Spot urine sodium in acute heart failure: differences in prognostic value on admission and discharge

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Abstract

Aims Most studies examined spot urine sodium’s (sUNa+) prognostic utility during the early phase of acute heart failure (AHF) hospitalization. In AHF, sodium excretion is related to clinical status; therefore, we investigated the differences in the prognostic information of spot UNa+ throughout the course of hospitalization for AHF (admission vs. discharge).

Methods and results The study population were AHF patients (n = 172), who survived the index hospitalization. We compared the relationship between early (on admission, at 24 and 48 h) and discharge sUNa+ measurements with post-discharge study endpoints: composite of 1 year all-cause mortality and AHF rehospitalization (with time to first event analysis) as well as with each event in separation. There were 49 (28.5%) deaths, 40 (23.3%) AHF rehospitalizations, while the composite endpoint occurred in 69 (40.1%) during 1 year follow-up. The sUNa+ had prognostic significance for the composite endpoint when assessed on admission, at 24 and at 48 h: hazard ratios (HRs) with 95% confidence intervals (CIs) (per 10 mmol/L) were 0.88 (0.82–0.94); 0.87 (0.81–0.91); 0.90 (0.84–0.96), all P < 0.005. In contrast to early, active decongestive phase, discharge sUNa+ had no prognostic significance HR (95% CI) (per 10 mmol/L): 0.99 (0.93–1.06) P = 0.79 for the composite endpoint, which was independent from the dose of oral furosemide prescribed at that timepoint (average causal mediation effects: −0.38; P = 0.71). Similarly, discharge sUNa+ was neither associated with 1 year mortality HR (95% CI) (per 10 mmol/L): 0.97 (0.89–1.05) P = 0.48 nor with AHF rehospitalizations HR (95% CI) (per 10 mmol/L): 1.03 (0.94–1.12), P = 0.56. The comparison of longitudinal profiles of sUNa+ during hospitalization showed significantly higher values within the early, active decongestive phase in those who did not experience composite endpoint when compared with those who did: admission: 94 ± 34 vs. 76 ± 35; Day 1: 85 ± 36 vs. 65 ± 37; Day 2: 84 ± 37 vs. 67 ± 35, all P < 0.005 (mmol/L), respectively. There was no difference between those groups in discharge sUNa+: 73 ± 35 vs. 70 ± 35 P = 0.82 (mmol/L).

Conclusions Spot UNa+ assessed at early phase of hospitalization and at discharge have different prognostic significance, which confirms that it should be always interpreted along with clinical context.

Keywords Acute heart failure; Spot urine sodium; NT-proBNP

Background Impairment of sodium/water homeostasis is one of the foundations of heart failure (HF) pathophysiology. Recent investigations focused on urine sodium excretion and its prognostic utility mainly during the early phase of acute HF (AHF) hospitalization.1–5 However, the interpretation of spot urine sodium (sUNa+) requires thorough approach given its relationship to diuretic administration, patient’s fluid volume status (the lower the volume, the lower sodium excretion—i.e. braking phenomenon), neurohormonal activity and possibly also the timing of hospitalization.6,7 Thus, we speculate that...
discharge spot UNa⁺ may have a different biological significance when compared with admission measurements.8

Aims

We sought to investigate the differences in the prognostic information of sUNa⁺ throughout the course of hospitalization for AHF (admission vs. discharge) in patients who survived index hospitalization.

Methods

This is a single-centre, prospective study that was run between January 2016 and September 2017. Apart from routine clinical assessments, all patients had sUNa⁺ measured on admission, 24 h, 48 h, and discharge, but treating physicians were blinded to the results. The detailed information regarding study conduction, exclusion criteria, urine collection, laboratory measurements and study procedures were presented elsewhere.2 As we excluded patients who died during the index hospitalization or had missing sUNa⁺ assessments on discharge the original cohort was narrowed from 219 to 172 patients.2 At Days 1 and 2 of hospitalization, we assessed the first morning urine samples after diuretic administration, not first morning void. Analogically, at discharge, patients received the morning oral furosemide first, and then the urine samples were collected. However, the exact time between diuretic administration and sampling was not recorded. For the purpose of the current study, we divided the AHF hospitalization into two phases:

- early/active decongestive phase [gross fluid overload and/or clinical congestion (from admission to Day 2)]
- discharge/stabilization phase (patients were classified as euvolemic based on clinical assessment by the treating physicians and discharged home).

