

# Fractional Excretion of Sodium

## Exceptions to Its Diagnostic Value

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• Determining the cause of acutely deteriorating renal function is a common problem in clinical nephrology. The fractional excretion of filtered sodium (FENa) has been demonstrated to be a reliably discriminating test between prerenal azotemia and acute tubular necrosis. However, with increasing clinical use of the FENa, numerous reports of low FENa (<1%) have appeared. The clinical settings of these reports include oliguric and nonoliguric acute tubular necrosis, urinary tract obstruction, acute glomerulonephritis, hepatorenal syndrome, renal allograft rejection, sepsis, and drug-related alterations in renal hemodynamics. One particular urinary index cannot be expected to reliably discriminate between prerenal azotemia and acute renal failure in all cases. The utility of the FENa test in the differential diagnosis of acute renal failure must be interpreted in conjunction with the patient's clinical course and the use of additional urinary and serum tests.

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A common problem in clinical nephrology is determining the cause of acutely deteriorating renal function. The major categories of renal insufficiency are prerenal (functional) azotemia, obstructive uropathy, and intrinsic renal disease. Simple, noninvasive, yet reproducible tests are desirable for the accurate differentiation of these broad categories of renal insufficiency. However, the commonly used urinary diagnostic indexes (Table 1)—urinary sodium level, urine osmolality, and the urine-plasma creatinine ratio—often fail to discriminate among the various entities causing renal dysfunction. To avoid diagnostic uncertainty, Espinel and Gregory<sup>1,2</sup> prospectively calculated the fractional excretion of filtered sodium (FENa) and demonstrated it to be a reliably discriminating index between prerenal azotemia and acute tubular necrosis (ATN).

### DEFINITION

The FENa is the quotient of the urine-plasma sodium and creatinine ratios multiplied by a factor of 100. Since it is the

Table 1.—Urinary Findings in Prerenal Azotemia and Acute Renal Failure

Laboratory Test	Prerenal Azotemia	Acute Renal Failure
Urinary sodium concentration, mEq/L	<20	>40
Urine-plasma creatinine ratio	>40:1	<20:1
Urine osmolality	>100 mOsm above plasma value	≤Plasma value
Urinary sediment	Normal	Casts, cellular debris

excreted fraction of filtered sodium, its derivation is as follows:

$$\begin{aligned} \text{FENa} &= (\text{Na Excreted}/\text{Na Filtered}) \times 100\% \\ &= [U_{\text{Na}} (\dot{V})/P_{\text{Na}} (\text{GFR})] \times 100\% \\ &= \{[U_{\text{Na}} (\dot{V})/P_{\text{Na}}]/[U_{\text{Cr}} (\dot{V})/P_{\text{Cr}}]\} \times 100\% \\ &= \{[(U_{\text{Na}})(P_{\text{Cr}})]/[(P_{\text{Na}})(U_{\text{Cr}})]\} \times 100\% \\ &= [(U/P)_{\text{Na}}/(U/P)_{\text{Cr}}] \times 100\%, \end{aligned}$$

where U and P represent concentrations in urine and plasma, respectively;  $\dot{V}$ , minute urinary flow rate; Cr, creatinine; and GFR, glomerular filtration rate.

Espinel and Gregory<sup>1,2</sup> claimed that the determination of the FENa has many inherent advantages as a diagnostic tool in acute renal failure (ARF). First, it is a physiologic measure of sodium resorption, which has been considered a most sensitive gauge of renal function. Second, it takes into account both creatinine and sodium clearances; thus, both filtration and resorption of sodium are expressed. Third, the FENa increases before the oliguric phase is established and can thus be predictive of incipient renal failure. Fourth, its determination is noninvasive, simple, and rapid. An FENa value of less than 1% suggests the diagnosis of prerenal azotemia or acute glomerulonephritis, whereas a value greater than 1% to 3% indicates ATN<sup>2,3</sup> (Table 2). Miller et al<sup>4</sup> noted that although urinary indexes were discriminating in 80% of subjects, approximately 20% of patients with ARF had nondiagnostic values. However, an FENa value of less than 1% was noted in 94% and 4% of patients with prerenal azotemia and oliguric ARF, respectively.<sup>4</sup> According to Oken,<sup>5</sup> most patients with a clinical appearance typical of vasomotor nephropathy have an FENa of 6% or higher. Many of his study group exhibited

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Table 2.—Diagnostic Indexes in Acute Renal Failure\*

