Acid base disturbances in naturally occurring feline chronic renal failure patients

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Introduction

Metabolic acidosis is said to be an inevitable consequence of chronic renal failure (CRF) and, therefore, part of the uraemic syndrome. The adverse effects of metabolic acidosis to the renal failure patient are wide-ranging and serious. Even mild metabolic acidosis stimulates protein catabolism and reduces protein synthesis and so contributes to the chronic wasting characteristic of renal failure [1, 2]. Dyslipoproteinaemias are also common in CRF [3] and it has been suggested that metabolic acidosis plays a role in the pathophysiology of disturbed lipid metabolism associated with renal failure. Severe metabolic acidosis (arterial pH < 7.2) has haemodynamic effects, reducing myocardial contractility, cau-
sing arteriolar vasodilation and peripheral venoconstriction [4]. Gastrointestinal abnormalities occur in the uraemic syndrome, leading to vomiting, nausea and gastric atony. Metabolic acidosis may contribute to these abnormalities.

With sustained acidosis, perhaps the most important effects in human medicine are on the skeletal system because a negative calcium balance ensues. Increased bone resorption occurs and is coupled with reduced bone formation thus contributing to uraemic osteodystrophy [5]. In children, effects on bone turnover can be striking leading to marked stunting of growth, effects which can be reversed by alkali therapy. Excessive dietary acidification in normal cats can cause increased urinary loss of calcium and reduced bone mineral density [6]. Finally, metabolic acidosis has been suggested to be one of the factors which may play a role in the progression of chronic renal failure because increased ammonia production within the tubular cells has been linked to complement fixation and tubulo-interstitial damage [7, 8].

By altering dietary intake of certain acidifying amino acids, providing a source of bicarbonate and modifying the ash content of the diet, it may be possible to correct the acid-base disturbances that occur in CRF patients, improve their quality of life and, possibly, slow the progression of their disease. It is important, however, to recognise which CRF patients would in fact benefit from such treatment by understanding the degree and severity of disturbances in acid-base balance which occur in naturally occurring feline CRF patients. This paper reviews the literature on acid-base disturbances in renal failure, particularly in relation to the cat and presents some preliminary data on acid base balance in naturally occurring CRF cases presenting to first opinion clinics.

ACID BASE BALANCE AND THE ROLE OF THE KIDNEY

The cat, an obligate carnivore, is generally fed a diet that is rich in protein. As a consequence, its kidneys are required to excrete a non-volatile acid load each day in order that acid-base balance is maintained. In blood and extracellular fluid, the non-volatile acid is buffered leading to a decrease in plasma bicarbonate concentration and reduction in buffering capacity of other important buffers such as haemoglobin. The kidneys reverse this process by excreting the excess acid and in the process, regenerating the bicarbonate used to buffer it. In addition, the kidney must reabsorb all the bicarbonate it filters (sometimes termed 'reclamation of bicarbonate'). Finally, bicarbonate losses occur in the faeces and the kidneys need to regenerate bicarbonate to replace faecal losses if acid-base balance is to be maintained [9].

Reclamation of filtered bicarbonate occurs predominantly in the proximal tubule of the nephron, the cells of which possess both intracellular and apical brush border carbonic anhydrase enzymes to facilitate this process [9] (see Figure 1). Intracellular carbonic anhydrase catalyses the hydration of carbon dioxide to form carbonic acid which then dissociates into hydrogen ions and bicarbonate ions. Hydrogen ions required for bicarbonate reclamation are transported into the tubular lumen via the Na⁺ / H⁺ antiporter located in the lumen membrane. The carbonic anhydrase present on the brush border of the proximal tubular cells can convert carbonic acid (formed by the addition of secreted hydrogen ions to the filtered bicarbonate ions) back to carbon dioxide and water. Carbon dioxide can diffuse freely into the tubule cell and be absorbed into the blood stream as bicarbonate. In this way, the filtered bicarbonate ions are returned to the plasma and extracellular fluid.

