Journal of Critical Care 48 (2018) 90–96

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Urine electrolyte measurement as a "window" into renal microcirculatory stress assessment in critically ill patients

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ARTICLE INFO

Available online xxxx
Keywords:
Urine electrolytes
Microcirculation
Acute kidney injury
Monitoring

ABSTRACT

Urine electrolyte assessment has long been used in order to understand electrolyte concentration disturbances in blood and as an easy tool for monitoring renal perfusion and structural tubular damage. In the last few years, great improvement in the pathophysiology of acute kidney injury (AKI) has occurred, and the correlation between urine biochemistry (UB) behavior and renal perfusion was frequently questioned. Many authors have suggested abandoning UB monitoring due to its unclear role in AKI monitoring. Our group has been working in this field in the critically ill population, and we believe that, although UB is indeed very useful, a different point of view regarding the interpretation of the data should be used. The aim of this review is to explain the rationale of these new concepts and make suggestions for their adequate use in daily ICU practice, especially in low-income countries where more sophisticated and expensive AKI biomarker assessments are not available.

1. Introduction

Acute kidney injury (AKI) is a major concern in critically ill patients, and its pathophysiology is still not completely elucidated. It is clear, however, that microcirculatory impairment is one of the main components of AKI development through disturbed homeostasis between nitric oxide, reactive oxygen species and renal oxygenation [1,2]. Cellular and microvasculature disturbances may in fact lead to oliguria and increases in serum creatinine (sCr) even in the presence of adequate (or even increased) global renal blood flow (RBF), especially in inflammatory states [1]. Intrarenal shunts, afferent arteriole vasoconstriction and predominant efferent arteriole vasodilation are some possible mechanisms of altered glomerular filtration rate (GFR) despite optimized cardiac output and renal perfusion [3].

Most physicians still make a straightforward association between AKI (or oliguria) and impaired renal perfusion in common critical scenarios such as postoperative and sepsis, in which an inflammatory state may dissociate macro- and microhemodynamics. Experimental studies with endotoxin-induced sepsis have demonstrated AKI development despite progressively increased RBF [4]. Since RBF is not currently a parameter easily assessed at the bedside in most ICUs, physicians are usually unaware of the real situation at the renal intimacy, and guide its management based on global perfusion markers, such as arterial blood pressure, cardiac output, lactate and urine output (UO). The "culture" of oliguria-based fluid infusion is particularly dangerous, leading frequently to unnecessary positive fluid balance and its harmful consequences, such as pulmonary edema, metabolic ileus and paradoxical worsening oliguria due to renal venous congestion and hyperchloremia-induced renal vasoconstriction [5-7].

There is still neither an easy way to evaluate renal microcirculation nor an available biomarker to signal its impairment. Oliguria itself is likely more representative of renal microcirculatory stress than reduced global RBF in most situations. It is important to emphasize that subtle and clinically imperceptible microcirculatory changes may precede frank circulatory shock in systemic inflammatory states, such as in sepsis. We could previously observe this phenomenon using sublingual capnometry, in which a hyperdynamic status (progressive increases in cardiac output) due to sepsis was followed by progressive increases in sublingual PCO_2, suggesting paradoxical microcirculatory stagnation [8]. In our ICU practice, we frequently observe septic patients developing oliguria before becoming hypotensive or having other markers of hypoperfusion, which is a clinical indicator that may signal a predominance of microcirculatory impairment in oliguria development, thus contrasting with the classic view of renal ischemia due to renal hypoperfusion [9].

2. Oliguria: a clinical sign of renal microcirculatory stress

Oliguria is not a single entity. There are some types of oliguria that are more "benign" than others, even considering the same UO. Indeed, oliguria is physiological and expected in certain circumstances, while clearly pathological in others. We may call this "adapted" and "non-adapted" oliguria. Discrimination between these two entities is not always easy to define clinically. In addition, the relation between decreases in UO and increases in sCr is complex, and involves urine

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https://doi.org/10.1016/j.jcrc.2018.08.011
0883-9441/

creatinine concentration (CrU) and creatinine production [10]. A decrease in UO is not always followed by increases in sCr, and increases in sCr may occur despite normal or even increased UO ("non-oliguric AKI").

We believe that urine electrolyte composition is a crucial parameter that can improve renal function monitoring and oliguria interpretation. In our opinion, a great mistake for decades was considering urine electrolytes (particularly sodium) to be a marker of global RBF and perfusion [11]. Urine biochemistry must be evaluated for monitoring renal microcirculation because it is a result of the interaction between glomerular hemodynamics and tubular function, both of which are not mandatorily related to RBF and perfusion.

