STUDIES ON BICARBONATE REABSORPTION IN CHRONIC RENAL FAILURE

A Borghetti, A Guariglia, M Minari, L Borghi, A Curti, A Montanari, A Novarini

Istituto di Semeiotica Medica dell'Università di Parma, Italy

Summary

The role of nephron loss, extracellular fluid volume (ECFV) expansion and body potassium stores on bicarbonate reabsorption in chronic renal failure (CRF) was evaluated. In 17 CRF and 3 control subjects, tubular HCO₃⁻ reabsorption was studied by HCO₃⁻ 1M titration technique; ECFV (²²Na space at 4th hour) and cell K content (muscle biopsy) were also determined. Nephron loss per se does not cause any change of HCO₃⁻ reabsorption rate per unit GFR. With ECFV expansion induced by HCO₃⁻ infusion, a Tm HCO₃⁻ is rapidly reached only in controls and in CRF patients showing a significant basal ECFV expansion. In these subjects reabsorbed HCO₃⁻/Na ratio is constant, suggesting that under these conditions, HCO₃⁻ reabsorption depends on the same mechanisms that control Na reabsorption. In cell K depleted CRF patients, HCO₃⁻ reabsorption rises more than in controls and no Tm HCO₃⁻ is detected, at least within the limits of isotonic ECFV expansion induced by titration; in these subjects HCO₃⁻ reabsorption does not appear to be limited by natriuretic factors. In CRF subjects with normal ECFV and cell K, there is a greater HCO₃⁻ tolerance to ECFV expansion induced by titration technique than in controls.

Introduction

Metabolic acidosis is a constant finding in chronic renal failure [1,2] (CRF): when glomerular filtration rate (GFR) falls below 30–40% of the normal value, a chronic positive balance of hydrogen ions occurs, mainly due to impaired excretion of ammonia [1,3].

Urine pH is usually acid in CRF; however, a reduced HCO₃⁻ reabsorptive (HCO₃⁻ R) capacity, with consequent urinary HCO₃⁻ loss, could play a role in uraemic acidosis [4,5]. As found by these authors, either extracellular fluid (ECFV) expansion [5,6] or increased parathyroid hormone (PTH) activity [4] could induce an impairment of HCO₃⁻ R. In contrast, more recent experimental work in animals has shown an increased HCO₃⁻ R per unit GFR, when nephron population is reduced [7,8].

491
### TABLE I: Individual Data for Each Subject; mean values ± SD for each group of subjects; and statistical differences for all the groups are reported.

**CGLN** = Chronic glomerulonephritis; **CPN** = chronic pyelonephritis; **PKD** = polycystic kidney disease; **HKD** = hypertensive kidney disease

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**STATISTICS** —

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Finally, it is well known that cell K depletion, which is a frequent finding in CRF [9–11] enhances HCO₃ R. The present work was performed in men to study the role of GFR reduction, ECFV expansion and body K stores on HCO₃ R in CRF.

Methods

The study was carried out in 3 control and 16 subjects with CRF (GFR varying from 50 to 5 ml/min). In each subject, HCO₃ reabsorption was evaluated using a conventional titration technique, by 1 M sodium bicarbonate infusion at a rate of 0.04 mEq/kg BW/min. During titration, 5–7 clearance periods, each of 20 min, were performed; from urine of each period, collected by vesical catheter under mineral oil, volume, creatinine (Technicon Autoanalyzer), Na, K (IL 543 flame Photometer), pH, pCO₂ (Radiometer BHS3), were measured. From arterial blood (indwelling microcatheter into femoral artery), at each period, pH, pCO₂, Na, K and creatinine were also determined. Blood and urine bicarbonate were calculated by the Henderson-Hasselbalch equation, using a solubility coefficient of 0.0301 and of 0.0309 respectively. On the day prior to the titration, each subject (excluding controls) was submitted to measurement of ECFV (²²Na distribution space at the fourth hour, expressed as % body weight). Muscle needle biopsy from the quadriceps was also carried out [12]; the muscle sample was divided into two pieces, the first being assayed for muscle K (Kₘ) [11] and the other after digestion with N/10 NaOH, for alkali soluble protein nitrogen (ASPN) [7]. ASPN was chosen as the reference basis for Kₘ, because it represents the protein content of muscle cells only, excluding collagen or elastin [12,13]; for this, ASPN can be considered an expression of muscle cell mass. Normal values for ECFV were derived from 10 controls, and for muscle data from 21. For statistical analysis Student’s ‘t’ test was performed.

