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Urinary Sodium Profiling in Chronic Heart Failure to Detect Development of Acute Decompensated Heart Failure

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ABSTRACT

OBJECTIVES This study sought to determine the relationship between urinary sodium (U_{na}) concentration and the pathophysiologic interaction with the development of acute heart failure (AHF) hospitalization.

BACKGROUND No data are available on the longitudinal dynamics of U_{na} concentration in patients with chronic heart failure (HF), including its temporal relationship with AHF hospitalization.

METHODS Stable, chronic HF patients with either reduced or preserved ejection fraction were prospectively included to undergo prospective collection of morning spot U_{na} samples for 30 consecutive weeks. Linear mixed modeling was used to assess the longitudinal changes in U_{na} concentration. Patients were followed for the development of the clinical endpoint of AHF.

RESULTS A total of 80 chronic HF patients (71 ± 11 years of age; an N-terminal pro-B-type natriuretic peptide [NT-proBNP] concentration of 771 [interquartile range: 221 to 1,906] ng/l; left ventricular ejection fraction [LVEF] 33 ± 7%) prospectively submitted weekly pre-diuretic first void morning U_{na} samples for 30 weeks. A total of 1,970 U_{na} samples were collected, with mean U_{na} concentration of 81.6 ± 41 mmol/l. Sodium excretion remained stable over time on a population level (time effect $p = 0.663$). However, interindividual differences revealed the presence of high (88 mmol/l U_{na} [n = 39]) and low (73 mmol/l U_{na} [n = 41]) sodium excreters. Only younger age was an independent predictor of high sodium excretion (odds ratio [OR]: 0.91; 95% confidence interval [CI]: 0.83 to 1.00; $p = 0.045$ per year). During 587 ± 54 days of follow-up, 21 patients were admitted for AHF. Patients who developed AHF had significantly lower U_{na} concentrations ($F_{[1.80]} = 24.063$; $p < 0.001$). The discriminating capacity of U_{na} concentration to detect AHF persisted after inclusion of NT-proBNP and estimated glomerular filtration rate (eGFR) measurements as random effects ($p = 0.041$). Furthermore, U_{na} concentration dropped ($U_{na} = 46 \pm 16$ mmol/l vs. 70 ± 32 mmol/l, respectively; $p = 0.003$) in the week preceding the hospitalization and returned to the individual's baseline ($U_{na} = 71 \pm 22$ mmol/l; $p = 0.002$) following recompensation, while such early longitudinal changes in weight and dyspnea scores were not apparent in the week preceding decompensation.

CONCLUSIONS Overall, U_{na} concentration remained relatively stable over time, but large interindividual differences existed in stable, chronic HF patients. Patients who developed AHF exhibited a chronically lower U_{na} concentration and exhibited a further drop in U_{na} concentration during the week preceding hospitalization. Ambulatory U_{na} sample collection is feasible and may offer additional prognostic and therapeutic information. (J Am Coll Cardiol HF 2019;7:404–14) © 2019 by the American College of Cardiology Foundation.

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Chronic sodium retention is a hallmark of the heart failure (HF) syndrome, leading to extracellular volume expansion, which contributes to the occurrence of congestion and clinical instability (1). Although all ingested sodium is completely absorbed in the gastrointestinal tract, a neutral sodium balance is retained in a compensated patient through tightly regulated renal sodium excretion and interstitial buffering (2,3). However, in HF, the renal natriuretic response to any given volume status is hampered by unrestrained neurohumoral activation and hemodynamic alterations (4,5). An increasing body of evidence has investigated the role of urinary sodium (U_{na}) concentration (in spot samples and continuous urine collections) during episodes of acute HF (AHF), linking low U_{na} concentration to a diminished diuretic response, ongoing congestion, and an increased risk for developing HF readmission or cardiovascular mortality (6–11). However, no (longitudinal) data are available for U_{na} concentration in patients with chronic HF. Additionally, a relationship between alterations in chronic renal sodium excretion and the risk of developing AHF has not been established in chronic HF. Therefore, insights into chronic renal sodium handling may help to understand the instigating mechanisms of stable HF patients who develop AHF. This study consisted of performing an exploratory and hypothesis-generating prospective analysis to assess profiles of U_{na} concentration in patients with stable HF. Furthermore, the relationship between ambulatory spot U_{na} concentration and the risk of developing AHF resulting in hospitalization was assessed.