	SUN, mg/dL	Serum Cr, mg/dL	Urine Na, mEq/L	Urine/Plasma Cr Ratio	Urine Osmolality, mOsm/kg H <sub>2</sub> O	FENa, %
Acute tubular necrosis (N=22)	107±12	6.5±0.7	50±7	12±2	310±19	3.48±0.5
Nonoliguric acute tubular necrosis (N=18)	76±13	3.7±0.3	43±6	16±2	304±21	2.28±0.4
Urinary tract obstruction (N=12)	84±13	4.5±0.7	52±9	14±2	304±35	4.11±1.0
Acute glomerulonephritis (N=14)	79±13	4.1±0.5	23±4	56±1	331±23	0.31±0.1
Prerenal azotemia (N=21)	110±17	5.4±0.8	17±3	37±5	396±28	0.36±0.1

\*Modified from Espinel and Gregory.<sup>2</sup> Values are given as mean ± SEM. SUN represents serum urea nitrogen; Cr, creatinine; Na, sodium; and FENa, fractional excretion of sodium.

Table 3.—Low Fractional Excretion of Sodium in Acute Renal Failure (ARF)

Source, yr	No. of Patients	Daily Urine Volume	Clinical Setting
Hong et al, <sup>32</sup> 1979	17	Oliguric	Renal allograft rejection
Hilberman et al, <sup>7</sup> 1979	17	Nonoliguric	After cardiac surgery
DeStrihou, <sup>44</sup> 1979	1	Oliguric	Acute interstitial nephritis
Fang et al, <sup>6</sup> 1980	12	Oliguric	Contrast-induced ARF
Diamond and Yoburn, <sup>8</sup> 1982	6	Nonoliguric	Cirrhosis and ARF
Planas et al, <sup>41</sup> 1982	11	Nonoliguric	Burns
Steiner, <sup>18</sup> 1982	2	Oliguric	Myoglobinuria-induced ARF
Vaz, <sup>42</sup> 1983	2	Oliguric	Sepsis
Ebert, <sup>45</sup> 1983	1	Oliguric	Acute interstitial nephritis
Fotino and Sporn, <sup>30</sup> 1983	1	Nonoliguric	Converting-enzyme inhibition
Corwin et al, <sup>19</sup> 1984	14	Oliguric	Myoglobinuria- and hemoglobinuria-induced ARF

FENa values between 3% and 6%, and a small minority have had values between 2% and 3%. In these cases, the diagnosis of vasomotor nephropathy was less than certain. With an FENa at or above 6%, the urine-plasma creatinine ratio cannot exceed 15 unless the urinary sodium concentration is over 100 mEq/L.<sup>5</sup> Thus, at this higher differentiating value for FENa of 6%, the urinary sodium concentration as well as the urine-plasma creatinine ratio predictably fall within the "classic" limits.<sup>5</sup>

### CLINICAL EXPECTATIONS

With increasing clinical use of the FENa, numerous reports of low FENa (ie, <1%) in both oliguric and nonoliguric ARF have appeared (Table 3). Certain characteristics of the patients with ARF and low FENa values suggest common underlying pathophysiologic aberrations to explain the findings.

### Sodium-Avid State

Low FENa values may be seen in patients with sodium-avid states in whom ARF develops. Fang et al<sup>6</sup> noted FENa values of consistently less than 1% in 12 patients with contrast-induced ARF during their initial, transient

oliguric phase. In their series, six of the 12 patients were thought to have compromised cardiac output due to valvular or ischemic heart disease, while one additional patient had cirrhosis. Hilberman et al<sup>7</sup> noted that the mean FENa value for a group of 17 patients with nonoliguric ARF following cardiac surgery was 0.61%. These patients had lower mean arterial BP, cardiac index, GFR, and effective renal plasma flow and higher mean pulmonary capillary wedge pressure and filtration fraction than a group of 22 patients with normal postoperative renal function and 12 patients with postoperative prerenal azotemia. Diamond and Yoburn<sup>8</sup> identified six cirrhotic patients with nonoliguric ARF secondary to nephrotoxicity, all of whom had FENa values less than 1%. It is of interest that in the prospective analysis of urinary diagnostic indexes by Miller et al,<sup>3</sup> patients with cirrhosis were excluded from the study.