The endpoints of the study were the composite of all-cause death or HF rehospitalization within 1 year of index hospitalization, whichever occurred first and each of two events in separation (all-cause death and HF rehospitalization). Cox proportional-hazards regression models in time to first event manner for each endpoint was performed. The hazard ratios (HRs) with 95% confidence intervals (CIs) for sUNa⁺ are presented per 10 mmol/L. To examine the impact of dose of

| Parameter                              | Admission | Discharge | P     |
|----------------------------------------|-----------|-----------|-------|
| Sex (male)                             | 127 (74%) |           |       |
| Age (years)                            | 70 ± 13   |           |       |
| Left ventricle ejection fraction (%)   | 37 ± 14   |           |       |
| Acute heart failure (de novo)          | 76 (44%)  |           |       |
| Heart failure aetiology                |           |           |       |
| Ischaemic                              | 92 (54%)  |           |       |
| Hypertension                           | 80 (46%)  |           |       |
| Heart rate (beat/minute)               | 92 ± 25   | 74 ± 10   | <0.0001|
| Systolic blood pressure at admission (mmHg) | 135 ± 32  | 119 ± 17  | <0.0001|
| Diastolic blood pressure at admission (mmHg) | 80 ± 16   | 71 ± 10   | <0.0001|
| Dyspnoea                               | 8.2 ± 2.1 | 2.3 ± 2.2 | <0.0001|
| Oedema no/+/++/+ ++                   | 50/40/43/39 | 143/25/3/1 | 0.05  |
| NYHA I/II/III/IV                       | 0/2/43/127 | 28/113/30/1 | <0.05  |
| Pulmonary congestion no/<1/3/1/3–2/3/2/3 | 15/96/41/20 | 152/8/0/0 | <0.05  |
| Blood count                            |           |           |       |
| Haemoglobin (g/dL)                     | 13.2 ± 2.0 | 13.2 ± 2.0 | 0.28   |
| White blood count (g/L)                | 9.2 ± 4.3  | 7.4 ± 3.2  | <0.0001|
| Platelets (G/L)                        | 210 ± 90   | 216 ± 91   | 0.23   |
| Bilirubin (mg/dL)                      | 1.0 [0.7–1.7] | 1.0 [0.6–1.3] | <0.05  |
| Aspartate transaminase (IU/L)          | 28 [20–41] | 26 [20–33] | <0.05  |
| Alanine transaminase (IU/L)            | 30 [21–56] | 25 [19–37] | <0.05  |
| Na (mmol/L)                            | 139 ± 4    | 139 ± 3    | 0.88   |
| Creatinine (mg/dL)                     | 1.3 ± 0.5  | 1.2 ± 0.4  | <0.0001|
| Urea (mg/dL)                           | 49 [38–75] | 51 [37–66] | 0.93   |
| NT-proBNP (pg/mL)                      | 8305 [3368–11 154] | 5061 [1820–6596] | <0.0001|
| Troponin I (ng/mL)                     | 0.1 [0.0–0.2] | NA        |       |
| Lactate (mmol/L)                       | 2.2 ± 1.0  | 1.9 ± 0.9  | 0.07   |
| Oxygen saturation (%)                  | 92 ± 6     | 93 ± 6     | 0.06   |
| Urine Na⁺                               | 86.9 ± 35.5 | 72.0 ± 34.6 | <0.0001|

Table 1 Comparison of admission and discharge characteristics of patients with acute heart failure (n = 172)

NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

ESC Heart Failure (2021) DOI: 10.1002/ehf2.13372
the furosemide prescribed at discharge on study endpoints and discharge sUNa+, we have calculated the sUNa+ per dose of furosemide as well as we have performed the mediation analysis.9

The goal of mediation analysis was to examine the indirect effect of furosemide on study endpoints and see if it’s statistically significant. The follow-up was obtained directly from patients or their relatives (telephone contact and clinic