Results

Table I summarises individual data from all the subjects; CRF subjects were divided into groups on the basis either of GFR (Group B, when GFR was above 20 ml/min; Groups C and D below 20 ml/min) or of detection, by titration, of a maximum tubular reabsorption for HCO₃ (HCO₃ Rmax) (group D).

No significant changes in serum Na (not reported in Table I) were found in any of the subjects during titration.

Figure 1 shows the slope of HCO₃ R (mEq% ml GFR) during titration. In 8 subjects a HCO₃ Rmax (Tm phenomenon) below the normal value is reached; whilst in the other 8 subjects HCO₃ R increases over the normal value.

Table I shows that in group D ECFV is significantly increased either compared with the control (p 0.005) or with groups B and C (p 0.005), that have normal ECFV. GFR is more impaired in group D than in groups B and C, but 4 subjects from group C have the same GFR values as group D. Therefore, HCO₃ R impairment is mainly associated with ECFV expansion; when ECFV is normal, HCO₃ R is near to or above the normal value (2.65 mEq% ml GFR).

494
Figure 1. HCO₃⁻ reabsorption (HCO₃⁻ R) per unit GFR plotted against HCO₃⁻ P increases during titration.
Table I shows also that in all CRF subjects, muscle K is significantly reduced in relation to controls.

Although $K_m$ does not differ significantly between groups B and C and group D, it was more reduced in comparison with the controls in groups B and C (0.001) than in group D (0.05).

$K_m$/ASP ratio was also lower in groups B and C than in group D (0.02); these findings suggest that a true K depletion is associated with increased HCO$_3$ R.

![Figure 2. Ratio between absolute reabsorption of HCO$_3$ and sodium plotted against HCO$_3$ P](image)

Figure 2 plots the ratio of absolute HCO$_3$ R to absolute Na reabsorption against HCO$_3$ P in all the subjects. This ratio increases as HCO$_3$ P rises in groups B and C: on the contrary, in group D, it becomes constant, as in normal subjects, but at lower values of HCO$_3$ P. This finding clearly demonstrates that the subjects without HCO$_3$ max have a greater HCO$_3$ reabsorption capacity than Na R, in the proximal tubule; but in the subjects with HCO$_3$ Rmax, this strictly depends on Na reabsorption.

In Figure 3 urine HCO$_3$ excretion per unit of GFR (HCO$_3$ E) is plotted against HCO$_3$ P in group D (upper part) and in groups B and C (lower part).

In group D a rapid increase of HCO$_3$ excretion begins at HCO$_3$ P levels lower
Figure 3. HCO₃⁻ excretion per unit GFR is plotted against HCO₃⁻ P in subjects with Tm phenomenon (upper part) and in subjects with increased HCO₃⁻ R than in normal subjects. In groups B and C, on the contrary, HCO₃⁻ E rises more slowly than in controls; at any HCO₃⁻ P level, HCO₃⁻ E is above normal values in group D and below normal values in groups B and C.

Discussion

The titration technique used in our study, based on hypertonic Na bicarbonate infusion, actually induces an isotonic ECFV expansion, as does Na bicarbonate isotonic infusion, as demonstrated by the finding of a constant serum Na, during all the experiments; more rapid extracellular acid-base changes are also found.
As seen by other authors [4,6], HCO$_3^-$ Rmax achievement in normal subjects depends on ECFV expansion, induced by infusion.

