Renin-Angiotensin-Aldosterone Activation in Heart Failure, Aldosterone Escape

To the Editor:

Important and otherwise excellent articles by Weber1,2 and Schrier and Abraham3 strongly characterize persistent renin-angiotensin-aldosterone system (RAAS) activation in congestive heart failure, a hypervolemic state, as “inappropriate” based on their view that the primary role of the RAAS is to prevent salt deprivation or intravascular volume contraction (hypovolemia).

Actually, as the authors state but apparently dismiss, it is renal hypoperfusion not hypovolemia per se that activates the RAAS. Since hypoperfusion is hypoperfusion whether a result of heart failure (HF) or hypovolemia, RAAS activation is in fact no more inappropriate in HF than, say, a high thyrotropin in an ahhyroidic.

RAAS activation is exquisitely sensitive to low cardiac output (CO) low renal perfusion, responding to mere postural changes.1 Reduced CO in early HF prompts RAAS-activated fluid retention, which increases ventricular preload and CO until CO again meets the RAAS activation threshold. RAAS activation is maintained at this higher set-point to preserve the compensated CO. With sufficient further ventricular dysfunction, CO can no longer reach the RAAS activation threshold.4 Thus unable to achieve a new higher set point, the RAAS is persistently activated in proportion to the CO shortfall in a futile attempt to raise the intractably low CO.4 Since low CO stimulates the RAAS feedback control loop, RAAS activation is never inappropriate when CO is low or compensated, but when it raises venous pressure above the onset of the Starling plateau it is many things, including “ineffective” and “excessive” (because it no longer significantly increases CO), “congestive,” and even “toxic” (due to its cardiovasculopathic effects as well described by Weber).1

Weber4 appropriately contrasts HF patients, whose hyperaldosteronism results in near-complete sodium reabsorption and edema, with: “Normal subjects given aldosterone and patients with primary (renin-independent) hyperaldosteronism (Conn’s syndrome) who escape the salt-retaining effects of aldosterone and do not have edema.” He points out that these subjects lack the elevated angiotensin II levels typical of HF, and because angiotensin II contributes to renal tubular sodium reabsorption, renal sodium conservation is incomplete. As he alludes, this could at least partly account for the escape phenomenon.1 But these subjects also lack the CO ceiling characteristic of HF. Thus, their aldosterone-enhanced preload increases CO above normal resting levels and this in turn increases BP and renal perfusion. Combined with the lesser angiotensin II levels, the increased renal perfusion reestablishes salt and water balance and thus curtails volume accumulation before its overt expression as edema.

The characterization of persistent RAAS activation in congestive HF as “inappropriate” unfortunately fuels the popularity of the “neurohormonal”/”salt-avid kidney”4 HF model, which among other currently fashionable models including the cellular, molecular, genetic, inflammatory6 and even the (understood to be facetious) febrile6 model, regrettably obscures the reality that low CO remains, as always, the true pathophysiologic basis of HF.

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References


Metabolic Alkalosis and Cystic Fibrosis

To the Editor:

Metabolic alkalosis is not uncommon in patients with cystic fibrosis. It has been associated with chloride depletion and avid urinary chloride retention in infants and children,1,2 suggesting appropriate renal tubular handling of chloride in this setting. We report urinary chloride excretion values for several patients with cystic fibrosis and metabolic alkalosis, and compare these values to previous reports.

We reviewed medical records of our patients with cystic fibrosis hospitalized during the last 4 years, looking for patients with metabolic alkalosis as well as urine chloride and creatinine concentrations. Three patients hospitalized on four occasions were identified (Table 1). Metabolic alkalosis—simple or

Table 1—Hospitalized Patients With Cystic Fibrosis and Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Admission Diagnoses</th>
<th>Age, yr</th>
<th>Genotypes</th>
<th>Serum Sodium/Chloride, mmol/L</th>
<th>Urinary Sodium/Chloride, mmol/L</th>
<th>Molar Urinary Chloride:Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dehydration, diarrhea*</td>
<td>1.3</td>
<td>N1303K/ΔF508</td>
<td>115/65</td>
<td>&lt; 5/2</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>Postpartum/acute pulmonary exacerbation†</td>
<td>28</td>
<td>W1282X/W1282X</td>
<td>134/93</td>
<td>113/119</td>
<td>43.4</td>
</tr>
<tr>
<td>3</td>
<td>Acute pulmonary exacerbation ‡</td>
<td>29</td>
<td>Unknown</td>
<td>139/94</td>
<td>131/144</td>
<td>116.4</td>
</tr>
</tbody>
</table>

*Successfully treated with chloride repletion.
†Simple metabolic alkalosis.
‡Acute pulmonary exacerbation.

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mixed—was defined using the results of an arterial blood gas analysis with reference to the acid-base diagram of Stinebaugh and Austin,⁴ while the molar urinary chloride/creatinine ratio was used to indicate urinary chloride excretion (low, < 8.4; normal, 8.4 to 50.1; elevated, > 50.1).¹,²

Consistent with previous reports¹,² of children with metabolic alkalosis and cystic fibrosis, the molar urinary chloride/creatinine ratio was low in our pediatric patient, while it was normal or elevated in our adult patients. If metabolic alkalosis in our adult patients was the result of respiratory alkalosis superimposed on respiratory acidosis (posthypercapnic metabolic alkalosis), urinary chloride excretion would be low. Inability to conserve chloride in the urine during metabolic alkalosis is associated with hyperaldosteronism, hypokalemia, refeeding syndrome, and diuretic therapy. Aldosterone levels were low in all episodes involving adult patients. Hypokalemia and refeeding syndrome were not present. None of the patients was receiving diuretic therapy. Alternative explanations for the lack of appropriate urinary chloride retention in adults with cystic fibrosis and metabolic alkalosis, such as an age-related change in renal tubular function or the renal expression of defective cystic fibrosis transmembrane conductance regulator, have not been described.

Whatever the cause, metabolic alkalosis may have a deleterious impact on ventilation and density of mucus secretions.¹ We suggest that some adults with cystic fibrosis and metabolic alkalosis lack avid urinary chloride retention, that the etiology of this process is unknown, and that chloride repletion may be warranted.

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REFERENCES