The distal nephron is largely responsible for regenerating bicarbonate [9]. Although quantitatively this is a much smaller amount than that reclaimed by the proximal tubule, distal tubular acidification of the urine is the final regulator of acid-base balance. The tubular cells also contain intracellular carbonic anhydrase, which through the hydration of carbon dioxide and the formation of carbonic acid, produces hydrogen ions and bicarbonate ions. Bicarbonate ions return to the blood stream whereas the hydrogen ions are secreted into the tubular fluid. This is because the cells possess an electrogenic proton pump which transports hydrogen ions from the tubular cell into the tubular lumen against their electrochemical gradient, a process that is driven by the hydrolysis of ATP. Secretion of hydrogen ions occurs independently of, but is functionally linked to, sodium ion reabsorption (see Figure 2). In essence, the distal renal tubule reverses the reaction that occurred when non-volatile acid was added to plasma:

\[
\text{HA} + \text{NaHCO}_3 \leftrightarrow \text{NaA} + \text{H}_2\text{O} + \text{CO}_2
\]

returning the sodium bicarbonate to the blood and excreting the non-volatile acid (HA) in the urine.

Large pH gradients can be generated in the distal parts of the tubule (see Figure 2). Excretion of hydrogen ions is assisted, however, by the presence of urinary buffers enhancing the number of protons that can be excreted by the distal tubular cells. Phosphate and ammonia are the two major urinary buffers. Phosphate is an ideal urinary buffer since the phosphate buffer pair has a pKa of 6.8 and so functions most efficiently around the pH of tubular fluid.

\[
\text{HPO}_4^{2-} + \text{H}^+ \leftrightarrow \text{H}_2\text{PO}_4^{-}
\]

Ammonia is a weak base, with a pKa of 9.4 that combines with hydrogen ions to form the ammonium cation. At physiological urine pH (4.5 to 8.5), virtually all the ammonia released into the urine will accept a proton and become charged. In the cationic form, ammonium is unable to cross mammalian cell membranes and so is trapped in the tubular lumen. Ammonia is made by the distal tubular cells when glutamine is metabolically converted to glutamate by the enzyme glutaminase. Production of ammonia is increased by low urine pH and chronic metabolic acidosis.

In summary, therefore, under normal physiological conditions in cats fed a standard feline maintenance diet that presents a high load of non-volatile acid, the kidneys ensure acid-base balance is achieved by:

(i) reclaiming all the filtered bicarbonate such that virtually no bicarbonate appears in the urine,

(ii) regenerating all the bicarbonate used to buffer the dietary non-volatile acid by secreting hydrogen ions into the urine, a process which regenerates plasma bicarbonate,

\[\text{Revue Méd. Vét., 2000, 151, 7, 585-592}\]
(iii) producing ammonia to assist in buffering urine hydrogen ions and therefore increasing the kidney’s capacity to excrete acid.

It follows that net acid excretion (NAE) by the kidney can be calculated from:

\[
\text{NAE} = (\text{ammonium excretion} + \text{titratable acid excretion}) - \text{bicarbonate excretion}
\]

**ACID BASE BALANCE IN CHRONIC RENAL FAILURE**

With a reduction in functioning nephrons the ability to excrete the acid taken in the diet is compromised because net acid excretion falls [10]. Some renal diseases may have a disproportionate effect on tubular function initially, reducing the ability to reclaim or regenerate bicarbonate thus increasing urine bicarbonate loss and decreasing titratable acid excretion. However, with loss of nephrons adaptation of the remaining functioning nephrons may compensate to allow acid-base balance to be achieved until the disease reaches a severe stage. This would involve reclaiming all the filtered bicarbonate (provided an active disease process does not affect the ability of the remaining tubules to do this) and regenerating sufficient bicarbonate to remain in balance by increasing the generation of ammonia by the distal tubules. However, the ability of the feline kidney to respond to metabolic acidosis by increasing its production of ammonia has been questioned [11]. In addition, as the number of functioning nephrons falls in CRF one might expect the capacity of the kidney to produce ammonia in response to increased urine acidity to be reduced.

Another way the animal with CRF could remain in acid-base balance would be by chronically buffering the dietary excess of acid by the release of carbonate and bicarbonate from bone, allowing balance to be maintained but at the expense of progressive bone demineralisation [5]. How our feline CRF patients seen in first opinion practice adapt to the challenges of maintaining acid-base balance remains to be established. Studies of cases referred to second opinion hospitals in the USA suggest that metabolic acidosis with a high anion gap is very common in feline CRF patients.