In our controls (Figure 1) a Tm phenomenon rapidly appears even after a small bicarbonate load (1.3 ± 0.3 mEq/kg BW): natriuretic forces are effective both in HCO$_3^-$ and Na reabsorption, and the absolute HCO$_3^-$ R/absolute Na R (Figure 2) rapidly becomes constant.

In CRF subjects without previous ECFV expansion, isotonic expansion induced by titration does not lead to a Tm phenomenon, even after a greater load (up to 3 mEq/kg). These subjects therefore seem not to be influenced by ECFV expansion: absolute HCO$_3^-$ R progressively rises in comparison with that of Na, suggesting that factors other than natriuretic forces control HCO$_3^-$ R in the proximal tubule, when ECFV is not previously expanded.

Our data are consistent with the hypothesis that cell K depletion is one of these factors. The subjects with increased HCO$_3^-$ R have muscle cell K significantly more reduced than the subjects with max HCO$_3^-$ R, in comparison with controls. Furthermore, in groups B and C muscle K appears lower than in group D if expressed with reference to ASPN. This muscle pattern could confirm that B and C subjects are relatively more K depleted than D subjects. However, the validity of ASPN as a reference basis for muscle potassium is not yet established [12].

In the max HCO$_3^-$ R group, the condition of ECFV expansion clearly overrides every other factor. In ECFV expanded subjects the titration induces a Tm phenomenon as early as maximum Na reabsorption is achieved. Bicarbonate excretion pattern, under these conditions, demonstrates not only a low bicarbonate threshold but also the rapid development of a high bicarbonate loss in the urine.

We can deduce that this bicarbonate wastage at low HCO$_3^-$ P levels could contribute, in some CRF subjects, to the maintenance of uraemic acidosis. In subjects with increased HCO$_3^-$ R, the bicarbonate appears in the urine early (low threshold), always in smaller amounts than in normal subjects even for high [HCO$_3^-$] P: this is due to lack of a Tm phenomenon, at least within the limits of our experimental design.

A low threshold could be dependent on either functional disparity of the nephrons or a distal acidification defect; however, neither of these factors is otherwise able to produce an effective HCO$_3^-$ wastage.

Nephron loss per se does not affect HCO$_3^-$ R; in fact the tubular HCO$_3^-$ R is increased in both group B (GFR averaging 40 ml/min) and group C (GFR = 10 ml/min). Otherwise the finding of a Tm phenomenon in subjects with a severely reduced GFR (group D) appears dependent on ECFV expansion, which occurs more frequently under these conditions.

In a few cases we have measured the serum PTH levels: high values of circulating PTH are found in each group. This could suggest that the PTH has a slight effect on HCO$_3^-$ R in CRF; however, because of the small number of cases, more work is required to elucidate this point.

In summary, in CRF there is increased HCO$_3^-$ sparing, when an acute HCO$_3^-$ load is infused. The mechanisms responsible for this phenomenon (cell K depletion, intracellular acidosis or other unknown factors) seem to act independently from the factors controlling Na R.

On the other hand, acid-base homeostasis in CRF seems to be affected by
external factors, such as ECFV expansion, and these are able to reduce HCO₃⁻ R severely in the proximal tubule. From our data we conclude that correction of acidosis in CRF should be undertaken with regard to either ECFV status or K body stores.

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References

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Open Discussion

KOCAK (Istanbul) When you give bicarbonate to patients with end-stage renal disease, bicarbonate soon appears in the urine. How do you explain that?

MINARI The wastage of bicarbonate you find in early urine after giving bicarbonate is probably because reabsorption is limited and is dependent upon the expansion of extracellular volume independent of GFR. The lack of a Tm for bicarbonate is mainly related to the changes in ECFV and maybe to depletion of intracellular potassium rather than changes in glomerular function.