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Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure

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Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure.

Background. Fractional excretion of sodium (FE_{Na}) has been used in the diagnosis of acute renal failure (ARF) to distinguish between the two main causes of ARF, prerenal state and acute tubular necrosis (ATN). However, many patients with prerenal disorders receive diuretics, which decrease sodium reabsorption and thus increase FE_{Na}. In contrast, the fractional excretion of urea nitrogen (FE_{UN}) is primarily dependent on passive forces and is therefore less influenced by diuretic therapy.

Methods. To test the hypothesis that FE_{UN} might be more useful in evaluating ARF, we prospectively compared FE_{UN} with FE_{Na} during 102 episodes of ARF due to either prerenal azotemia or ATN.

Results. Patients were divided into three groups: those with prerenal azotemia ($N = 50$), those with prerenal azotemia treated with diuretics ($N = 27$), and those with ATN ($N = 25$). FE_{Na} was low only in the patients with untreated plain prerenal azotemia while it was high in both the prerenal with diuretics and the ATN groups. FE_{UN} was essentially identical in the two pre-renal groups (27.9 ± 2.4% vs. 24.5 ± 2.3%), and very different from the FE_{UN} found in ATN (58.6 ± 3.6%, $P < 0.0001$). While 92% of the patients with prerenal azotemia had a FE_{Na} <1%, only 48% of those patients with prerenal and diuretic therapy had such a low FE_{Na}. By contrast 89% of this latter group had a FE_{UN} <35%.

Conclusions. Low FE_{UN} (≤35%) was found to be a more sensitive and specific index than FE_{Na} in differentiating between ARF due to prerenal azotemia and that due to ATN, especially if diuretics have been administered.

Identifying the cause of acute renal failure is a common problem in clinical practice. The fractional excretion of filtered sodium (FE_{Na}) has been shown to discriminate reliably between prerenal azotemia and acute tubular necrosis (ATN) [1–4]. However, there are several reports of low FE_{Na} (less than 1%) in conditions associated with intrinsic acute renal failure, such as sepsis, contrast nephropathy, myoglobulinuria and nonoliguric ATN [1–17]. Furthermore, a common major limitation in the use of FE_{Na} stems from the fact that diuretic agents are employed frequently in the treatment of prerenal conditions such as congestive heart failure, liver failure with ascites, or to enhance urine output in oliguric patients. In addition, the excessive use of diuretics in a formerly euvolemic subject may lead to a prerenal state, often with increased urinary Na and thus increased FE_{Na}. Other situations also exist where prerenal azotemia is associated with increased urinary sodium and increased FE_{Na}. Most prominent among them is volume depletion and prerenal azotemia due to vomiting or nasogastric suction. In such cases the ensuing bicarbonaturia maintains urinary sodium and FE_{Na} at high levels [18]. In an attempt to find a more useful guide, we evaluated the fractional excretion of urea nitrogen (FE_{UN}). We demonstrate that FE_{UN} is at least as sensitive and specific as FE_{Na} in the usual prerenal cases and, in contrast to the latter, does not lose its sensitivity or specificity in diagnosing prerenal azotemia in the presence of diuretic therapy.

Key words: fractional excretion of sodium, acute tubular necrosis, prerenal ARF, diuretic therapy, azotemia, intensive care.

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METHODS

This was a prospective, Institutional Review Board approved study that took place at Nassau County Medical Center, a large (612 beds) public hospital. One hundred two consecutive adult patients referred to the Nephrology service (mostly from the Intensive Care Units) for evaluation of acute renal failure, comprised the subjects of this study. The major reason for consultation was a rapidly increasing blood urea nitrogen (BUN) and creatinine (BUN >30 mg/dL and creatinine >1.5 mg/dL) with or without oliguria. Urine output measurements were available for most patients, in particular all the ATN patients who were typically found in one of the ICUs, all of whom had Foley catheters. In all cases, the diagnosis was made by the consulting attending nephrologist, based on the medical history, physical examination, and

Table 1. Criteria for diagnosis of acute renal failure and to allow to differentiate prerenal azotemia and acute tubular necrosis (ATN)

A. Criteria for diagnosing acute renal failure
   1. Azotemia—rapidly increasing BUN and creatinine (BUN >30 mg/dL and creatinine >1.5 mg/dL) with or without oliguria.
   2. Serum creatinine increase in excess of 0.5 mg/dL in the preceding 2 days.