The anion gap is calculated from the difference between the sum of the measured cations (sodium and potassium) and the sum of the measured anions (chloride and bicarbonate). In normal animals an excess of 10 to 20 mmol/l of measured cations is found. In metabolic acidosis due to an inability of the kidneys to excrete the dietary load of non-volatile acid, the plasma bicarbonate falls as bicarbonate ions are replaced (due to buffering of the acid) by the non-volatile acid anions (e.g. sulphates) which are not routinely measured. This leads to a metabolic acidosis with an increased anion gap. If, however, metabolic acidosis occurs due to a renal tubular defect leading to an inability to reabsorb (reclaim) the filtered bicarbonate anions, a different pattern of electrolyte changes would ensue. Plasma bicarbonate ion concentration would fall but this would be accompanied by a compensatory rise in...
the plasma chloride ion concentration (chloride ions being reabsorbed in place of bicarbonate ions) leading to metabolic acidosis with hyperchloraemia and a normal anion gap [10].

LULICH et al., [12] reported that 36 of 41 cats with CRF had a blood pH of <7.30, 33 of which had blood bicarbonate concentrations of <17 mmol/l and 22 had a raised anion gap (>25 mmol/l). In another study, total venous CO₂ concentrations were measured in 59 cases of CRF presenting for treatment at another second opinion hospital and 37 of these had concentrations <15 mmol/l [13]. These previous studies suggest that metabolic acidosis is commonly associated with feline CRF. In these cases, the type of metabolic acidosis identified was a normochloraemic metabolic acidosis with a high anion gap.

In first opinion practice, however, cases of feline CRF can present at many different stages of their disease [14] and the management regimens necessary to treat these animals effectively differ according to the severity of the disease. From the two studies referred to above, animals admitted to hospitals when their renal failure has recently deteriorated have metabolic acidosis and many may benefit from alkali therapy to stabilise their condition. The acid-base status of cats with mild to moderate stable CRF remains to be established. The aim of our study was to determine the prevalence of metabolic acidosis in a group of cats with varying severity of CRF presenting to first opinion clinics within central London.

**Materials and methods**

Cases of feline CRF were recruited to these studies through two first opinion clinics in central London over a twelve month period. Animals showing clinical signs typical of CRF were fully evaluated. In addition, geriatric health screens and pre-anaesthetic blood tests were offered. The diagnosis of CRF was based on a history that suggested signs of disease had been present for several weeks. In addition, blood plasma biochemistry showed that the plasma creatinine concentration was greater than 177 µmol/l and remained elevated when the test was repeated 7 to 21 days later if the cat survived for that period of time. Cases were sub-grouped on the basis of their plasma creatinine concentration into three categories of renal failure namely mild (creatinine 177 to 250 µmol/l), moderate (creatinine 251 to 400 µmol/l) and severe (creatinine >400 µmol/l). Animals in the mild and moderate renal failure groups were blood sampled before any treatment was administered or change of diet attempted. Some animals in the severe group had received clinical diets designed for the management of renal failure, potassium gluconate supplementation and antihypertensive medications for varying periods of time before their acid base status was assessed. Three cases were moved from the moderate to the severe category during the course of the study and changes in their acid base status were documented. Owners were asked to withhold food for eight hours prior to presentation at the clinic.

**SAMPLE COLLECTION AND ANALYSIS**

Blood samples were collected by jugular venepuncture into heparinised tubes and stored anaerobically for less than five minutes before being analysed using an iSTAT analyser (SDI Devices Ltd., USA) for venous blood pH, bicarbonate, total carbon dioxide and ionised calcium concentrations. The packed cell volume of the blood collected was measured by a microhaematocrit centrifuge method. Heparinised plasma was then separated and a full biochemical profile analysed by routine clinical chemistry laboratory methods. The plasma anion gap was calculated from the sum of the sodium and potassium ion concentrations minus the sum of the chloride and bicarbonate concentrations. Where possible, urine was collected by cystocentesis as part of a routine screen for urinary tract infections. Urine pH was measured immediately using a portable pH meter (HI 9224 pH meter; Hanna Instruments, Italy). Urine specific gravity was measured by refractometry and microscopic examination of the urine sediment was undertaken. If evidence of bacterial urinary tract infections was found, the urine pH data from these cases were excluded from the data analysed.