Although it is not known what produces a low FENa in these groups of patients, the common denominator of decreased effective blood volume may have created a sodium-avid state. The relative fullness of the arterial vascular tree, as determined by cardiac output and total peripheral resistance, has been suggested to define effective blood volume.<sup>9</sup> Low cardiac output initiates the increased retention of sodium and water and may explain why patients with contrast-induced ARF and ARF following cardiac surgery have low FENa values. Total peripheral resistance is decreased in most patients with cirrhosis who are retaining sodium and water. The total plasma volume may be increased in patients with cirrhosis, but the relative fullness of the arterial tree is diminished. Skorecki and Brenner<sup>10</sup> postulated that hepatic venous outflow obstruction is the primary abnormality required for sodium retention in cirrhosis. It has been thought that the increased hepatic lymph flow resulting in the formation of ascites and an expanded splanchnic circulation promotes an altered intravascular volume status relative to capacitance. Hence, intravascular volume depletion is perceived by intravascular volume sensors, which then signal the kidney to retain salt and water, despite excess extravascular fluid. The immersion studies of Epstein et al<sup>11,12</sup> in cirrhotic patients suggest that a diminished effective blood volume is the major determinant of enhanced tubular resorption of sodium. Water immersion, which is sensed as a redistribution of volume to the central intravascular compartment, resulted in an increased FENa whereas stopping immersion resulted in a prompt decrease.<sup>12</sup> It has been postulated<sup>8</sup> that the decreased effective blood volume is the stimulus for avid tubular sodium resorption and, therefore, results in a low FENa.

Skorecki and Brenner<sup>10</sup> reviewed changes in proximal peritubular capillary Starling forces favoring sodium con-

servation in states of diminished effective blood volume. Real or perceived renal hypoperfusion may enhance adrenergic innervation to the kidney and stimulate the cortical release of renin, resulting in augmented angiotensin II (AII) generation. This may then cause enhanced efferent arteriolar tone and result in an increased filtration fraction while diminishing peritubular capillary hydrostatic pressure.<sup>10</sup> The net effect of this mechanism is enhanced proximal solute and water resorption.<sup>10</sup> Blythe<sup>13</sup> reviewed the role of AII in maintaining GFR, by augmenting efferent arteriolar tone, in states of renal hypoperfusion (ie, autoregulation).

Another potential efferent factor in mediating enhanced sodium resorption in these states of diminished effective blood volume is hyperaldosteronism. Using hepatic cirrhosis as the prototype, Arroyo et al<sup>14</sup> demonstrated, in a large cirrhotic population without azotemia, that activation of the renin-angiotensin-aldosterone axis is associated with avid sodium retention. Since these patients had normal GFRs, as evidenced by inulin clearance, Arroyo et al suggested that the early avid sodium retention is due to increased distal tubular sodium resorption. Gregory et al<sup>15</sup> demonstrated that spironolactone administration can by itself produce enhanced sodium excretion with marked reduction in ascites in many cirrhotic patients. Wilkinson et al<sup>16</sup> hypothesized that the distal tubule becomes "supersensitive" to the sodium-retaining influence of aldosterone and fails to "escape" from the sodium-retaining state of the hormone.

Thus, as Better and Schrier stated,<sup>17</sup> in early and moderately advanced cirrhosis, hyperaldosteronism associated with impairment of the escape phenomenon is of major importance in sodium retention and ascites formation. When the liver disease progresses, distal delivery of sodium declines, probably secondary to a fall in GFR and an increase in proximal tubule resorption.

#### Intratubular Obstruction

There have been some reports of less common causes of ARF associated with a low FENa. During the oliguric phase of myoglobinuria-induced ARF, two patients were noted to have low FENa values.<sup>18</sup> Corwin et al<sup>19</sup> similarly observed FENa values of less than 1% among 14 patients with either myoglobinuria- or hemoglobinuria-induced ARF. It was postulated that since intratubular obstruction by cellular debris, Tamm-Horsfall protein, uric acid, or pigmented casts may play a role in the development of ARF,<sup>20,21</sup> this pathophysiologic mechanism may also mediate reduced urinary sodium excretion. Regarding contrast-induced ARF, radioiodinated contrast agents are uricosuric and cause precipitation of Tamm-Horsfall proteins in vitro.<sup>20</sup> Recent clinical success with mannitol in ameliorating the course of these disorders by promoting a solute and water diuresis may involve prevention of intratubular obstruction, as animal experiments suggest.<sup>22</sup>