3. Avid sodium retention as a marker of renal microcirculatory stress, not renal perfusion

In the well-known "pre-renal paradigm" [12], avid sodium retention leading to low fractional excretion and low sodium concentration in urine (NaU) is associated with low renal perfusion, and many clinicians implement measures such as fluid challenge or inotropic infusion to improve it. Notably, except in cases where microcirculatory impairment is a function of macrocirculatory impairment, as in hypovolemia, these measures are usually ineffective and harmful. We would like to change this old paradigm [11,12]. In critically ill patients, who frequently receive great sodium charge in medication dilution and maintenance/resuscitation fluids [13], low NaU levels represent a marker of renal microcirculatory stress, which usually precedes AKI and may be a result of low renal perfusion, although it frequently is not. Intrarenal alterations due to inflammation, oxidative stress and shunts may activate avid sodium-retaining mechanisms independent of global renal perfusion [11].

4. High natriuresis as a sign of absent or resolved inflammation

High NaU values, previously interpreted as acute tubular necrosis [14], are actually a specific marker of normal or improving renal function when greater than serum sodium values [15]. Such high NaU values are, in our point of view, a sign of absence of significant microcirculatory stress and/or resolution of inflammation. Indeed, this finding usually parallels clinical improvement, decreases in C-reactive protein and hemodynamic recovery [16]. It is probably the result of high GFR and deactivated sodium-retaining mechanisms, which characterize "non-stressed kidneys". Unfortunately, it is not very sensitive, and thus, the absence of very high NaU levels does not exclude normal renal function, although such levels are expected in the presence of the combination of high sodium load and unimpaired microcirculation.

5. Urine sodium: a continuous, not categorized, parameter

A single assessment of NaU level is a frequent cause of misinterpretation [17]. Except for extreme values (very high is usually good, and very low is usually bad), the trend in NaU level is more relevant and informative than an isolated value. Abrupt decreases usually sign for renal microcirculatory stress development. The use of the classic cut-offs 20 and 40 mEq/L of NaU to define functional (transient) or structural (persistent) AKI [14] is an outdated concept. In fact, there seems to exist a continuum between these two points in the AKI spectrum, where the latter is usually a more severe presentation of the same pathophysiological process than the former [18]. NaU is expected to decrease from normal values (approximately 100 mEq/L) [19] towards very low levels during AKI development; the magnitude of this change depends on the balance between decreased GFR, renin-angiotensin-aldosterone activation and tubular damage. Such damage is responsible for the inability to reabsorb sodium in the late stages of AKI leading to increases in NaU. Of note, such pathologically increased NaU is usually substantially lower than the very high levels observed in "non-stressed kidneys" [17], mainly because there is less tubular sodium availability due to less glomerular filtration of sodium as well as simultaneous sodium backleak out of tubular lumen.

6. Fractional excretion of potassium: combining blood and urine for the accurate measurement of renal microcirculatory stress and serum creatinine behavior

In addition to sodium retention, another valuable marker of renal microcirculatory stress development is an increase in the fractional excretion of potassium (FEK) [20]. Increases in FEK usually precede increases in sCr [17,20], and is inversely related to GFR, a phenomenon that helps avoid life-threatening hyperkalemia until late stages of AKI [21]. It is particularly useful when sCr is still normal. Considering normal values of serum potassium (sK) and sCr (both part of FEK calculation), the remaining variables are urine K concentration (KU) and CrU. The KU/CrU ratio is particularly important because it is a practical tool to evaluate creatinine excretion adequacy (Fig. 1). KU is usually inversely related to UO: low UO is associated with high KU, whereas high UO is associated with low KU [22]. This is an interesting finding since tubular flow is one of the main determinants of K excretion. Hence, high tubular flow increases K excretion but is not due to increases in the KU. Occasionally, we observe a high KU despite a normal or increased UO. Most of these findings were postoperative, and such high KU and FEK values usually indicate renal microcirculatory stress independent of the presence of oliguria.

7. "Adapted" versus "non-adapted" oliguria: the role of the KU/CrU ratio and FEK

The CrU behavior in comparison to KU can determine if creatinine excretion is adapted to UO. A high CrU could be a result of high creatinine excretion (considering normal sCr level) or can merely be due to a low urine volume. If CrU (in mg/dL) is proportionally low in relation to KU (in mEq/L), it means that creatinine excretion is not adapted to UO and a high FEK is observed, thus indicating an increased risk of AKI. In contrast, if CrU is proportionally high in relation to KU, creatinine excretion is adapted to UO, even in cases of oliguria, suggesting a more benign course and lower or even no subsequent increases in sCr. In our experience, a KU/CrU lower than or equal to 0.5 is indicative of good equilibrium between UO and creatinine excretion.

