International Journal of Cardiology 254 (2018) 189–194

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Long-term prognostic significance of urinary sodium concentration in patients with acute heart failure

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ARTICLE INFO

Article history:
Received 26 May 2017
Received in revised form 12 August 2017
Accepted 21 August 2017

Keywords:
Acute heart failure
Urinary sodium concentration
Prognosis
Worsening renal function
Renin-angiotensin-aldosterone system

ABSTRACT

Background: Lower urinary sodium concentration (UNa) may reflect impaired renal perfusion, higher neurohormonal activity and diuretic resistance. However, the prognostic impact of UNa in patients with acute heart failure (AHF) has not been fully elucidated.
Methods: We investigate the association between UNa and clinical outcomes in 669 patients admitted with AHF in our prospective registry. Patients were stratified into tertiles based on UNa in a spot urine sample on admission.
Results: Patients with lower UNa were more likely to have a history of prior heart failure admission, β-blockers and diuretics use, and had lower blood pressure and serum sodium level, and higher blood urea nitrogen, estimated glomerular filtration rate, blood glucose and troponin T levels on admission than those with higher UNa. Plasma renin activity, aldosterone, cortisol and dopamine levels were also significantly higher in patients with lower UNa (all $p < 0.001$). Furthermore, patients with lower UNa had significantly less weight loss, lower net fluid loss/furosemide equivalent dose and higher incidence of worsening renal function during hospitalization than those with higher UNa (all $p < 0.01$). During a median follow-up period of 560 days, lower UNa was significantly associated with the composite of all-cause death and worsening heart failure ($p < 0.001$). In multivariable Cox-proportional hazards model, UNa remained an independent determinant of long-term adverse events (HR, 1.24, 95% CI, 1.06–1.45, $p = 0.006$).
Conclusions: Lower UNa was associated with worse long-term clinical outcomes along with increased neurohormonal activities, impaired response to diuretics and higher incidence of worsening renal function in patients with AHF.

1. Introduction

Acute heart failure (AHF) is a complex syndrome involving multiple organs and neurohormonal systems [1]. Despite the evolution of medical therapy over the past several decades, the morbidity and mortality of AHF remain high [2]. Identification of patients at high risk for future unfavorable adverse events is helpful in guiding medical decision making in the management of patients with AHF. Although a large number of studies have reported the prognostic impact of serum markers as well as clinical characteristics in AHF patients [3–10], urinary markers are still relatively unexplored.

Urinary sodium concentration (UNa) is simple and easy to measure, and is widely used in clinical practice such as the differential diagnosis of acute renal failure and hyponatremia [11,12]. Originally, lower UNa was proposed as a marker of prerenal failure [12–14], which can be caused by impaired organ perfusion in patients with decreased cardiac output or effective circulating blood volume. Several small-scale studies have reported an association between lower UNa and worse short-term clinical outcomes in patients with AHF [15,16]. However, the prognostic impact of UNa on short- and long-term clinical outcomes has not been investigated in a relatively larger-scale study. In addition, although several factors such as increased neurohormonal activity and impaired diuretic response have been speculated as underlying mechanisms for the relationship between lower UNa and worse clinical outcomes, supportive data are still lacking.

Therefore, the aim of this study was to investigate the short- and long-term prognostic significance of UNa on admission, and its

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http://dx.doi.org/10.1016/j.ijcard.2017.08.053
0167-5273/

association with neurohormonal activity and diuretic response in patients with AHF.

2. Methods

2.1. Study design

Data from the NaDEF (National cerebral and cardiovascular center acute DEcompensated heart Failure) registry, which were obtained between January 2013 and August 2015, were retrospectively analyzed. The design of the NaDEF registry has been described previously [17]. Briefly, it is a single-center, observational, on-going, prospective cohort that includes all consecutive patients aged >20 years requiring hospitalization at our institution for the first time with a diagnosis of AHF from January 2013. This study has been approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M22-025) and is registered under the Japanese UMIN Clinical Trials Registration (UMIN000017024).