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METHODS

STUDY POPULATION RECRUITMENT. Patients were prospectively enrolled in a single tertiary HF clinic between January 2016 and October 2016. Subjects were eligible if they were older than 18 years of age and able to provide written informed consent. Inclusion criteria consisted of: 1) stable HF with no HF hospitalization in the previous 3 months; 2) a diagnosis of HF with reduced ejection fraction (HFrEF) defined as previously symptomatic HF with a left ventricular ejection fraction (LVEF) below 45% or a diagnosis of HF with preserved ejection fraction (HFpEF) defined as previously symptomatic HF with a LVEF above 50% and, additionally, an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration of >1,000 ng/l and echocardiographic signs of diastolic dysfunction (increased left ventricular wall mass or diastolic dysfunction >grade I or an increased left atrium volume index with cutoff values as defined by European Society of Cardiology (ESC) HF guidelines (12); and 3) receiving stable doses of guideline-recommended disease-modifying therapies for at least 3 months, in the case of HFrEF. Exclusion criteria consisted of: 1) the clinical impression by the study team that the patient was unable to adhere to the study protocol; 2) patients were undergoing or planned for renal replacement therapy; and 3) there was an absence of a freezer at home. Patients were followed by a multidisciplinary HF team in close collaboration with primary care physicians and were instructed about a low-sodium diet according to ESC HF guidelines (12). The study was carried out in accordance with tenets of the Declaration of Helsinki. The study protocol was approved by the local institutional review board, and all patients provided written informed consent. The manuscript was drafted according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational studies (13).

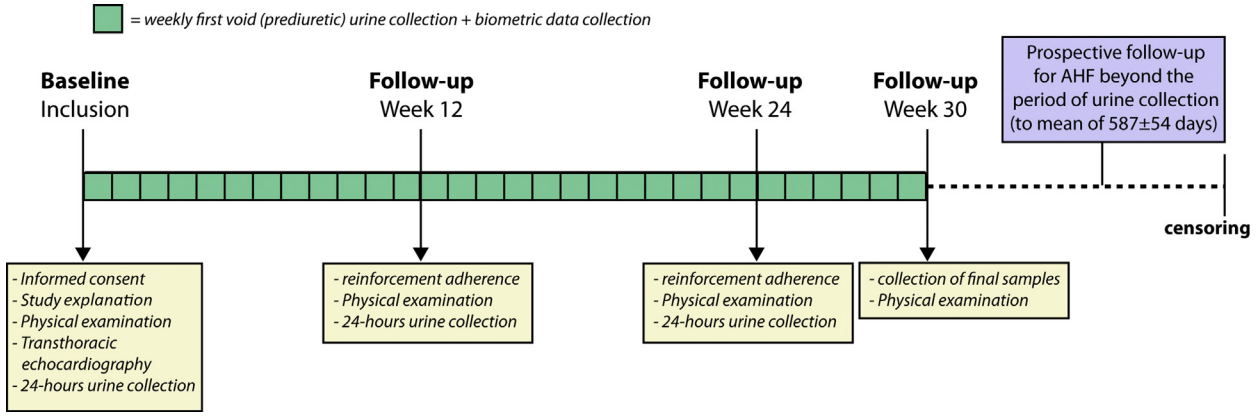
BASELINE DATA COLLECTION. After patients completed their informed consent, they underwent standardized baseline evaluation consisting of a history of functional status, a medical history and baseline medication evaluation, a physical examination, an electrocardiogram, a transthoracic echocardiogram, blood sampling, and 24-h urine collection.

Weekly urine sampling and storage. During the baseline visit, patients received a thorough explanation of how to collect ambulatory spot urine samples. Briefly, patients were instructed to collect a once-weekly first void morning urine sample. The patients who were taking diuretic medicines in the morning were instructed to take the diuretic only after collection of the first morning void. Patients were instructed to always collect the morning urine sample on the similar day of consecutive weeks (only weekdays were allowed, not Saturday or Sunday). Urine was collected in a disposable urine collection cup. Afterward, a spot sample was aspirated from the sealed collection cup by using the aspiration port (Online Figure 1). The patients were to immediately place the labeled vacuum tube containing the urine in their freezer (with a commercial standard of approximately −18°C). On the same morning, patients filled in a biometric data questionnaire consisting of dyspnea scoring (visual analog scale [VAS]), weight, blood pressure, and loop diuretic dose and indicated if obvious changes in diet compared with the previous week were made. Both the urinary tube and the

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure
CI = confidence interval
eGFR = estimated glomerular filtration rate
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
HFpEF = heart failure with preserved ejection fraction
NT-proBNP = N-terminal pro-B-type natriuretic peptide
OR = odds ratio
U_{na} = urinary sodium
VAS = visual analog scale

FIGURE 1 Overview of the Study Design



AHF = acute heart failure.

biometric data questionnaire contained an identification corresponding to the correct week (e.g., week 1, week 2, and so forth). Just before freezing the urine sample, the patient signed a safety check confirming that both the urine sample and the biometric questionnaire had been double-checked with the appropriate week's labeling.