B. Criteria to differentiate ATN from prerenal azotemia
   1. History (volume depletion, decreased cardiac output or vasodilation related to sepsis, liver failure and anaphylaxis favor prerenal azotemia, while exogenous toxins such as medications, or endogenous toxins as in the case of myoglobin, or even prolonged renal hypoperfusion that became unresponsive to appropriate corrective measures or to high dose of loop diuretics, all favor ATN).
   2. Physical examination (blood pressure, heart rate, orthostatic changes, cardiac sounds, pulmonary findings, presence of ascites or pedal edema).
   3. Findings of the urine analysis (urinary sediment non-revealing in pre-renal, presence of muddy brown granular casts in patients with ATN) as performed by a member of the renal service. Retrospective confirmation (response to therapy) also was recorded.
   4. The urinary indices evaluated at the time of consultation were:
      —Urinary sodium (U_{Na}): U_{Na} <15 mEq/L favors prerenal, while a value higher than 20 is consistent with ATN.
      —Urinary to plasma creatinine ratio (U/P_{Cr}). U/P_{Cr} >20 is consistent with prerenal while levels <15 suggest ATN.
      —Fractional excretion of sodium (FE_{Na}). FE_{Na} <1% is suggestive of prerenal azotemia, while levels >1% indicate the presence of ATN.
      —Urinary sodium/potassium ratio (U_{Na}/K; a reflection of prerenal conditions with associated hyperaldosteronism). If U_{Na}/K is less than ¼, this favors prerenal azotemia.

evaluation of urine sediment morphology and composition, as suggested by standard textbooks [1], and is shown in Table 1. The members of the renal service used the usual urinary indices as described in Table 1. Urinary urea nitrogen was not available at the time of consultation, but was measured later in batches of urine specimens from 5 to 10 patients. Twenty-seven of the patients had received diuretic therapy (furosemide or thiazides, up to the day of consultation). Patients with acute interstitial nephritis, acute glomerulonephritis, and obstructive nephropathy were not included in the present study as there were a small number of patients in each category (3, 1, and 1, respectively) that would not allow for drawing any meaningful conclusions.

Prerenal azotemia was the result of circulatory failure secondary to various causes such as sepsis, gastrointestinal bleeding, hepatic, respiratory or cardiac failure. The diagnosis of prerenal azotemia was established in circulatory failure when improvement of heart function, cessation of diuretic therapy, or treatment of shock effected a prompt increase in urinary output and creatinine clearance. Of the 50 cases of prerenal azotemia, 16 had sepsis, 10 congestive heart failure, 7 hepatic failure and 7 gastrointestinal bleeding. The remaining patients had miscellaneous or less definite diagnoses. Twenty-four were men and 26 were women, with an average age of 49 ± 2 years (mean ± SEM). The demographics were actually quite similar in all subgroups where the representation of men to women were 14 to 13 in the group of prerenal on diuretics and 13 to 12 in the ATN group. The mean ages were 51 ± 3 and 47 ± 3 in these two groups, respectively.

As expected, the majority of the prerenal cases receiving diuretics were subjects with congestive heart failure. Acute tubular necrosis (ATN) resulted from nephrotoxic drugs (aminoglycoside antibiotics), myoglobinuria, sustained circulatory failure, or massive surgical volume losses unresponsive to replacement. Thirteen patients had protracted sepsis, although the exact role of coexistent factors such as major surgical procedures (8 of these) or use of nephrotoxins (5 were on aminoglycoside therapy) does not allow for a clear-cut identification of the underlying etiology. Myoglobinuria caused six cases of ATN (3 due to cocaine, 1 due to alcohol, 1 due to phosphorus depletion and 1 due to trauma). The remainder of the cases had a mixed and often less well identified etiology.