Table 2 Prognostic value of UNa+ assessed at active decongestive phase of hospitalization and at discharge for study endpoints (univariate models)

| Variable                                | Composite endpoint | 1 year mortality | AHF rehospitalization |
|------------------------------------------|--------------------|------------------|------------------------|
|                                          | HR (95% CI)        | P                | HR (95% CI)            | P            | HR (95% CI) | P            |
| UNa+ at admission (per 10 mmol/L)        | 0.88 (0.82–0.94)   | <0.001           | 0.88 (0.81–0.95)       | 0.002        | 0.90 (0.83–0.98) | <0.05 |
| UNa+ at Day 1 (per 10 mmol/L)            | 0.87 (0.81–0.91)   | <0.0001          | 0.84 (0.77–0.92)       | <0.0001      | 0.84 (0.76–0.92) | <0.0005  |
| UNa+ at Day 2 (per 10 mmol/L)            | 0.90 (0.84–0.96)   | <0.005           | 0.86 (0.79–0.94)       | 0.0005       | 0.89 (0.81–0.98) | <0.05 |
| UNa+ at discharge (per 10 mmol/L)        | 0.99 (0.93–1.06)   | 0.79             | 0.97 (0.89–1.05)       | 0.48         | 1.03 (0.94–1.12) | 0.56 |
| UNa+ at discharge/dose of furosemide (mmol/L/mg) | 0.81 (0.59–1.10)   | 0.18             | 0.75 (0.50–1.11)       | 0.15         | 0.97 (0.67–1.41) | 0.89 |

AHF, acute heart failure; CI, confidence interval; HR, hazard ratio.

Table 3 Comparison of admission and discharge characteristics of acute heart failure patients stratified by 1 year composite endpoint

| Parameter                                | Event free patients (n = 103) | Death or rehospitalization (n = 69) | P      |
|------------------------------------------|-------------------------------|-------------------------------------|--------|
| Sex (male)                               | 77 (75%)                      | 50 (73%)                            | 0.73   |
| Age (years)                              | 70 ± 13                       | 70 ± 13                             | 0.91   |
| Heart rate (beat/minute)                 | 74 ± 11                       | 73 ± 10                             | 0.45   |
| Systolic blood pressure at discharge (mmHg) | 123 ± 17                     | 114 ± 16                            | <0.005 |
| Diastolic blood pressure at discharge (mmHg) | 72 ± 9                       | 70 ± 10                             | 0.13   |
| Left ventricle ejection fraction (%)     | 36 ± 15                       | 38 ± 14                             | 0.25   |
| De novo                                  | 60 (59%)                      | 16 (24%)                            | <0.001 |
| Loop diuretics before admission (yes)    | 36 (35%)                      | 47 (68%)                            | <0.001 |
| Coronary artery disease (yes)            | 62 (60%)                      | 40 (58%)                            | 0.78   |
| Hypertension (yes)                       | 87 (84%)                      | 48 (70%)                            | 0.02   |
| Hyperlipidaemia (yes)                    | 40 (39%)                      | 22 (32%)                            | 0.35   |
| Diabetes mellitus (yes)                  | 40 (39%)                      | 27 (39%)                            | 0.97   |
| Blood count at discharge                 |                               |                                     |        |
| Haemoglobin (g/dL)                       | 13.3 ± 1.9                    | 13.0 ± 2.0                          | 0.24   |
| White blood count (G/L)                  | 8.9 ± 3.6                     | 9.6 ± 5.1                           | 0.31   |
| Platelets (G/L)                          | 214 ± 111                     | 204 ± 73                            | 0.47   |
| Bilirubin at admission (mg/dL)           | 1.0 [0.7–1.6]                 | 1.2 [0.8–1.7]                       | 0.25   |
| Aspartate transaminase at admission (IU/L) | 29 [20–47]                   | 26 [21–33]                          | 0.27   |
| Serum Na+ at admission (mmol/L)          | 140 ± 4.0                     | 138 ± 4.7                           | 0.02   |
| Serum Na+ at discharge (mmol/L)          | 139 ± 2.6                     | 138 ± 3.8                           | 0.06   |
| Creatinine at admission (mg/dL)          | 1.5 ± 0.6                     | 1.3 ± 0.4                           | 0.02   |
| Creatinine at discharge (mg/dL)          | 1.1 ± 0.4                     | 1.3 ± 0.5                           | 0.04   |
| Serum urea at admission (mg/dL)          | 52 ± 27                       | 69 ± 37                             | <0.001 |
| Lactate at admission (mM)                | 2.1 ± 0.9                     | 2.3 ± 1.2                           | 0.31   |
| Days of hospitalization                  | 7 [5–8]                      | 7 [5–8]                             | <0.05  |
| NT-proBNP at admission (pg/ml)           | 5052 [2951–8757]             | 6312 [4 082–13 828]                 | <0.005 |
| NT-proBNP at discharge (pg/ml)           | 2635 [1427–4564]             | 4781 [2717–8460]                    | <0.0001 |
| Urine Na+ at admission (mmol/L)          | 94 ± 34                       | 76 ± 35                             | <0.005 |
| Urine Na+ at Day 1 (mmol/L)              | 85 ± 36                       | 65 ± 37                             | <0.0005 |
| Urine Na+ at Day 2 (mmol/L)              | 84 ± 37                       | 67 ± 35                             | <0.0005 |
| Urine Na+ at discharge (mmol/L)          | 73 ± 35                       | 70 ± 34                             | 0.82   |
| Total intravenous dose of furosemide     | 120 [60–140]                 | 120 [80–160]                        | 0.41   |
| within the first 48 h of hospitalization |                               |                                     |        |
| Median day of switch to oral furosemide  | 3 [3–5]                      | 5 [3–8]                             | 0.001  |
| Medications at discharge                 |                               |                                     |        |
| Oral furosemide dose at discharge (mg)   | 80 [40–120]                  | 80 [80–120]                         | 0.005  |
| Other diuretics                          | 18 (19%)                     | 14 (23%)                            | 0.59   |
| Mineralocorticoid-receptor antagonist    | 50 (49%)                     | 36 (52%)                            | 0.57   |
| Angiotensin-converting enzyme            | 92 (89%)                     | 57 (83%)                            | 0.44   |
| inhibitors/angiotensin-receptor blockers | 98 (97%)                     | 57 (89%)                            | 0.04   |