It has been demonstrated experimentally that acute ureteral obstruction leads to diminished urinary sodium values.<sup>23</sup> Canton et al<sup>24</sup> noted that acute elevations of ureteral pressure were accompanied by decrements in both net glomerular capillary hydrostatic pressure and GFR. Each of these perturbations favors proximal tubular resorption of solute and fluid. Elevated tubular hydrostatic pressure following obstruction may also produce increased renal vascular resistance resulting in a reduction in renal blood flow,<sup>25</sup> which would similarly enhance proximal tubular resorption of sodium. Harris and Yarger<sup>26</sup> evaluated renal function and hemodynamics after the release of unilateral ureteral obstruction in rats. Whole-kidney GFR was re-

duced to 18% and renal plasma flow to 33% of the control values. Distal sodium delivery in superficial nephrons was markedly reduced, due to decreased single-nephron GFR (33% of the control value) and increased proximal fractional resorption. Thus, either acute extrarenal or intrarenal obstruction may alter renal hemodynamics to promote enhanced sodium resorption by the proximal tubule. Low urinary sodium values in the setting of acute obstructive uropathy have been noted.<sup>23</sup> However, as renal injury secondary to obstruction progresses, the urinary indexes may be more consistent with those of ATN. Miller et al<sup>3</sup> stated that urinary indexes in obstructive uropathy were dependent on the duration of obstruction and the severity of azotemia.

#### Renal Hemodynamic Alterations

Local changes in renal vascular hemodynamics may similarly serve as major stimuli favoring sodium conservation, analogous to the systemic hemodynamic alterations in sodium-avid states. Low FENa values have been reported in association with drugs that interfere with renal autoregulation, transplant rejection, and the hepatorenal syndrome. These conditions appear to be prime examples of how hemodynamic alterations producing a diminution in renal blood flow act as potent "prerenal stimuli."

Renal blood flow and GFR remain relatively constant despite marked variations in systemic arterial pressure.<sup>18</sup> Termed *autoregulation*, this phenomenon leads to a variety of hemodynamic changes that alter proximal peritubular capillary Starling forces. The role of AII in maintaining GFR in states of renal hypoperfusion by enhancing efferent arteriolar tone has been reviewed.<sup>13,27</sup> Interference with this renal autoregulatory mechanism may be the cause of captopril-induced ARF in patients with bilateral severe renal artery stenosis or renal artery stenosis in a solitary kidney.<sup>28,29</sup>

A similar report<sup>30</sup> of nonoliguric ARF after captopril therapy associated with low FENa values at first seems contradictory. Angiotensin blockade might be expected to enhance natriuresis by relaxing efferent arteriolar tone and increasing proximal peritubular capillary hydrostatic pressure. However, AII plays a pivotal role in maintaining systemic arterial pressure, and its blockade may also cause systemic arterial hypotension and renal hypoperfusion.<sup>30</sup> Relaxed efferent arteriolar tone secondary to converting-enzyme inhibition will also decrease GFR as glomerular capillary hydrostatic pressure is reduced. Second, as Dunn and Zambraski<sup>31</sup> emphasized, intrarenal vasodilatory prostaglandins are extremely important in maintaining renal blood flow under conditions of elevated circulating AII levels, decreased effective blood volume, and increased sympathetic tone. Converting-enzyme inhibition may indirectly reduce the compensatory release of vasodilatory renal prostaglandins in the foregoing physiologic circumstances, thereby reducing intrarenal blood flow with consequent production of a "prerenal" state. We recently observed a low FENa value (0.3%) in an elderly hypertensive man in whom azotemia and oliguria occurred suddenly coincident with the administration of indomethacin. The urinary sediment was unremarkable, and a prompt diuresis with a fall in serum creatinine level was noted when the nonsteroidal anti-inflammatory agent was discontinued.

