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This infomation is current as of March 15, 2012.
Assessing acid retention in humans

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TO THE EDITOR: Dr. Troels Ring (8) has asked important questions about our recent publication in the American Journal of Physiology-Renal Physiology (12) that interprets its data as supporting that humans with reduced estimated glomerular filtration rate (eGFR) have acid retention, detected using indirect techniques, that is not evident by plasma acid-base parameters. We assessed the presence of acid retention by giving subjects an acute oral NaHCO3 bolus, 0.5 mg/kg body wt, then measured subsequent 8-h urine net acid excretion (8h NAE). We surmised that higher urine NAE after an NaHCO3 bolus would indicate higher acid retention in subjects with moderately reduced [CKD stage 2 (60–90 ml/min) eGFR or CKD 2] compared with normal [CKD stage 1 (>90 ml/min) eGFR or CKD 1] eGFR, each without metabolic acidosis by plasma acid-base parameters. We surmised that more of the administered HCO3 would be titrated to CO2 and H2O by the hypothesized greater acid retention, leaving less HCO3 to be excreted in the urine. We reported that CKD 2 subjects did indeed have higher 8h NAE following NaHCO3 bolus than CKD 1 (11). Furthermore, 30 days of oral NaHCO3 @ 0.5 meq·kg body wt·day−1 reduced post-NaHCO3 bolus 8h NAE in CKD 2 but not CKD 1 subjects, and we reported that these latter data supported that chronic NaHCO3 therapy reduced acid retention in CKD2 subjects. In his commentary, Dr. Ring questions whether these studies definitively establish that CKD 2 subjects without metabolic acidosis do indeed have acid retention, recognizing that the technique used to demonstrate it is indirect. He also suggests that changes in endogenous acid production rather than, or possibly in addition to, titration of administered NaHCO3 by acid-titrated body buffers (the mechanism suggested by our group) might be an alternate or additional explanation for the higher 8h NAE observed in CKD 2 than CKD 1 subjects in response to the acute oral NaHCO3 bolus td. With this background, we will now address the specific questions asked and/or implied by Dr. Ring.

First, we indeed did not measure net acid production, but classic studies suggest no differences between subjects with reduced and normal GFR (2). Other studies support that when endogenous acid production is not increased, changes in urine NAE contribute more to challenges to acid-base balance than do changes in net acid production (3). Consequently, our method of assessing acid retention assumed no difference in endogenous acid production between subjects with reduced eGFR and normal GFR and that a decrease in urine NAE contributed more to the response to the NaHCO3 bolus than did an increase in endogenous acid production. As stated by Dr. Ring, we measured urine net acid excretion using the classic method of urine NH4+ + titratable acidity − HCO3− (5).

Second, Dr. Ring questions whether the smaller decrease in NAE (i.e., greater persistent 8h NAE) in CKD 2 than CKD 1 subjects in response to the acute NaHCO3 bolus truly indicates greater acid retention in CKD 2 subjects as we state (12). Table 1 shows the components of NAE in CKD 1 and CKD 2 time controls and after the acute NaHCO3 bolus @ 0.5 meq/kg body wt. Higher post-HCO3 bolus 8h NAE in CKD 2 compared with CKD 1 was mediated predominantly by greater urine excretion of NaHCO3 (UHCO3V) in CKD 1 with no statistically significant reductions of urine excretion of ammonium (UNH4V) and titratable acidity (UTAV). Table 2 shows the fate of the acute HCO3 bolus assuming a HCO3 space of distribution of 50% of lean body weight (1). Eight hours after the HCO3 bolus, CKD 2 subjects had lower percent excretion of the HCO3 dose, a smaller increment in plasma total CO2 (TCO2), and a greater amount of administered HCO3 unaccounted for by urine excretion plus the rise in plasma TCO2. We assert that this greater unaccounted HCO3 in CKD 2 was titrated to CO2 and H2O by greater retained acid. Table 3 supports this assertion, showing that CKD 2 and CKD 1 subjects had lower 8h NAE than those not ingesting NaHCO3 chronically.

Third, Dr. Ring asks whether CKD 1 and CKD 2 subjects chronically ingesting oral NaHCO3 @ 0.5 meq·kg body wt·day−1 had lower 8h NAE than those not ingesting NaHCO3 chronically. Indeed, during the steady state of

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>8 h UHCO3V, mM</th>
<th>8 h UHCO3V, mM</th>
<th>8 h UNH4+V, mM</th>
<th>8 h UNH4+V, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>14.6 ± 4.8</td>
<td>11.6 ± 3.7</td>
<td>0.4 ± 0.1</td>
<td>24.7 ± 2.9</td>
</tr>
<tr>
<td>After NaHCO3 bolus</td>
<td>13.3 ± 4.3</td>
<td>9.1 ± 2.8</td>
<td>12.9 ± 4.2</td>
<td>9.5 ± 3.3</td>
</tr>
<tr>
<td>CKD 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time control</td>
<td>15.2 ± 5.0</td>
<td>12.9 ± 4.2</td>
<td>0.22 ± 0.8</td>
<td>24.6 ± 5.0</td>
</tr>
<tr>
<td>After NaHCO3 bolus</td>
<td>13.9 ± 4.7</td>
<td>8.9 ± 3.2</td>
<td>4.5 ± 1.5†</td>
<td>18.2 ± 5.1†</td>
</tr>
</tbody>
</table>