2.2. Study population

A total of 751 consecutive patients with AHF were registered in the NaDEF registry. Patients with acute coronary syndrome (n = 40) and those without measurement of UNa on admission (n = 42) were excluded. Finally, 669 patients were included in this study. Patients were stratified into tertiles based on UNa. Patients excluded because of no UNa measurement on admission were younger, more likely to have a history of chronic kidney disease and chronic hemodialysis, had lower estimated glomerular filtration rate (eGFR), serum sodium, blood glucose, HbA1c, and total bilirubin levels, and had higher blood urea nitrogen levels, when compared with those with UNa measurement (Supplementary Table 1).

2.3. Blood sampling and urinary sodium measurement

Venous blood samples were obtained for measurement of routine laboratory parameters, plasma renin activity and aldosterone level on admission. Plasma dopamine and serum cortisol levels were also measured as a representative of neurohormonal activity on admission. Spot urine samples were collected as soon as possible after admission. In patients with an indwelling urinary catheter, urine samples were collected at the time of insertion of the urinary catheter, which was soon after the initial treatment in the emergency department. In those without the use of urinary catheter, urine samples were collected at the time of first spontaneous micturition after admission.

2.4. Clinical outcomes

The primary study outcome was the composite of all-cause death and worsening heart failure (HF), which was defined as worsening symptoms and signs of HF requiring intensification of intravenous therapy or initiation of mechanical support after stabilization with initial treatment during hospitalization [18,19] or readmission due to HF after discharge. We also evaluated net fluid loss during 48 h after admission, weight loss at 48 h, net fluid loss/furosemide equivalent dose (24-hour net fluid loss [ml]/intravenous loop diuretic dose [mg]) for evaluation of diuretic response, and the incidence of worsening renal function defined as an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) or an increase in serum creatinine to ≥1.5 times baseline during hospitalization [20].

2.5. Statistical analyses

Continuous variables are presented as mean ± standard deviation or median (interquartile range: IQR). Categorical variables are shown as frequency with percentage of nonmissing values. Differences among baseline characteristics, laboratory data, initial treatment, plasma renin activity, aldosterone, dopamine and cortisol levels and in-hospital outcomes across UNa tertiles were analyzed using the Cochrane-Armitage test for trend. Multivariable linear regression analysis was applied to explore independent determinants of UNa on admission. Univariable factors that had a value of $p < 0.10$ were entered into a multivariable model. Furthermore, stepwise selection with a p-value of 0.10 for backward elimination was used to select the best predictive model. Long-term cumulative incidence of all-cause death and worsening HF were estimated using Kaplan-Meier curves, and log-rank (Mantel-Cox) test was performed to assess differences according to UNa tertiles. Cox proportional hazard modeling, which included considerable prognostic factors for AHF (based on previous prognostic reports in patients with AHF [3,5–8,10]) or potential confounders of the UNa-risk relationship, was performed to assess the association between these factors and risk of adverse events defined as the composite of all-cause death and worsening HF. These variables included age, gender, prior history of HF admission, New York Heat Association (NYHA) functional class at discharge, systolic blood pressure, brain natriuretic peptide (BNP), blood urea nitrogen, troponin T, hemoglobin and serum sodium levels, and use of loop diuretics, β-blockers and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Moreover, stepwise selection with a p-value of 0.10 for backward elimination was used to select the best predictive model. Adding to the main effect, the interactions between UNa and the use of heart failure medications (loop diuretics, β-blockers, and ACE inhibitors or ARBs), as well as prior history of HF admission, were also examined. In addition, we have conducted a multivariable regression spline model to investigate the best prediction for adverse event (composite of all-cause death and worsening HF) with UNa. The listwise deletion was employed to address the missing data in the multivariable Cox proportional hazard models and multivariable regression spline model. Analyses were performed using statistical software STATA® version 14 (College Station, TX) and JMP® 10.0.2 (SAS Institute Inc., Cary, NC). Statistical significance was defined as a p-value <0.05.