Considering that normal FEK is approximately 10% [23], a patient who has a sCr of 1.0 mg/dL and a sK of 4 mEq/L must have a KU/CrU of 0.4 (or lower) to have FEK of 10% (or lower). For instance, if the FEK is 20%, this means that KU/CrU is 0.8, thus indicating that creatinine excretion is not adapted to UO, and this finding precedes increases in sCr. In other words, we would expect a higher creatinine excretion for this rate of UO.

In postoperative patients, an increased FEK is frequent at ICU admission as a surrogate of surgery-induced renal microcirculatory stress

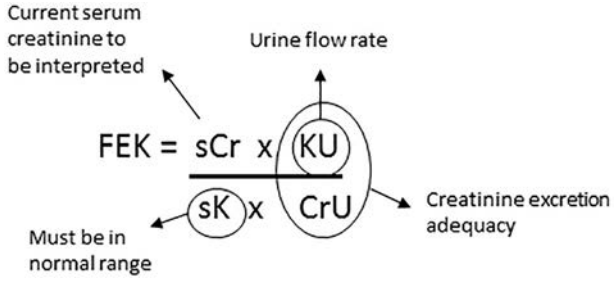

Fig. 1. Relevant information obtained from FEK assessment, facilitating a more timely interpretation of current sCr. See the text for more detailed information about each component of the formula. sCr: serum creatinine; sK: serum potassium; KU: urine potassium concentration; CrU: urine creatinine concentration; FEK: fractional excretion of potassium.

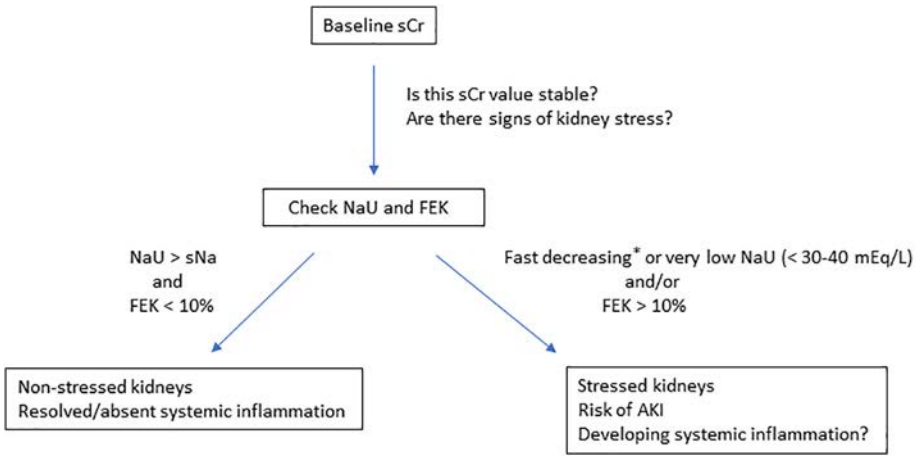

Fig. 2. The importance of simultaneous urine biochemistry assessment in order to diagnose renal microcirculatory stress, which usually precedes overt AKI. *A rapid decrease in NaU is usually regarded as a reduction by greater than 50% within a few hours. sCr: serum creatinine; sNa: serum sodium; NaU: urine sodium concentration; FEK: fractional excretion of potassium; AKI acute kidney injury.

[24,25]. Most of these patients have normal sCr and sK, and thus the increased FEK is a function of a high KU/CrU ratio. This could happen in the absence or presence of oliguria. In our point of view, the KU/CrU ratio is more relevant than oliguria itself. A "benign" ("adapted") oliguria could be defined as oliguria with a low KU/CrU ratio. Since KU is increased in oliguria, "benign" oliguria has a very high CrU in order to counterbalance KU and keep KU/CrU at low levels (usually lower than 0.5). This is a frequent, self-limited situation in oliguric postoperative patients, and increases in sCr, if they occur, are usually only subtle and transient because no major decreases in creatinine excretion occur (a benign course).

On the other hand, a decrease in FEK in patients with an increased sCr level may be a marker of recovery. Mathematically, an increase in sCr leads to an increase in FEK (Fig. 1). Therefore, considering a stable sK value, a decrease in FEK must be a result of major decreases in KU/CrU. As previously mentioned, low KU/CrU ratio is usually a sign of adequate or improved creatinine excretion, leading to subsequent decreases in sCr. However, KU/CrU ratio and FEK data must be interpreted carefully in the presence of high levels of sCr because the creatinine excretion rate is the product of sCr concentration and creatinine clearance. Consequently, increases in CrU may be a result of increased creatinine clearance but may also merely be a result of significantly increased sCr [26]. In these cases, FEK is a better tool than KU/CrU ratio because both sCr and CrU are evaluated simultaneously and because an increased CrU is (at least partially) counterbalanced by an increased sCr (Fig. 1).