The indices evaluated at the time of consultation were urinary sodium (U_{Na}), urinary sodium/potassium ratio ($U_{Na/K}$; a reflection of prerenal conditions with associated hyperaldosteronism), urinary to plasma creatinine ratio (U/P_{Cr}), and fractional excretion of sodium (FE_{Na}). Fractional excretion of urea (FE_{UN}) was determined later. The FE_{Na} was calculated as [(urine sodium/ plasma sodium)/(urine creatinine/plasma creatinine)] × 100. The FE_{UN} was calculated as: [(urine urea nitrogen/ blood urea nitrogen)/(urine creatinine/plasma creatinine)] × 100. In well-hydrated individuals, the FE_{UN} is 50 to 65% [19]. In the presence of oliguria and prerenal azotemia, FE_{UN} less than or equal to 35% with progressive decline has been found as urine volume decreases to about 0.5 mL/min or less [19]. Indeed, as urine volume decreases to oliguric levels (<0.35 mL/min or 500 mL/day) FE_{UN} decreases proportionally to urine flow [20]. For that reason, we selected a FE_{UN} value of 35% to signify prerenal azotemia. On the other hand, in intrinsic renal failure the clearance of urea decreases to an equal degree or less than the clearance of creatinine. Thus, an FE_{UN} more than 50% indicates acute tubular necrosis. Blood chemistries were performed on a Beckman automated analyzer for serum electrolytes, creatinine and urea (Beckman Instruments, Fullerton, CA, USA). Urine electrolytes were determined by flame photometry. Urine urea nitrogen and creatinine were determined spectrophotometrically on spot urine samples collected at the bedside. In one part of the study the measured FE_{UN} (as described earlier in this article) was compared with the expected FE_{UN} from the study of Dole, where $FE_{UN} = 0.57\ e^{-(0.36/V)}$ [19]. In a few prerenal cases where accurate $\dot{V}$ (urine flow in mL/min) was difficult to assess, the $\dot{V}$ calculated from U/P_{Cr} was used with $\dot{V} = 100/(U/P_{Cr})$ as described previously by Homer Smith [21].

Statistical analysis was performed using the appropriate statistical method [22]. One way analysis of variance

Table 2. Evaluation of the significance of the different indices in the different forms of acute renal failure

ARF (type)	*N*	BUN	Creatinine	BUN/Cr	U_{Na}	U_{Na}/K	FE_{Na}	FE_{UN}	U/P_{Cr}
PR	50	43 ± 4	1.6 ± 0.2	30 ± 2	18 ± 2[a]	0.6 ± 0.1[a]	0.4 ± 0.1	28 ± 2	98 ± 21
PR-diur.	27	48 ± 6	1.9 ± 0.2	26 ± 2	58 ± 7	3.7 ± 1.4	2.1 ± 0.6	24 ± 2	62 ± 11
ATN	25	63 ± 6	5.9 ± 0.5	11 ± 2[a]	61 ± 7	5.1 ± 1.0	8.9 ± 2.2[a]	59 ± 3[a]	9 ± 1

BUN and serum creatinine (Cr) are given in mg/dL, FE_{Na} and FE_{UN} are expressed as %. BUN/Cr and U/P_{Cr} represent the ratio of BUN to serum creatinine and that of urine to plasma creatinine values, respectively. All results are given as mean ± SEM. PR stands for prerenal, PR-diur represents the prerenal group that was on diuretics. The symbol *N* represents the number of subjects in each group.

[a]A one way analysis of variance (ANOVA) was statistically significant with $P < 0.001$, and this type of ARF was statistically significant different than the other two types by Bonferroni *t* test. In the case of FE_{Na}, if the Student *t* test was used, as if prerenal azotemia was compared without vs. with diuretics, then a very high statistical significance would have been found ($P = 0.0004$). However, when an ANOVA and a Bonferroni *t* test were employed, this comparison just fails to reach signicance. In the case of U/P_{Cr} the ANOVA was significant but only PR against ATN reached statistical significance by the Bonferroni *t* test.