**ANALYSIS OF DATA**

Data are expressed as mean ± 1SD. Twenty two normal healthy cats were used to define working reference ranges for the apparatus we used in our clinic by calculating the mean ± 2SD for each analyte. Comparisons were made between the four groups (normal animals, mild, moderate and severe CRF cases) by a one way analysis of variance followed by Fisher's test using Minitab version 12.0 (Minitab Ltd. Coventry, UK). A paired t-test was used to compare the acid-base status of six cases where renal function deteriorated markedly during the study with the measurements made at the visit prior to their deterioration.

**Results**

Forty two cats were identified in CRF, thirteen of which were classified as severe, fifteen as moderate and fourteen as mild renal failure cases based on their plasma creatinine concentration. Renal function deteriorated in three cases during the study such that they moved from the moderate to the severe group during the course of the study making the total number of animals in this group sixteen. Twenty two cats were sampled as part of a routine health check and deemed to have normal renal function based on plasma creatinine or urea concentration and urine specific gravity. The ages of the cats did not differ significantly between the groups with the mean ages being 14.0 ± 4.5 (severe CRF), 12.9 ± 4.2 (moderate CRF), 13.9 ± 3.5 (mild CRF) and 12.4 ± 3.0 (normal animals). The majority (73 %) of the cats entered into the study were domestic short-haired with 17 % being domestic long-haired cats. The other breeds represented included Persian, Burmese and Birman.

The laboratory data used to categorise the renal function of the four groups of cats are presented in Table I. The plasma creatinine concentrations were significantly different between all groups. All CRF groups had urine specific gravities that differed significantly from the normal animals. The severe CRF group also had significantly lower urine specific gravity than the mild CRF group. Fifty six percent of the
severe CRF group were anaemic whereas only 13% of the moderate CRF group and none of the mild CRF group had PCVs below the reference range. Ionised calcium concentrations were significantly lower in the severe CRF group when compared to all other groups.

The acid-base and electrolyte data from the four groups of cats are presented in Table II. The data from the group of age-matched normal healthy cats has been used to derive reference ranges for the acid base parameters measured in our clinic. Ten of the sixteen (62.5%) cats presenting with severe renal failure had venous blood pH values below the bottom of the reference range and so could be defined as acidic. Only four other renal failure cases were acidic. Twelve of the fourteen cats with low plasma pH values had venous blood bicarbonate concentrations of ≤16 mmol/l and the venous blood bicarbonate and total CO₂ concentrations of the severe CRF group were significantly lower than all the other groups. The anion gap tended to be higher in cats with severe CRF.

Of the acidic animals, however, six cases had an increased anion gap (> 22 mmol/l), six had a normal anion gap and in two cases the anion gap could not be calculated due to missing laboratory data. There was a trend for urine pH to decrease as the severity of the CRF increased. Urine pH was significantly lower in the severe and moderate CRF groups compared to both the control and mild CRF groups. There was no significant difference between the control and mild CRF groups, however.

There were six cases where a significant deterioration in renal function occurred during the course of the study. In four of these cases, plasma creatinine increased by more than 100% from the previously recorded value. The mean plasma creatinine concentration of these six cases increased from 286 ± 99 to 589 ± 183 µmol/l (P = 0.025). Over the same period of time the weight of these cats decreased from 3.78 ± 0.91 to 3.22 ± 0.80 kg (P = 0.002) and the owners reported a decrease in the animal’s appetite and general well being. The

<table>
<thead>
<tr>
<th>Laboratory analyte (reference range)</th>
<th>Normal cats</th>
<th>Mild renal failure</th>
<th>Moderate renal failure</th>
<th>Severe renal failure</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (40 - 177 mmol/l)</td>
<td>116.8 ± 25.0a</td>
<td>189.4 ± 23.6b</td>
<td>284.6 ± 26.37c</td>
<td>557.5 ± 152.8d</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine specific gravity (0.27 - 0.45 l/l)</td>
<td>1.052 ± 0.011a</td>
<td>1.020 ± 0.006b</td>
<td>1.017 ± 0.004c</td>
<td>1.012 ± 0.002e</td>
<td>0.034</td>
</tr>
<tr>
<td>Packed cell volume (1.16-1.40 mmol/l)</td>
<td>0.38 ± 0.05a</td>
<td>0.36 ± 0.04a</td>
<td>0.36 ± 0.05a</td>
<td>0.26 ± 0.05b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ionised calcium (1.16-1.40 mmol/l)</td>
<td>1.28 ± 0.06a</td>
<td>1.25 ± 0.06a</td>
<td>1.24 ± 0.07a</td>
<td>1.21 ± 0.08b</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Values within a row that bear a different superscript letter are significantly different from each other (one way ANOVA followed by Fisher’s test; P < 0.05 taken as significant)

Table I. — Laboratory data used to assess the renal function in cats.