NT-proBNP, N-terminal pro-B-type natriuretic peptide.

ESC Heart Failure (2021) DOI: 10.1002/ehf2.13372
appointments), from the HF clinic database, from the hospital system or from the national citizen registry by the investigators who were blinded to the UNa+. No patient was lost to follow-up.

Results
Prognostic significance of admission and discharge sUNa+ on post-discharge outcomes
The study population (n = 172) was composed of predominantly men (74%), with a mean ejection fraction of 37 ± 14 (%) and median [interquartile range] N-terminal pro-B-type natriuretic peptide (NT-proBNP): 8305 [3368–11 154] pg/dL. Clinical signs of peripheral/pulmonary congestion were present in 71%/91% of patients on admission, respectively (Table 2).

After hospital discharge, 49 (29%) patients died and 40 (23%) were rehospitalized due to AHF, while the composite endpoint occurred in 69 (40%) patients during 1 year follow-up. The sUNa+ had high prognostic significance for the composite endpoint when assessed on admission, 24 and 48 h: HR (95% CI) (per 10 mmol/L) were 0.88 (0.82–0.94); 0.87 (0.81–0.91); 0.90 (0.84–0.96), all P < 0.005. In contrast to active decongestive phase, discharge sUNa+ had no prognostic significance HR (95% CI) (per 10 mmol/L): 0.99 (0.93–1.06) P = 0.79 for the composite endpoint, which was independent from the dose of oral furosemide prescribed at that timepoint average causal mediation effects: −0.38; P = 0.71.

Similarly, sUNa+ measured at admission, Days 1 and 2 had predictive significance for 1 year mortality HR (95% CI) were 0.88 (0.81–0.95), 0.84 (0.77–0.92), and 0.86 (0.79–0.94), respectively, all P < 0.002, and AHF rehospitalizations HR (95% CI) were 0.90 (0.83–0.98), 0.84 (0.76–0.92), 0.89 (0.81–0.98), respectively, all P < 0.05. In contrast, discharge sUNa+ did not have an association with mortality HR (95% CI): 0.97 (0.89–1.05) P = 0.48 or rehospitalizations alone HR (95% CI): 1.03 (0.94–1.12) P = 0.56 (Table 2).

Comparison of groups stratified by post-discharge composite endpoint occurrence
Comparison of admission and discharge characteristics of AHF patients stratified by 1 year composite endpoint is presented in Table 3. There was no difference in dose of furosemide administrated within the first 2 days of hospitalization in both groups. However, the group who experienced the endpoint received significantly higher doses of oral furosemide at discharge, when compared with event free patients: 80 [80–120] vs. 80 [40–120] P = 0.006 and had longer hospital stay: 7 [6–11] vs. 7 [5–8] P < 0.05 (Table 3). The comparison of longitudinal changes of sUNa+ during hospitalization showed significantly higher values of sUNa+ within the active decongestive phase in event free patients when compared with those who experienced the event: admission: 94 ± 34 vs. 76 ± 35; Day 1: 85 ± 36 vs. 65 ± 37; Day 2: 84 ± 37 vs. 67 ± 35, all P < 0.005 (mmol/L), respectively. There was no difference between those groups in discharge sUNa+: 73 ± 35 vs. 70 ± 35 P = 0.82 (mmol/L) (Figure 1).