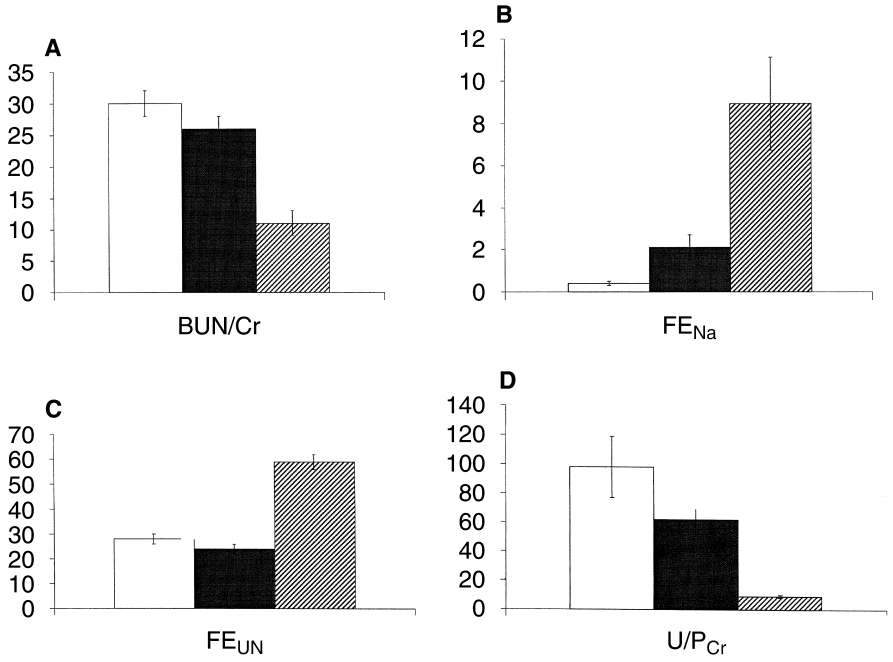

Fig. 1. Levels of blood urea nitrogen/creatinine (BUN/Cr; *A*), fractional excretion of sodium (FE_{Na}; *B*), fractional excretion of urea nitrogen (FE_{UN}; *C*), and urinary plasma to creatinine ratio (U/P_{Cr}; *D*) are schematically represented for each category of acute renal failure. BUN/Cr and U/P_{Cr} are ratios and have no units. FE_{Na} and FE_{UN} are expressed as %. Please note that FE_{UN} is similar among prerenal patients, irrespective of their use or nonuse of diuretics. Note a rather substantial variability with other indices.

(ANOVA) was used when more than two groups were evaluated. Comparison among the groups was tested using the Bonferroni-corrected *t* test. In paired experiments between two groups, the paired Student *t* test was used. Linear regression was calculated by using the least squares method and the Pearson product moment analysis. All tests were performed using Sigma Stat®, a statistical software program of the Jandel Corporation (Corte Madera, CA, USA). In tests presented in nominal (categorical) form, we determined the sensitivity, the specificity, the positive predictive value, and the negative predictive value. These tests also were compared by using the receiver operated characteristic (ROC) curves [22].

RESULTS

The patients were divided into three groups. The first group was composed of 50 patients with prerenal failure, the second group had 27 patients with prerenal azotemia but also given diuretics (furosemide), and the third group had 25 patients with established ATN. The indices evaluated in ARF are shown in Table 2. It is clear that while FE_{Na} was characteristically low (<1%) in the prerenal group, it was substantially higher than 1% in both the prerenal group given diuretics and the ATN group. In contrast, the increased BUN/creatinine ratio, the urine-to-plasma creatinine ratio (U/P_{Cr}) and, more impressively, the FE_{UN}, were consistently different in both prerenal groups from those in the ATN group (Fig. 1). Indeed, the FE_{UN} was essentially identical in the two prerenal groups (27.9 ± 2.4% vs. 24.5 ± 2.3%), significantly different from the FE_{UN} found in ATN (58.6 ± 3.6%, $P < 0.0001$).

Table 3 and Figure 2 show the importance of the indices in patients in whom a given test was positive. It appears that FE_{Na}, FE_{UN}, and U/P_{Cr} are the indices that discriminate best among the different types of acute renal failure. While 92% of the patients with prerenal azotemia had a FE_{Na} <1%, only 48% of patients who were prerenal and on diuretic therapy had a low FE_{Na}. By contrast, 89% of this latter group had a FE_{UN} <35%. If one combines all

Table 3. Number of patients with positive urinary indices in each ARF group

ARF type	BUN/Cr (>15)	U_{Na}/K (<1)	FE_{Na} (1%)	FE_{UN} (<35%)	U/P_{Cr} (>20)
PR	44/50	40/50	46/50	45/50	45/50
PR-diur	23/27	11/27	13/27	24/27	17/27
Pr total	67/77	51/77	59/77	69/77	62/77
ATN	5/25	2/25	1/25	1/25	3/25

Abbreviations are the same as in Table 1. PR total represents the entire prerenal group to include both the traditional prerenal subjects as well as the ones prescribed diuretics.

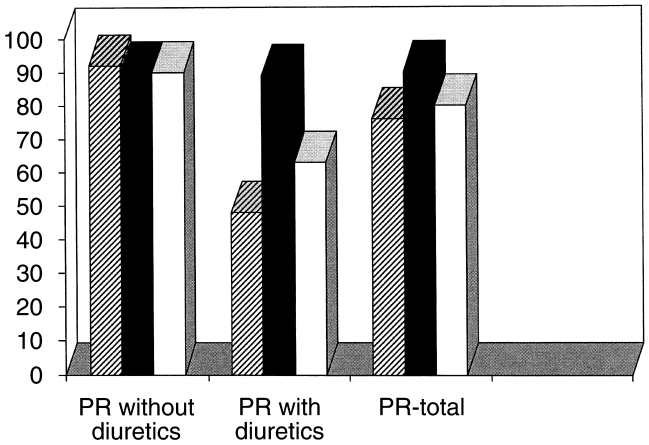

Fig. 2. Sensitivity of the three major indices for patients with prerenal situations with or without diuretic use, and patients with ATN. The units shown on the vertical axis represent %. Please note that while all three indices are equally effective in patients with prerenal situations who did not use diuretic therapy, only FE_{UN} retains its high sensitivity even in prerenal patients who use diuretics. Symbols are: (▨) FE_{Na}; (■) FE_{UN}; (□) U/P_{Cr}.