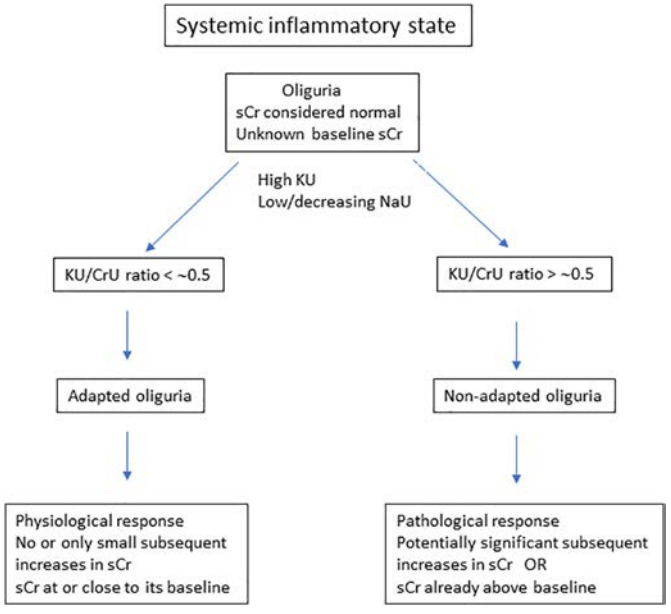

Fig. 3. Urine biochemical profile distinguishing cases of systemic inflammation-induced adapted and non-adapted oliguria. sCr: serum creatinine; KU: urine potassium concentration; NaU: urine sodium concentration; CrU: urine creatinine concentration.

A major advantage of simultaneous blood and spot urine sample evaluation is that it allows a more dynamic and real-time interpretation of sCr data, because isolated sCr interpretation is delayed in comparison to ongoing GFR (Fig. 2). An increased KU/CrU ratio in the presence of a theoretically normal sCr may be interpreted as "stressed kidneys", which is a step that precedes AKI, or it may also suggest that the present sCr value is above the unknown baseline sCr of the patient so that this "normal" sCr might actually be existing AKI (Fig. 3). The real baseline sCr would only be known after normalization (decrease) in KU/CrU ratio and the subsequent decrease in sCr level. Very low KU/CrU is observed only in recovering kidneys or "non-stressed kidneys" (Fig. 4).

It is noteworthy that KU/CrU ratio is a classic tool for the investigation of hypokalemia. To our knowledge, we were the first to propose its utility as an AKI monitoring tool in critically ill patients with sK and sCr in their normal ranges.

8. Medications that interfere with the urine electrolyte measurement and data interpretation

Diuretics are by far the medications that interfere most with the interpretation of urine electrolyte data. Furosemide, the most frequently prescribed diuretic in ICUs, increases the NaU and decreases the KU in parallel with increases in UO. As mentioned above, the KU (not K excretion!) is usually inversely correlated with UO. Therefore, the avid sodium retention, which is a marker of renal stress, may be artificially blocked with furosemide. On the other hand, FEK increases with furosemide [27], but in this context, it does not correlate with decreases in GFR or increases in renal stress. We have observed that these effects are transient and a new urine assessment some hours (preferably, at least 12 h) after diuretic administration could reveal the real status of renal stress (avid sodium retention) [28]. A low natriuretic response to loop diuretics is a sign of poor prognosis in heart failure [29] and likely in any other avid sodium retaining situation, such as sepsis-induced AKI and hepatorenal syndrome in advanced hepatic cirrhosis.

Renin-angiotensin-aldosterone (RAA) system is responsible for many pathophysiological alterations that occur in glomerular hemodynamics and tubular handling of electrolytes. Activation of this system seems to explain most of the urine biochemistry alterations that

