with hypertonic saline): GFR and ERPF did not change. There was a marked osmotic diuresis. Cardiac index was essentially unchanged. Plasma osmolality increased in the period from 0 to 60 min.

Group II

Hypercapnic acidosis with hypertonic saline: urine volume, GFR, ERPF and osmolar clearance (Cₒₐₘ, 6.8 ± 5 to 4.7 ± 2.1) all declined significantly. Cardiac index did not change. This was the only group where Cₒₐₘ fell significantly (P < 0.05). Plasma osmolality increased comparably to group I.

Group III

Hypercapnic acidosis buffered with sodium bicarbonate: hypercapnia persisted at the same level as in group II, but most of the fall in extracellular pH was prevented. Under these conditions there was a significant increase in urine volume. GFR, ERPF and cardiac index were unchanged. Plasma osmolality increased as in the previous two groups.

Group IV

Hypercapnic acidosis buffered with Tham: GFR was significantly depressed and ERPF was unchanged. As in Group III, there was a significant increase in urine volume. Cardiac index was essentially unchanged. Plasma osmolality increased comparably to Group I.

Group V

Metabolic acidosis (hydrochloric acid and hypertonic saline): GFR and ERPF and cardiac index

¹ Abbreviations: Tham, trihydroxymethylaminomethane; ERPF, effective renal plasma flow; GFR, glomerular filtration rate.
Renal function during acidosis in dogs

### Table 1. Serial renal, haemodynamic and blood gas data in control animals and animals with respiratory acidosis

Mean values ± SD are given. Significance of differences (unpaired t-test) between values at 0 min and at 60 min:

- \( P < 0.05 \)
- \( P < 0.025 \)
- \( P < 0.005 \)
- \( P < 0.001 \)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group I (0.55 mol/l NaCl)</th>
<th>Group II (13% CO₂ + 0.55 mol/l NaCl)</th>
<th>Group III (13% CO₂ + 0.5 mol/l NaHCO₃)</th>
<th>Group IV (1 mol/Tham)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>GFR (ml min⁻¹ m⁻²)</td>
<td>ERPF (ml min⁻¹ m⁻²)</td>
<td>Urine flow (ml min⁻¹ m⁻³)</td>
<td>Cardiac index (l min⁻¹ m⁻²)</td>
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<tr>
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### Table 2. Serial renal, haemodynamic and blood gas data in control animals and animals with metabolic acidosis

Mean values ± SD are given. Significance of differences is indicated by asterisks (see Table 1).

<table>
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<tr>
<th>Time (min)</th>
<th>Group I (0.55 mol/l NaCl)</th>
<th>Group V (0.5 mol/l HCl + 0.55 mol/l NaCl)</th>
<th>Group VI (0.5 mol/l HCl + 0.5 mol/l NaHCO₃)</th>
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Note: The values are presented with standard deviation and significance levels are indicated by asterisks.
were all significantly reduced at 1 h, and urine volume increased significantly. The fall in pH was comparable to that in group II, as was the increase in plasma osmolality.

**Group VI**

Metabolic acidosis buffered with sodium bicarbonate: results here were similar to those in group I with the exception of a significant decrease in the cardiac index.

**Group VII**

Metabolic acidosis buffered with Tham: there was a fall in cardiac index comparable to that of group VI. Furthermore, there was a significant fall in both GFR and ERPF in this group. Plasma osmolality was similar to group VI.

The blood gas data in all groups at 30 min did not differ significantly from the blood gas data at 60 min. Packed cell volume and mean blood pressure showed no significant change in any of the experiments.

**Discussion**

The experimental conditions chosen for these studies allow for a comparison between the effects of respiratory acidosis and the effects of metabolic acidosis both with and without added buffer. Since buffering the degree of acidosis produced by 13% carbon dioxide gas or by 0·5 mol/l hydrochloric acid requires infusion of hypertonic solutions (Nahas, Hassam, Holmdahl & Manger, 1962; Pitts, 1953, 1963; Rector, Seldin, Roberts & Smith, 1960; Relman, Etsten & Schwartz, 1953), the control animals (group I) were given 0·55 mol/l sodium chloride to raise plasma osmolality to a level comparable with that of the various experimental groups. The results obtained in this control group are similar to those reported by others: hypertonic saline infused at less than 8 ml/min has little effect on either GFR or ERPF, but does produce an osmotic diuresis (Wesson, 1969; Wesson, 1957).