Table 4. Number of patients at different levels of the three most significant indices

	PR	PR-diur	PR total	ATN
	N (%)			
FE_{Na}				
<0.6	39/50 (78)	7/27 (26)	46/77 (60)	0/25 (0)
<0.8	45/50 (90)	11/27 (41)	56/77 (73)	1/25 (4)
<1.0	46/50 (92)	13/27 (48)	59/77 (77)	1/25 (4)
<1.2	47/50 (94)	18/27 (67)	65/77 (84)	2/25 (8)
<1.5	47/50 (94)	19/27 (70)	66/77 (86)	5/25 (20)
<2	48/50 (96)	20/27 (74)	68/77 (88)	7/25 (28)
<3	50/50 (100)	22/27 (81)	72/77 (94)	11/25 (44)
FE_{UN}				
<30	31/50 (62)	18/27 (67)	49/77 (64)	1/25 (4)
<35	45/50 (90)	24/27 (89)	69/77 (90)	1/25 (4)
<40	46/50 (92)	25/27 (93)	71/77 (92)	5/25 (20)
<50	49/50 (98)	27/27 (100)	76/77 (99)	8/25 (32)
U/P_{Cr}				
>40	30/50 (60)	12/27 (46)	42/77 (55)	0/25 (0)
>30	38/50 (76)	15/27 (56)	53/77 (69)	0/25 (0)
>20	45/50 (90)	17/27 (63)	62/77 (81)	2/25 (8)
>15	45/50 (90)	22/27 (81)	67/77 (87)	2/25 (8)
>12	46/50 (92)	23/27 (85)	69/77 (90)	5/25 (20)
>10	49/50 (98)	24/27 (89)	73/77 (95)	8/25 (32)

Please note that the absolute numbers and % represent the cumulative numbers at this level and not the number of cases between two levels. For example, the presence of 1 out of 25 patients with ATN at FE_{UN} <35% indicates the presence of one such patient with FE_{UN} between 0 and 35%, and not an additional patient between 30 and 35%.

the prerenal cases, FE_{UN} had the best sensitivity and specificity (90 and 96%, respectively), and the best positive and negative predictive value (99 and 75%, respectively) of all the indices examined in this study.

Table 4 evaluates the positivity of different levels of the three most important indices in patients with acute renal failure. Again, when examining the combined prerenal group compared with that of ATN, FE_{UN} was the best discriminatory index. For instance, a FE_{Na} of less than 1% was present in 77% of prerenal patients and in about 4% of patients with ATN, while FE_{UN} <35% was found in 90% of prerenal patients and again in 4% of patients with ATN. U/P_{Cr} appears to be an intermediate differentiator. When a ratio higher than 15 was used as the cutoff value, 90% of patients with prerenal azotemia were positive, with only a small number of patients with ATN having such a level (8%). Figures 3 and 4 show the ROC curves for these data.

We evaluated the equations that describe the relationship between the FE_{UN} and U/P_{Cr} in our subjects. This was based on previous findings regarding such a relationship (see discussion below for details). We found major differences among the different groups. In prerenal azotemia, $FE_{UN} = 27.9–0.029\ (U/P_{cr})$, $r = 0.28$, $P = 0.015$, and was similar for the two groups of prerenal patients (prerenal alone or prerenal in the presence of diuretic therapy). In patients with ATN a very different relationship was noted: $FE_{UN} = 70.3–1.26\ (U/P_{Cr})$, $r = 0.439$, $P = 0.028$, consistent with very different mechanisms of the generation of such a relationship.

Finally, the predicted FE_{UN} was examined using Dole's equation as described in the **Methods** section. In the prerenal patients, the expected FE_{UN} was 25 ± 4% and 22 ± 4% for the prerenal group without and with diuretic use, respectively. These values were not statistically different from the ones actually found (27 ± 2% and 24 ± 3%, respectively), suggesting that indeed the mechanism for the decreased volume (decreased renal perfusion and increased water reabsorption) also was responsible for the decreased excretion of urea. In contrast, in the cases of ATN the calculated FE_{UN} was very different from the one actually determined (18 ± 3% vs. 58 ± 6%, $P <$ 0.0001), suggesting that the oliguria found in this condition is not related to reabsorption of water and urea from functional tubules, but rather due to minimal glomerular filtration through injured nephrons.