<table>
<thead>
<tr>
<th>Laboratory analyte (reference range)</th>
<th>Normal cats (n)</th>
<th>Mild renal failure (n)</th>
<th>Moderate renal failure (n)</th>
<th>Severe renal failure (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous pH (7.28-7.4326)</td>
<td>7.358 ± 0.0375a</td>
<td>7.354 ± 0.0399a</td>
<td>7.343 ± 0.091c</td>
<td>7.270 ± 0.0576b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood bicarbonate (13.37-23.08 mmol/l)</td>
<td>18.23 ± 2.43a</td>
<td>19.42 ± 2.02a</td>
<td>18.80 ± 2.98a</td>
<td>15.50 ± 3.20b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CO₂ (13.9-24.19 mmol/l)</td>
<td>19.05 ± 2.57a</td>
<td>20.58 ± 2.11a</td>
<td>19.88 ± 2.97a</td>
<td>16.37 ± 3.05b</td>
<td>0.001</td>
</tr>
<tr>
<td>Anion gap (7.30-22.01 mmol/l)</td>
<td>14.71 ± 3.65a</td>
<td>18.19 ± 4.49a</td>
<td>16.18 ± 5.67a</td>
<td>23.39 ± 5.10b</td>
<td>0.001</td>
</tr>
<tr>
<td>Urine pH</td>
<td>6.22 ± 0.56a</td>
<td>6.25 ± 0.49a</td>
<td>5.76 ± 0.61b</td>
<td>5.52 ± 0.42b</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma sodium (145-157 mmol/l)</td>
<td>153.96 ± 2.69a</td>
<td>155.93 ± 2.81a</td>
<td>154.73 ± 7.14a</td>
<td>152.87 ± 7.70b</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma potassium (3.5 - 5.5 mmol/l)</td>
<td>3.94 ± 0.33a</td>
<td>4.13 ± 0.48a</td>
<td>3.98 ± 0.51b</td>
<td>3.89 ± 0.88b</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma chloride (100-124 mmol/l)</td>
<td>125.15 ± 2.97a</td>
<td>123.23 ± 3.98a</td>
<td>123.69 ± 10.17a</td>
<td>117.36 ± 7.89b</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Values within a row that bear a different superscript letter are significantly different from each other (one way ANOVA followed by Fisher’s test; P < 0.05)

* For venous pH, blood bicarbonate and total CO₂ concentrations and the anion gap, the reference range has been derived from the data obtained from normal cats (mean ± 2SD)

Table II. — Acid base and electrolyte data from normal cats and clinical cases of renal failure.
acid-base data before and after this deterioration in renal function are presented in Table III. Only one cat had a venous pH below the reference range before its renal function deteriorated whereas all six animals were acidic after the deterioration was noted. The plasma bicarbonate concentration decreased by 4 mmol/l on average such that five of the six cases had plasma bicarbonate concentrations below the lower limit of the reference range (13.4 mmol/l). Anion gap data were available on five of the six cases and increased by 10 mmol/l on average and exceeded 22 mmol/l in four cases after renal function had deteriorated. The chloride ion concentrations decreased in all five cases where these data were available whereas there was no significant change in the plasma sodium ion concentration. Plasma potassium ion concentration decreased in 5 out of 6 animals but this change did not reach statistical significance. Urine pH data were available on five cases and no significant change accompanied deterioration in renal function.

Discussion

In the present study, metabolic acidosis occurred in 62.5 % of the severe CRF group, 26.7 % of the moderate CRF group and none of the mild CRF cases. These data suggest in naturally occurring CRF cases, compensatory mechanisms maintain venous blood pH and bicarbonate concentrations within the normal range until the later stages of the disease.