Before base-line measurements, all animals received identical amounts of 155 mmol/l sodium chloride in order to ensure comparable volume expansion and a urine flow adequate for good clearances. This explains the slight degree of metabolic acidosis at zero time, which is, in fact, a dilution acidosis (Shires & Holman, 1948).

It is clear that hypercapnia alone (group II) causes the most significant alterations in renal function. This is the only group where urine flow, ERPF, GFR and $C_{osm}$ all fell significantly in spite of the concomitant infusion of hypertonic saline. There were no significant differences between this and any other group in the ratio of excreted/filtered sodium and in the free water clearance. Therefore, the fall in urine flow and $C_{osm}$ in group II can be attributed mainly to a reduction in filtered water and solute. These results are similar in direction to, but of lesser magnitude than, those reported by others (Bersentes & Simmons, 1967; Kopecky et al., 1952; Stone et al., 1958). It has been shown that hypertonic infusions of mannitol can completely reverse hypercapnia-induced diminutions in renal function (Norman, MacIntyre, Shearer, Craigen & Smith, 1970). Our studies indicate that the mechanism of this effect of mannitol is not due to any increase in osmolality. The addition of sodium bicarbonate to buffer the hypercapnic acidosis (group III) essentially reversed all of the abnormalities in renal function. This would support the view, proposed by others, that the alterations induced by hypercapnia may largely depend on extracellular $[H^+]$ excess. For instance, Struyvenberg, Morrison & Relman (1968) have shown that within the cells of isolated renal tubules the pH change produced at 1 h by changing the $P_{co_2}$ of the perfusate is significantly greater than that produced by changing the bicarbonate concentration.

In contrast to group III, dogs of group IV, in which hypercapnia was buffered with Tham, still showed a significant decrease in GFR.

Approximately 60% of infused Tham is distributed intracellularly after 1 h (Nahas, 1962; Robin, Wilson & Bromberg, 1961). In addition, Tham blocks the catecholamine release caused by hypercapnia, whereas sodium bicarbonate does not (Bersentes & Simmons, 1967; Ligou & Nahas, 1960). If the observed derangements in renal function were dependent primarily upon the lowering of intracellular pH within the renal tubular cell, Tham would be expected to be more effective than sodium bicarbonate in preserving renal function. Since the opposite was observed, such a hypothesis is not supported by our experiments.

In order to see if a comparable degree of metabolic acidosis would produce similar results, animals were infused with hydrochloric acid (group V). In this metabolic acidosis, renal function was
compromised less than in the hypercapnic animals, although the cardiac index fell significantly during metabolic acidosis. This difference in response has been noted previously (Bersentes & Simmons, 1967; Connolly, Kountz, Guernsey & Stemmer, 1963; Kittle, Aoki & Brown, 1965; Ligou & Nahas, 1960). However, our results cannot be directly compared as in many of these previous studies osmolality was not controlled, or measurements of renal function or systemic haemodynamic status were not made.

Again, sodium bicarbonate essentially reversed the effects of the acidosis (group VI). In contrast, when Tham was employed to buffer metabolic acidosis (group VII), both GFR and ERPF remained depressed. Thus whenever Tham was used as a buffer, either in respiratory or metabolic acidosis, renal function was less well preserved than with sodium bicarbonate as the buffering agent. Adverse, non-pH-dependent effects of Tham have been described, especially upon intracellular enzymes (Nahas, 1962), which could explain some of the observed results.

We conclude that hypercapnia-induced reduction in renal function is quite pronounced even in the face of osmotic loading with sodium chloride; that hypercapnic acidosis causes significantly greater impairment of renal function than comparable metabolic acidosis; that the mechanism of the renal functional impairment resulting from hypercapnia remains obscure, and that sodium bicarbonate is superior to Tham in preventing renal functional impairment due to either respiratory or metabolic acidosis.

References


CONNOLLY, J.E., KOOUNTZ, S.L., GUERNSEY, J.M. & STEMMER, E.A. (1963) Acidosis as a cause of renal shutdown during extracorporeal circulation: its correction by the use of