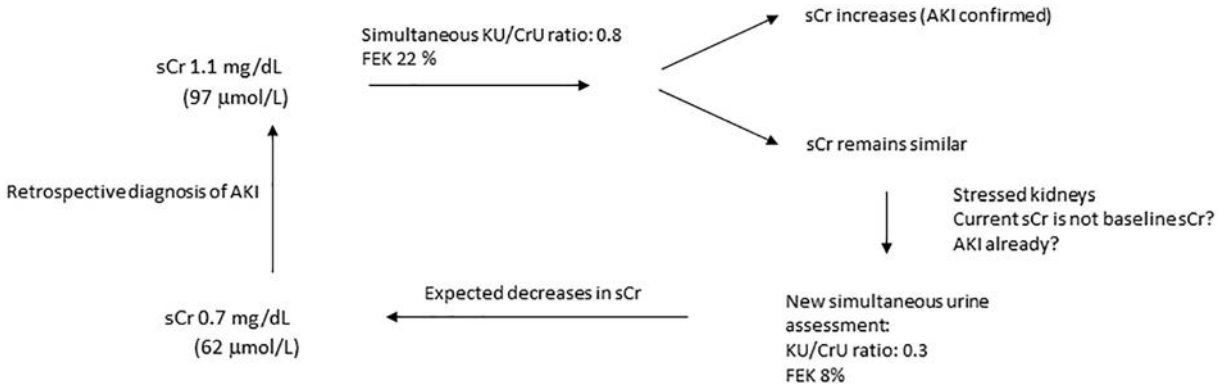

Fig. 4. Hypothetical case of the utility of assessing FEK and KU/CrU ratio for the correct interpretation of the current sCr level and expected subsequent trend in sCr. Note that the interpretation of a sCr level of 1.1 mg/dL is completely different according to the simultaneous urine biochemical profile. Serum K is considered 4 mEq/L. sCr: serum creatinine; KU: urine potassium concentration; CrU: urine creatinine concentration; FEK: fractional excretion of potassium.

ultimately characterize "renal stress". Medications that block this system, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are helpful in reducing blood pressure and attenuating avid sodium retention, as occur in heart failure. However, in critically ill and unstable patients, their use is more restricted due to concerns regarding their potential to significantly decrease blood pressure and renal function as well as induce hyperkalemia. Although is not well-established that such hyperkalemia is a result of decreases in FEK [30], urine electrolyte data interpretation in the presence of these medications must be performed carefully. Medications that also interfere with renal hemodynamics by inhibiting prostaglandin production, such as nonsteroidal anti-inflammatory drugs, may also act as confounders. Fortunately, for similar reasons to the RAA system blockers, these medications are usually not used in patients at increased risk of AKI development (the patients for whom we would like to monitor renal function more closely with FEK).

Other drugs that may interfere with FEK calculation and interpretation are those that reduce tubular secretion of creatinine, mainly at the proximal tubules (e.g., trimethoprim and salicylates) [31]. The resulting increase in sCr and decrease in CrU would lead to increases in FEK that are not directly related to decreases in GFR. Some drugs are also capable of modifying the creatinine production rate and release, making the sCr and FEK interpretation more difficult (e.g., corticosteroids). Medications that directly cause tubular injury (e.g., aminoglycosides) may affect sodium reabsorption, but simultaneous decreases in GFR (usually via tubuloglomerular feedback) lead to decreases in NaU levels.

It is important to emphasize that, except for diuretics, clear evidence for interference of all these medications with bedside interpretation of urine electrolyte data is lacking, and therefore, the real impact of their administration on urine biochemistry data interpretation is not currently known.

9. Is there enough evidence that urine biochemistry assessment is actually useful for kidney function monitoring in the critically ill?

Most of the recent literature using UB for kidney function monitoring in critically ill patients is based on small, single-center studies [15,22,24,32-34] as well as case reports [16,28,35]. Few studies have explored the dynamics of urine electrolytes using the concept of "renal microcirculatory stress monitoring" described above. Experimental and clinical studies with simultaneous evaluation of urine electrolytes as well as global RBF, renal microcirculatory oxygenation and perfusion (including optical techniques for direct visualization of microcirculatory vessels) will help to elucidate the complex pathophysiological changes of renal microcirculation that probably occur earlier than clinically evident AKI. This is of major relevance especially in systemic inflammatory states, such as postoperative and sepsis (still the most frequent cause of AKI in the ICU).

In addition, we still need to determine through future multicenter, prospective, randomized studies if routine urine electrolyte assessment will actually help diagnose AKI earlier or prevent AKI development to improve the prognosis of critically ill patients.

10. Conclusions

The relevance of urine biochemistry in acutely ill patients is currently undervalued, primarily because the old paradigm relates urine electrolytes to renal perfusion, which is an overly simplistic view of their potential utility. We propose a different view and interpretation of urine biochemical parameters that we believe could be very useful in daily AKI monitoring. Renal microcirculatory stress (which precedes AKI) induces changes in the urine biochemical profile, and its main utility seems to be when sCr is still in a normal range, in addition to its potential utility for anticipating AKI recovery. We hope to see more studies of different groups in this research area in order to confirm and improve our findings.

Declaration of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

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