The cases of CRF were sub-divided into mild, moderate and severe based on their plasma creatinine concentrations in the present study. The cut off points of 250 and 400 µmol/l for the sub-division of the renal failure cases were chosen based on previous clinical experience [14]. Plasma creatinine concentration, however, is a relatively crude index of the severity of CRF and depends on the muscle mass of the animal as well as glomerular filtration rate [15]. Ideally, renal function should have been assessed by direct measurement of GFR but this proved impractical for the present study. The data presented suggest that the groups did represent different stages of severity of CRF. In particular, the severe group had a significantly lower packed cell volume than the moderate and mild CRF groups with a greater proportion of the animals in this group being anaemic. Plasma ionised calcium concentration was also lower in the severe CRF group, consistent with the magnitude of secondary renal hyperparathyroidism previously reported in cases of severe feline CRF [16]. Urine specific gravity was lower in all CRF groups when compared with the control group. The mild CRF group had higher urine concentrating ability than the severe group suggesting a progressive loss in urine concentrating ability with severity of CRF as has been previously reported [14].

The acid-base data reported in this study are consistent with previously published data. LULICH et al., [12] presented acid-base data from 41 cats with chronic renal failure, 88 % of which had blood pH values < 7.30. It is not possible from the data presented in this paper to assess the severity of renal failure in the sub-group of cases where acid-base status was assessed. Nevertheless, the mean plasma creatinine concentration of 115 cases presented in this study was 561 µmol/l, a value which is similar to the CRF group in the present study. In another study, DIBARTOLA et al., [13] reported that 62.7 % of feline CRF cases had total CO₂ values of < 15 mmol/l. The plasma creatinine concentrations of the cats in this study cannot be directly related to their acid-base status but 67 % of cases had plasma creatinine concentrations > 327 µmol/l and more than half of these cases had plasma creatinine concentrations > 636 µmol/l.

### Table III. — Changes in acid/base and electrolyte parameters in six cats following a significant deterioration in renal function.

<table>
<thead>
<tr>
<th>Laboratory analyte (reference range)</th>
<th>Values recorded at stable renal function</th>
<th>Values recorded after renal function deteriorated</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous pH (7.2826-7.4326)</td>
<td>7.314 ± 0.060</td>
<td>7.221 ± 0.035</td>
<td>0.013</td>
</tr>
<tr>
<td>Blood bicarbonate (13.37-23.08 mmol/l)</td>
<td>16.67 ± 1.03</td>
<td>12.67 ± 1.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CO₂ (13.90-24.19 mmol/l)</td>
<td>17.50 ± 1.22</td>
<td>13.67 ± 1.75</td>
<td>0.001</td>
</tr>
<tr>
<td>Anion gap (7.30-22.01 mmol/l)</td>
<td>15.92 ± 2.92</td>
<td>26.60 ± 5.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Urine pH</td>
<td>5.38 ± 0.36</td>
<td>5.46 ± 0.50</td>
<td>NS</td>
</tr>
<tr>
<td>Ionised calcium (1.16-1.46 mmol/l)</td>
<td>1.26 ± 0.01</td>
<td>1.15 ± 0.05</td>
<td>0.003</td>
</tr>
<tr>
<td>Plasma sodium (145-157 mmol/l)</td>
<td>152.67 ± 3.98</td>
<td>147.17 ± 8.84</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma potassium (3.5 – 5.5 mmol/l)</td>
<td>4.48 ± 0.29</td>
<td>3.70 ± 1.13</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma chloride (100-124 mmol/l)</td>
<td>124.0 ± 2.83</td>
<td>111.2 ± 5.45</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* The values recorded after renal function deteriorated have been compared with those recorded when renal function was stable using a paired Student’s t-test with P < 0.05 taken to indicate statistical significance. NS denotes not significant.
It seems likely that acid-base status would be assessed in the most severely sick animals referred to teaching hospitals suggesting that the figures of 88% and 62.7% for the prevalence of acidosis in feline CRF should be applied to cases in the later stages of their disease only.