3. Results

3.1. Patient characteristics

The median UNa was 91 mg/dL (IQR 61-123) (Supplementary Fig. 1). Table 1 shows the baseline characteristics of the study population. Patients with lower UNa were more likely to have a history of prior HF admission, β-blockers and diuretics use on admission and lower systolic blood pressure than those with higher UNa. These patients also had lower levels of serum sodium and eGFR, and higher levels of blood urea nitrogen, blood glucose and troponin T than those with higher UNa. There were no significant trends across tertiles in the use of ACE inhibitors or ARBs and spironolactone on admission.

3.2. Renin-angiotensin-aldosterone system and neurohormonal activity stratified by urinary sodium concentration

The relationship between UNa and renin-angiotensin-aldosterone system (RAAS) and neurohormonal activity are shown in Table 1. Patients with lower UNa had higher plasma renin activity ($p_{trend} < 0.001$) and higher plasma aldosterone level than those with higher UNa ($p_{trend} < 0.001$). Similarly, serum cortisol and plasma dopamine levels were significantly elevated with decreasing UNa tertile ($p_{trend} < 0.001$ and <0.001, respectively).

3.3. Determinants of UNa on admission in patients with acute heart failure

Supplementary Table 2 shows the independent determinants of UNa on admission. In the multivariable analysis, plasma renin activity ($\beta = -0.38$, $p = 0.019$), aldosterone ($\beta = -0.04$, $p = 0.048$) and blood glucose ($\beta = -0.05$, $p = 0.050$) levels, the use of loop diuretics ($\beta = -10.44$, $p = 0.002$) and chronic kidney disease ($\beta = -8.13$, $p = 0.014$) were inversely associated with UNa, while serum sodium ($\beta = 2.85$, $p < 0.001$) level was positively associated with UNa.

3.4. Intravenous treatment, response to diuretic therapy and short-term clinical outcomes

Intravenous treatment during the acute phase, response to diuretic therapy and short-term clinical outcomes of the patients across UNa tertiles are shown in Table 2. Patients with lower UNa were more likely to receive inotropes, while there were no significant differences among groups in the use of diuretics and vasodilators. Across tertiles of UNa, lower UNa was associated with lower net fluid loss [2927 mL in 1st tertile (lowest UNa), 3140 mL in 2nd tertile, 3345 mL in 3rd tertile (highest UNa), $p_{trend} = 0.003$] and less weight loss at 48 h after admission (−1.0, −1.3, −1.5 kg, respectively, $p_{trend} = 0.003$). Among those who received intravenous furosemide, lower UNa was associated with lower net fluid loss/furosemide equivalent dose (66, 90, 95 mL/mg, respectively, $p_{trend} < 0.001$).

Overall, there were 14 all-cause deaths, 59 cases of worsening HF and 134 cases of worsening renal function during hospitalization. The incidence of in-hospital adverse events (all-cause death and worsening HF) was significantly higher in patients with lower UNa than in those with higher UNa [13.8% in 1st tertile (lowest UNa), 8.6% in 2nd tertile, 5.4% in 3rd tertile (highest UNa), $p_{trend} = 0.002$]. Furthermore, we observed a significant association between lower UNa and higher incidence of all-cause death (4.0%, 0.9%, 0.5%, respectively, $p_{trend} = 0.005$), worsening HF (11.6%, 8.6%, 4.9%, respectively, $p_{trend} = 0.011$) and worsening renal function (29.8%, 17.7%, 12.6%, respectively, $p_{trend} < 0.001$). Similarly, the incidence of adverse events at day 30 was significantly higher in patients with lower UNa (13.3%, 7.2%, 5.4%, respectively, $p_{trend} = 0.003$).