DISCUSSION

When urine excretion decreases as a result of water reabsorption, the level of urinary creatinine increases in

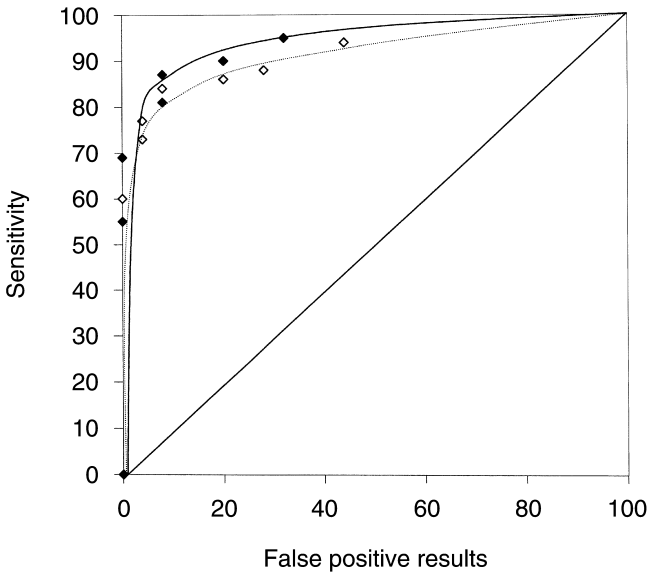

Fig. 3. Sensitivity and false positivity of different cut of levels are plotted for FE_{Na} (◇) and U/P_{Cr} (◆). The levels used are the same that are shown for the two parameters in Table 3. Sensitivity was defined by the % of patients who were positive for prerenal (either with or without diuretics) at a given level of each test. False positive was defined as the % of patients with ATN who had pre-renal values for any level.

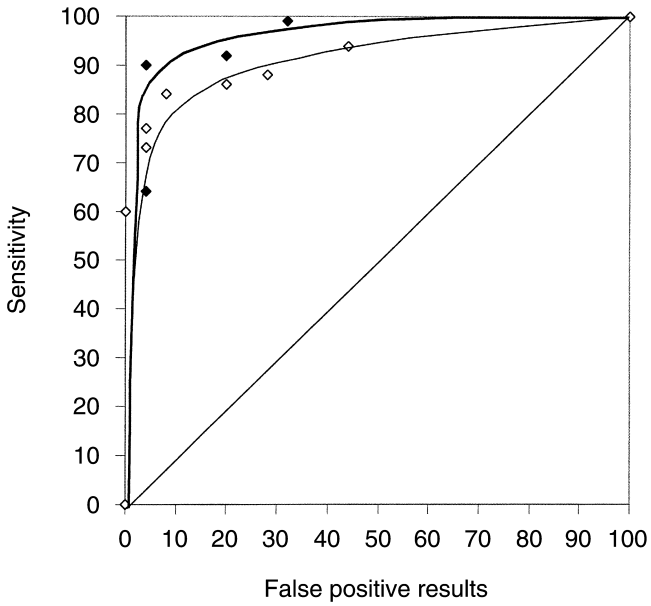

Fig. 4. Sensitivity and false positivity of different cut of levels are plotted for FE_{UN} (◆) and FE_{Na} (◇). The levels used are the same that are shown for the two parameters in Table 3. Sensitivity was defined as the % of patients who were positive for prerenal (either with or without diuretics) at a given level. False positive was defined as the % of patients with ATN who had prerenal values for any level. While the area under FE_{UN} is 97.2%, that under FE_{Na} is significantly less (88.9%).