In the present study, the cases with low venous pH tended to have low plasma bicarbonate concentrations and high anion gaps. These findings are consistent with metabolic acidosis resulting from an inability to excrete dietary acid, the situation one might expect to exist in uraemic acidosis where the fall in plasma bicarbonate concentration is matched by a rise in unmeasured anions [10]. If tubular function were affected by the renal disease disproportionately, the pattern of electrolyte changes might be different leading to loss of bicarbonate ions in the urine and a hyperchloraemic (normal anion gap) metabolic acidosis [17]. Only two of the fourteen acidic cases studied in the present study had plasma chloride ion concentrations greater than or equal to 131 mmol/l and a normal anion gap. Both of these cases had urine pH values less than 6.0 although measurement of urine bicarbonate concentrations have not been made to determine whether these cases were losing excessive amounts of bicarbonate in their urine. It would appear, therefore, that the majority of cases of CRF where metabolic acidosis was present, could be categorised as normochloraemic with a high or a high normal anion gap. This suggests that the problem was due to an inability to excrete the excess dietary acid and reclaim the bicarbonate used to buffer that excess acid. These conclusions are supported by the data from the group of cases whose renal function deteriorated during the course of the study. The occurrence of metabolic acidosis in these cases was accompanied by an increase in the anion gap and none of these cases became hyperchloraemic in association with the metabolic acidosis. In fact, the plasma chloride concentrations fell in all six cases with the onset of the metabolic acidosis.

The plasma chloride concentration also tended to be lower in those animals with severe CRF. Fifty four percent of the severe CRF cases were hypochloaemic using the reference range derived from the age-matched control animals (119-131 mmol/l). The reason for this decline in plasma chloride concentration in association with metabolic acidosis remains to be determined. Recent evidence suggests that an apical anion exchange transport protein can be found in intercalated cells of the cortical collecting ducts [18]. This transport protein secretes bicarbonate into the tubular fluid and reabsorbs chloride acting as a defence against metabolic alkalosis. It is tempting to speculate that under conditions of severe renal failure and metabolic acidosis, this transport process functions in reverse (secreting chloride and reabsorbing bicarbonate) in an attempt to reclaim as much of the filtered bicarbonate as possible in animals with uraemic acidosis. All data from severe cases of renal failure were obtained before intravenous fluid therapy had been given although a number of these cases were receiving clinical diets and drugs for the management of their renal disease. The finding of hyperchloaemia, therefore, could not be attributed to inappropriate fluid therapy in these cases.

One limitation of the present study was the relatively limited biochemical analysis of urine collected from these cases. The evaluation of urinary bicarbonate, chloride, phosphate, ammonium, sodium, calcium and potassium ions would have added to our interpretation of tubular function in these cases. However, it was only possible to collect single spot samples of urine and the correlation between single spot urine samples and 24 hour urine collection is questionable [19]. Nevertheless, urine pH was accurately measured whenever possible in these cases. The cats with moderate and severe CRF produced urine of lower pH than the mild CRF group or the control animals. Caution should be exercised in the interpretation of these data because there was no attempt to normalise dietary intake of these cases and direct comparison of urine pH may be inappropriate. However, of the fourteen acidic cases, eight had urine pH values > 5.5, three had urine pH values < 5.5 and urine samples were not available from three of these cases. Although the major determinant of urine pH is the buffer content of the urine, one would expect urine pH to be between 4.5 and 5.5 in an acidotic human [20] with normal renal function. The maximum capacity of the feline kidney to acidify urine has not been well characterised and it may not be accurate to extrapolate in this way. Nevertheless, these data suggest that net acid excretion was inappropriately low in these cases. Urine pH did not decrease in those animals whose renal function deteriorated during the course of this study, suggesting that the kidneys of these cats were unable to increase hydrogen ion excretion to compensate for the metabolic acidosis which accompanied a fall in glomerular filtration rate.

In conclusion, metabolic acidosis associated with CRF in the cat occurs in the late stages of the disease and affects over 60% of cases once plasma creatinine concentrations are above 400 µmol/l. It is associated with an increased anion gap and hyperchloaemia, the cause of which remains to be determined. Clinical cases with plasma creatinine concentrations below 400 µmol/l are usually able to maintain a normal venous blood pH, presumably by buffering the net load of dietary acid which the kidney fails to excrete within bone. Further work is necessary to determine the effect of dietary modification on acid-base balance in feline CRF and to determine the importance of acid-base balance on the progressive damage to remaining functioning nephrons in naturally occurring feline CRF.

References