Determinants of sUNa+
The active decongestive phase sUNa+ was correlated with age (r = 0.22), bilirubin (r = −0.22), serum sodium (r = 0.32), and systolic blood pressure (r = 0.20), all P < 0.05. In multivariable model, Day 1 sUNa+ was significantly related only with serum Na+ (β-coefficient−0.27). While the determinant of discharge sUNa+ was only ejection fraction (β-coefficient−0.28) P < 0.05.

Conclusions
For the first time, we demonstrate the lack of prognostic significance of discharge sUNa+ in AHF. To date, sUNa+ assessment is mostly limited to the early phase of hospitalization or in patients that required decongestion with unanimous results showing its strong relation to prognosis and ability to predict diuretic response.1,2,5,10 Our data fill a knowledge gap, showing that sUNa+ should be interpreted in relationship to the fluid volume status in AHF and timing of hospitalization.

Based on the available data, one might have expected that AHF patients with poor survival are unable to excrete enough
sodium with urine—as their sUNa⁺ within first 48 h of hospitalization was significantly lower than in patients who survived the first year. Surprisingly, at discharge, both groups had the same sUNa⁺, which challenges the current concept of sUNa⁺ as a universal HF biomarker. Moreover, the different clinical determinants of sUNa⁺ at active decongestive phase and at discharge further support our hypothesis. However, it is very important to stress that the same sUNa⁺ at discharge was a result of significantly higher doses of oral furosemide prescribed for that group. Importantly, the lack of predictive value of discharge sUNa⁺ was irrespective from dose of furosemide prescribed at that timepoint, which was confirmed by adjustments (mediation analysis and calculation of UNa⁺ per tablet of diuretic). We need to consider that some patients from both groups (and at all stages of the therapy) might have received insufficient doses of diuretics to their requirements. As there is no perfect marker that predicts diuretic demand, in everyday practice the therapy is mostly based on clinical experience and patient’s response. We think the important aspect of our analyses is that sUNa⁺ should not be considered as a universal marker of diuretic requirements as early phase vs. discharge sUNa⁺ had different biological meaning.

On the other hand, the urine excretion at an early stage of a HF hospitalization may actually reflect the magnitude of the neurohormonal/haemodynamic (or other) disturbances that triggered the episode of AHF. And those patients who might be exposed to the higher distress are clearly at higher risk of 1 year mortality and HF rehospitalization. Because many factors (volume status, diuretic dose, and neurohormonal activation) affect sodium excretion, one should not solely rely on sUNa⁺ as a biomarker without full appreciation of the clinical context.

The other aspect of the analysis is the general trajectory of UNa⁺ during hospitalization. Previous studies have shown that sodium excretion (represented by FeNa⁺) is related to the degree of extracellular volume: the higher the extracellular volume the higher the spot urine excretion. Thus, survivors experienced gradual ‘physiological’ decrease of UNa⁺ along with presumed decreasing congestion. The non-survivors had a stable sUNa⁺, with only numerical ‘pathological’ increase of UNa⁺ at discharge period, independently from shrinking extracellular volume. Wherever this disturbed water/sodium handling is of importance in HF needs further exploration.

Limitations

We are unable to provide the urine volumes and exact time between diuretic administration and urine collection. There was no strict diuretic treatment protocol to follow (in respect to doses and types of intravenous administration: bolus vs. short time infusion). The route of diuretics administration was different at active decongestive vs. discharge phase of AHF, which is a confounding factor, but it represents a clinical scenario as discharge urine sodium would be used.

Conflict of interest

Jan Biegus, Robert Zymlinski, Marat Fudim, Jeffrey Testani, Mateusz Sokolski, Dominik Marciniak, Barbara Ponikowska, Mateusz Guzik, Mateusz Garus, Szymon Urban, and Piotr Ponikowski declare that they have no conflict of interest.

Funding

This research was financially supported from the subsidy no. SUB.190.19.052 and SUB.190.21.105 from the Department of Heart Diseases, Wroclaw Medical University, Poland.

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