inverse proportion to the volume of urine output. Thus, the U/P creatinine ratio logically identifies whether oliguria is the result of increased water reabsorption, as in the case of prerenal situations (U/P_{Cr} >20) or is due to the loss of nephron function (U/P_{Cr} <20) [21]. As is often appreciated, sodium reabsorption also increases in prerenal states both as a result of an increase in aldosterone as well as the increased sodium and water reabsorption in the proximal tubule because of the increased filtration fraction found in such cases. A composite index has been developed and used clinically that incorporates both U/P_{Cr} and U_{Na}, the FE_{Na}. Following the initial report of Espinel [4], which showed that FE_{Na} discriminates best between the two most commonly encountered forms of ARF (prerenal and ATN), several subsequent reports substantiated this claim [1–4]. Currently it has become the dominant discriminatory index used for that purpose. On the other hand, coexistence of a prerenal state and natriuretic agents (diuretics) negate the effectiveness of this index [1]. Diuretics represent the mainstay of treatment for several prerenal states and may themselves produce volume depletion due to their natriuretic effect (even if given to initially euvolemic patients). Furthermore, these agents are used commonly in the hospital and even more in the intensive care unit, thus significantly decreasing the utility of FE_{Na} in the hospital setting. Hence, FE_{Na} does not give a clear-cut distinction in such cases. In addition to the use of diuretics, other situations are known to lead to both prerenal azotemia and increased FE_{Na}. Better understood among them is the case of volume depletion due to vomiting or nasogastric suction associated with increased FE_{Na} due to bicarbonaturia [18]. On the other hand, a number of clear-cut forms of ATN are associated with decreased FE_{Na}, for example: myoglobinuria [6, 7], sepsis [8], contrast nephropathy [11–13], obstructive uropathy [15], and non-oliguric ATN [2, 3, 5]. Low FE_{Na} also is found in other forms of acute intrinsic renal failure including acute glomerulonephritis [2, 3], urinary tract obstruction [2], and renal allograft rejection [2]. To emphasize the frequency with which patients with intrinsic acute renal failure have FE_{Na} <1%, suffice it to say that in a five year-period (1980 to 1985) more than 100 cases of documented ATN with FE_{Na} <1% were found in the published literature alone [17].

The relative clearance of urea denoted by the FE_{UN} is affected by decreased renal perfusion as seen in prerenal states. As early as 1921, Austin, Stillman and Van Slyke showed that the clearance of urea in man decreases substantially in dehydration somewhat proportionally to urine output [23]. In 1938, two seminal studies established that FE_{UN} relates inversely to U/P creatinine [24] and U/P inulin [25, 26], and therefore proportionally to urine volume. This was the classical teaching in renal physiology during that era [27, 28]. More recently, Goldstein, Lenz and Levitt evaluated the relationship of urine volume to urea excretion in humans [29]. Using proximal

and distal diuretic agents, they found that the percent of filtered urea excreted increased with proximal (mannitol and acetazolamide) but not with distal agents (mercaptomerin and ethacrynic acid). This suggests that urea is not reabsorbed significantly in the distal nephron. Given that most of the diuretics used clinically work at distal sites, FE_{UN} should not be affected by their use. This is in contrast to FE_{Na}, which is increased by all forms of diuretics. Only in patients with established chronic renal failure does the use of diuretics and the ensuing volume depletion also operate in distal sites [30], a finding with limited significance in the differential diagnosis of ARF.

In 1992, Kaplan and Kohn reported six prerenal patients with a discrepancy of FE_{UN} and FE_{Na} in the presence of diuretics [31]. In addition to the small number, most of those patients already had established renal failure, congestive heart failure and various treatments with angiotensin-converting enzyme inhibitors. The authors, in order to better understand the situation, retrospectively evaluated the charts of 87 patients with prerenal azotemia. They noted that the patients that had both low FE_{Na} and FE_{UN} had the usual type of prerenal azotemia. The group with low FE_{UN} but high FE_{Na} appeared to have prerenal azotemia but had been treated with a diuretic (39 out of 40). The authors concluded that FE_{UN} may be a better index to evaluate possible prerenal status in patients who receive diuretic agents.

We prospectively studied three groups of patients: patients with prerenal azotemia, patients with prerenal conditions receiving diuretics, and patients with acute tubular necrosis (ATN). We found that FE_{Na} failed to discriminate between prerenal patients given diuretics and those with ATN. FE_{UN}, on the other hand, was excellent in discriminating among all cases of prerenal azotemia and ATN irrespective of the use of diuretics. This has a potentially major practical application, given the frequency of diuretic use in the hospital setting. For instance, among our 77 unselected prerenal cases, 27 (35%) had been given diuretics.

Our study found that U/P_{Cr} is higher in prerenal cases, as has been shown before and as expected from the underlying physiology. Indeed, it appears that U/P_{Cr} is at least as good as FE_{Na} in separating prerenal azotemia from ATN. As was previously reported [24–28], there was a close inverse relationship between U/P_{Cr} and FE_{UN} in the prerenal group. This relationship was very different in the group with ATN. Furthermore, the prerenal patients appear to follow the prediction of Dole [19] in reference to expected FE_{UN} based on urine output. In short, these patients behaved the same way as a normal individual with decreased fluid intake and thus decreased urine output. In contrast, urine volume could not account for the FE_{UN} found in the ATN group.