Values are means ± SD. CKD 1, stage 1 chronic kidney disease; UHCO3V, UNH4V, UTAV, and UNAEV: urine excretion rate of NH4+ titratable acid, HCO3−, and net acid, respectively. *P < 0.05 vs. respective time control. †P < 0.05 vs. CKD 1.
chronic NaHCO3 ingestion for 30 days and before subjects received the NaHCO3 bolus, 8h NAE was 7.2 ± 6.0 meq less than the baseline of 24.6 ± 5.0 meq in CKD 2 subjects, and the decrease was similar in CKD 1 chronically ingesting NaHCO3. This decrease in steady-state 8h NAE in response to chronic daily NaHCO3 was predominantly due to significantly lower urine UNH4 (10.8 ± 3.4 vs. 16.3 ± 5.1 meq, P < 0.001) with a much smaller contribution of greater UHCO3V (0.8 ± 0.04 vs. 0.3 ± 0.1 meq, P < 0.001). The data were qualitatively similar for CKD 1 subjects. As stated by Dr. Ring, post-bolus NaHCO3 8h NAE in CKD 2 subjects decreased further to 13.0 ± 4.8 meq after the NaHCO3 bolus (12), a value lower than the 8h NAE post-bolus NaHCO3 in CKD 2 before chronic NaHCO3 therapy. This 8h NAE value for CKD 2 subjects remained higher than the post-bolus NaHCO3 8h NAE in CKD 1 (9.8 ± 3.4 meq) (12) after 30 days of the same chronic NaHCO3 therapy. When Dr. Ring says, “Since blood values were reported to be unchanged,” we assume he is referring to the steady state of chronic NaHCO3 ingestion because there were slight changes in plasma acid-base parameters in response to bolus NaHCO3 as reported in our publication (12) and for plasma TCO2 in Table 2 of this response.

Fourth, we will try to address Dr. Ring’s specific physiologic and pathophysiologic concerns. If we understand his statement “Insofar as the response was related to acid-base physiology, it seems an anomaly that it (reduction in urine NAE) only occurs in the acute setting” correctly, we have addressed this concern by stating that urine NAE decreased in CKD 1 and CKD 2 subjects in response to both acute and chronic NaHCO3. Dr. Ring also states “the argument for acid retention induced by increased dietary acid intake is chronically maintained with normal plasma acid-base parameters in animals with intact nephron mass as long as increased dietary acid intake continues and resolves only after the increment in dietary acid is discontinued (9).” We propose that acid retention occurs in animals and subjects with reduced GFR as described and is maintained as long as they ingest the acid-inducing diets typical of laboratory animal chow (6) and in humans eating the acid-inducing diets typical of industrialized societies (7). We further propose that acid retention increases kidney endothelin and aldosterone activity that contributes to the physiologically beneficial increase in distal nephron acidification in response to an increment in dietary acid (4). Ameliorating acid retention with dietary acid reduction in animals (10, 11) and humans (12) lowers plasma and urine levels of endothelin and aldosterone that mediate GFR decline in animal models of chronic kidney disease (6, 11). Consequently, our hypothesis is supported by data from other investigators in addition to data from our laboratory. Together, our published data and data published by other investigators support that acid retention in subjects with moderately reduced GFR is not only “plausible” but is strongly suggested by our indirect techniques to measure acid retention. We agree with Dr. Ring, however, that “How to model the findings in an optimal way is still an open question” and doing so will require further studies. Until then, dietary acid reduction should continue to be explored as a potential kidney-protective intervention as well as mechanisms for its apparent beneficial effects on kidney function.

Table 3.

<table>
<thead>
<tr>
<th>Na+ Dose, meq</th>
<th>UNa+, V, meq</th>
<th>%Na+ Dose Excreted</th>
<th>Calculated Retained Na+ Dose, meq</th>
<th>Expected Increase in Plasma Na+ Dose, meq/l</th>
<th>Observed Increase in Plasma Na+ Dose, meq/l</th>
<th>Not Accounted Na+ Dose, meq</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 1</td>
<td>42.0 ± 0.1</td>
<td>33.3 ± 9.1</td>
<td>79.3 ± 21.3</td>
<td>8.7 ± 2.3</td>
<td>0.22 ± 0.06</td>
<td>5.0 ± 1.3</td>
</tr>
<tr>
<td>CKD 2</td>
<td>42.1 ± 0.1</td>
<td>31.8 ± 8.9</td>
<td>75.5 ± 20.4</td>
<td>10.3 ± 3.0</td>
<td>0.28 ± 0.08</td>
<td>5.6 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 vs. CKD 1.
DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

REFERENCES