Low urine sodium concentrations and FENa values in acute allograft rejection<sup>32,33</sup> are thought to reflect decreased renal blood flow. Hong et al<sup>32</sup> reviewed evidence supporting decreased renal perfusion in association with kidney allograft rejection. Intrarenal ischemia is suggested by histologic changes in small vessels, such as fibrinoid necrosis,

microthrombi, and intrarenal intimal hyperplasia. Clinically, the diminished renal perfusion is manifested by oliguria with increased urine osmolality, increased plasma renin activity, and abnormal findings on testing with iodohippurate sodium I-131. Evidence of the maintenance of tubular integrity in the face of hypoperfusion from allograft rejection is the demonstration of augmented sodium resorption even before a decrease in GFR is noted. Of 31 episodes of acute rejection observed in 118 allograft studies, 17 were associated with decrements in FENa. Abnormally low FENa values usually preceded the initial rise in serum creatinine level by two or three days. In each case, the decrease in FENa occurred prior to the clinical diagnosis of acute rejection. Of these 17 cases, 15 responded to antirejection therapy, whereas only two of 14 cases where the FENa value did not fall responded to similar therapeutic interventions. This suggests that a low FENa value can be used as an early marker of acute allograft rejection. Failure to find a low FENa value during periods of renal dysfunction following renal transplantation may signify even more impaired tubular function, such as ATN.

In the hepatorenal syndrome, the most uniform findings are extremely low urinary sodium and FENa values.<sup>24,25</sup> Although the pathogenesis of this syndrome has not been fully delineated, there is evidence of reversible functional deficits,<sup>24,25</sup> most notably those precipitated by intrarenal vasoconstriction.<sup>26,27</sup> Xenon washout and angiographic studies indicate that acute cortical blood flow is the most strikingly reduced. Premortem angiograms in cirrhotic patients with ARF show beading and tortuosity of interlobar and early arcuate vessels without visualization of smaller vessels or visible nephrograms. Subsequent postmortem angiograms show normal contours in these same larger vessels with visualization of the smaller vessels not previously seen.<sup>28</sup>

Whether the direct mediator of renal circulatory changes in the hepatorenal syndrome is a deficiency of an intrarenal vasodilator (eg, kallikrein-kinin derivative),<sup>29</sup> a heightened vasoconstricting renin-angiotensin axis,<sup>12</sup> or decreased effective blood volume is unclear. However, renal vasoconstriction of such magnitude can result in renal hypoperfusion with consequent avid sodium resorption as tubular function remains intact.

#### Miscellaneous Clinical Settings

Additional, as yet unexplained mechanisms are likely involved in many settings producing low FENa in ARF. Several groups have reported low urine sodium and FENa values in patients with extensive burns who have non-

oliguric ARF.<sup>39-41</sup> Vaz<sup>42</sup> emphasized the potential role of sepsis accounting for low FENa values in two postoperative patients with ARF. These patients were neither cirrhotic nor nephrotic, and an adequate volume status was ensured with central hemodynamic monitoring. However, nephrotoxic antibiotics were used and the prior intraoperative courses were not delineated, and so the ARF may have been multifactorial.

Direct glomerular damage is still another mechanism by which "prerenal" urinary indexes may be produced. Early studies had suggested intact tubular function early in the course of acute glomerulonephritis as evidenced by high urine-plasma osmolality ratios.<sup>43</sup> Miller et al<sup>4</sup> subsequently reported seven cases of acute glomerulonephritis with a mean FENa value of 0.6%. Espinel and Gregory<sup>2</sup> obtained similar results (mean FENa value, 0.3%) in 14 patients with acute glomerulonephritis. In biopsy-proved cases of acute interstitial nephritis, DeStrihou<sup>44</sup> and Ebert<sup>45</sup> noted reduced urinary sodium and FENa values.

#### CONCLUSIONS

Urinary indexes in the early phase of ARF may be deceptive in a variety of states involving ureteral or intratubular obstruction, sodium-avid states, or clinical situations with altered intrarenal hemodynamics. Further discriminating tests are thus welcomed for the differential diagnosis of ARF. Surgical studies<sup>46,47</sup> have emphasized the early predictive value of depressed free-water clearance sequentially analyzed in patients postoperatively. Although the FENa test did not show a significant upward trend until after the serum creatinine level had risen in early renal dysfunction postoperatively, free-water clearance values were abnormal from the onset. Unfortunately, patients with sodium-avid states will also have impaired diluting and concentrating abilities because of their inadequate solute delivery to Henle's loop.

Simply stated, the causes of ARF are multifactorial and occur in a variety of conditions known to affect renal water and solute handling. One particular urinary index cannot then be expected to discriminate between prerenal azotemia and ARF. The utility of the FENa test in the differential diagnosis of ARF must be interpreted in conjunction with a thorough clinical history and physical examination, use of additional urinary and serum measures, and careful examination of the urinary sediment. Indeed, the diagnosis itself often may not be firmly established until a retrospective analysis of the patient's clinical course is undertaken.

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