We found that FE_{UN} has a high sensitivity (85%) a high specificity (92%) and more importantly a high positive predictive value (98%). The latter suggests that if a FE_{UN} of $<35\%$ is found, 98% of such cases will have prerenal azotemia. The relative importance of FE_{UN} to FE_{Na} would have been more impressive if our ATN patients had had some of the characteristics described in the literature. For example, low FE_{Na} is often found in patients with myoglobinuric ATN [6, 7]; however, in our study none of the six patients with well-documented myoglobinuria (history and urine analysis positive for myoglobin) had an FE_{Na} value less than 1. If the value had been greater, then the false-positive cases of low FE_{Na} in identifying pre-renal azotemia would have been even higher.

Fractional excretion of urea nitrogen to a great extent relates inversely to the proximal reabsorption of water. Proximal reabsorption of water (accompanied by urea) increases when renal perfusion decreases and filtration fraction increases. Thus, urea reabsorption leads to a decrease in FE_{UN} and an increase in the BUN/creatinine ratio. The use of indices that reflect proximal tubular function in acute renal failure have been suggested before. A recent textbook of nephrology suggests two such indices, the clearance of lithium and the clearance of uric acid [32]. It is apparent that the use of lithium clearance is quite impractical, given the limited availability of this determination in many laboratories and the need to administer lithium to such patients. Uric acid clearance does not appear to have any advantage over the use of urea, due to its rather complex renal metabolism.

It is certainly interesting, that if we modify the formula for $FE_{UN} = (U/P)UN/(U/P)Cr$, it becomes $FE_{UN} = U \cdot (UN/Cr)/(BUN/Cr)$, or even, $BUN/Cr = U\ (UN/Cr)/FE_{UN}$. This suggests that as proximal urea reabsorption increases and FE_{UN} decreases in prerenal states, the BUN/Cr ratio increases, as is the common teaching and is our own experience in the present study (Table 2). Another cause of increased BUN/Cr is increased urea production (and thus excretion), as in cases of hypercatabolism or consumption of high protein diets. This could be easily differentiated from prerenal azotemia, as in high urea production we have a high urine UN/Cr, much higher than the usual ratio of 5 to 10. The determination of urine urea nitrogen and FE_{UN} may be helpful in a few other conditions. For instance, the presence of a BUN/Cr ratio of 10 in the presence of a low U_{UN}/U_{Cr} (<5) suggests the existence of prerenal azotemia in a starving individual.

There are situations, however, where FE_{UN} may fail to indicate the ongoing prerenal status. Therefore, such possibilities should be kept in mind when FE_{UN} is used. For instance, in osmotic diuresis the proximal tubular absorption of salt and water is impaired and thus increased FE_{UN} is expected despite renal hypoperfusion. One of us (C.P.C.) has looked into this while working on another study (abstract; Vafadouste R et al, XV International Congress of Nephrology, Buenos Aires, Argentina, p 1999, 2001). In ten patients with osmotic diuresis

there was a mild increase of BUN (23 ± 3.3 mg/dL) with normal serum creatinine (0.9 ± 0.1 mg/dL), increased BUN/Cr to 27 ± 3, increased FE_{UN} 49 ± 8%, high normal FE_{Na} 0.7 ± 0.3% and high U/P_{Cr} of 41 ± 10. The same phenomenon is expected to happen when osmotic diuretics such as acetazolamide and mannitol are used. Indeed, this was our finding during that study. Similar findings also were reported before [29]. A similar picture emerges in patients given a high protein diet or having excessive catabolism. There, the enormous production of urea acts as the osmotic diuretic agent. On the other hand, FE_{UN} could be helpful in cases with prerenal azotemia in combination with a distal defect in sodium reabsorption. We recently encountered a young male with AIDS and Addison's disease. He had apparent volume depletion with dramatic changes in blood pressure and pulse rate with even the mildest tilting maneuvers. His BUN/Cr was high (84/2.3), and he had a high FE_{Na} (>2%), a FE_{UN} of 35% and a U/P_{Cr} of 27. This patient responded promptly to vigorous saline infusion, indicating that his major problem was that of volume depletion in the presence of impaired distal tubular Na^+ reabsorption.

Although FE_{UN} proved to be the best index under the clinical conditions encountered in our study, one must remember that none of the indices offers a 100% discriminatory ability. The three major indices allow evaluation of different sites of action, and differ in the technology needed for their determination, thus making it unlikely to have simultaneous laboratory errors in all of them. FE_{UN} allows insight to proximal peritubular forces, FE_{Na} mostly reflects distal forces (mostly aldosterone-dependent sites), and U/P_{Cr} indicates water reabsorption through the length of the nephron. Indices are tools and do not obviate the importance of history, physical examination, and direct urinalysis in making a diagnosis of acute renal failure.

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