Clinical follow-up and sample analysis. Patients returned for ambulatory follow-up at pre-defined intervals, namely, weeks 12, 24, and 30. Week 30 was the final date of ambulatory follow-up, but patients were followed prospectively for the development of AHF or all-cause mortality. A visual synopsis of the study is shown in Figure 1. At follow-up, patients brought the frozen urine samples to the clinic in a commercially available freezing bag. Upon arrival at the clinic, urine samples were immediately stored at −18°C, until the day of analysis. Urine samples were assessed in batches for U_{na} concentration (Cobas-8000 analyzer, Roche Diagnostics, Basel, Switzerland). Additionally, during the follow-up visit, patients underwent physical examination, laboratory assessments, and a repeat 24-h urine collection. All patients' electronic health records were tagged to prospectively assess development of AHF hospitalizations and all-cause mortality. An AHF hospitalization was defined as a hospitalization lasting at least 24 h with either 2 signs or symptoms of congestion necessitating the use of intravenous diuresis or, as signs of hypoperfusion, necessitating the use of intravenous vasoactive drugs. Censoring of the prospective events occurred on February 1, 2018.

Relationship between spot and 24-h urine collection sodium. In line with published studies of AHF, spot U_{na} concentration (expressed in mmol/l) was the primary marker of interest for the current analysis (6–11), especially because spot samples are more convenient to obtain than 24-h urine collection. However, to ensure that spot samples conveyed similar information as 24-h urine collection in the patient populations of interest (patients who did or did not develop AHF), the relationship between spot U_{na} concentration and continuous collection of U_{na} concentration was compared in these patients. The rationale for doing so was based on the observation that sicker patients, who were more likely to develop an AHF episode, could exhibit enhanced nocturnal diuresis, which might have diluted the morning spot U_{na} concentration in comparison to the 24-h U_{na} concentration sample.

STATISTICS. Continuous variables are mean ± SD if normally distributed or median (interquartile range [IQR]) if not normally distributed. Normality was checked by using the Shapiro-Wilk test, Q-Q plots, skewness, and kurtosis. Categorical data were expressed as numbers and percentages and compared by using the Pearson chi-square test or Fisher's exact test when appropriate. Continuous baseline variables were compared using Student's *t*-test or Mann-Whitney *U* test as appropriate. Longitudinal U_{na} profiles were assessed using linear mixed modeling for repeated measures. Because missing values were expected to occur during follow-up in the repeated-measure design, mixed modeling was preferred to repeated-measures analysis of variance. The time effect was modeled using first-order autoregressive. This method was chosen because it could be assumed that measurements of sodium taken closely together are more correlated to each other. Models were built to investigate the fixed effect of time, group

(development of AHF hospitalization), and a [group*time] effect. Additionally, random effects of intercept and [HF*time] were included in the model. The time variable was assessed in both a linear and a quadric fashion to assess the appropriateness of a linear mixed models versus a nonlinear mixed model. Fixed effects were analyzed using a sum-of-squares type III. Post hoc testing of the random effects was performed using a *t*-test to identify different profiles in slope and intercept of the curve (division between high and low sodium excreters). Additionally, to determine if U_{na} concentration was predictive, in addition to NT-proBNP and eGFR, these variables were included as random effects in additional analysis. For patients experienced an AHF hospitalization during the period of sodium sampling, the U_{na} concentrations before decompensation and the week of decompensation or week after decompensation were analyzed by using a paired *t*-test. To assess whether spot U_{na} concentrations in patients who developed an AHF hospitalization conveyed information similar to that of continuously collected U_{na} samples, patients with and without an AHF episode were compared. The spot U_{na} concentrations from all individually available samples were averaged and correlated with the U_{na} concentration from the 3 consecutive 24-h urine collections by using Pearson's correlation. The strength of the correlations were compared following R-to-Z Fisher transformation. Statistical significance was always set at a 2-tailed probability level of <0.05. Statistics were performed using SPSS version 22 software (IBM, Armonk, New York).

RESULTS

PATIENT POPULATION. A total of 100 patients were prospectively included between January 2016 and October 2016. However, 10 patients who underwent baseline evaluation and signed an informed consent did not return for study follow-up. Additionally, 10 patients were excluded because the ambulatory collection of urinary samples were performed incorrectly (missing week labels) or inconsistently (multiple samples missing). Therefore, the final patient population consisted of 80 patients. Baseline characteristics are reflected in the left column of Table 1. Patients were predominantly male, and most patients had HFrEF and an ischemic etiology. Patients had moderately impaired renal function (eGFR of 54.7 ± 19.4 ml/min per 1.73 m^2) and were only mildly symptomatic at baseline, as illustrated by the large

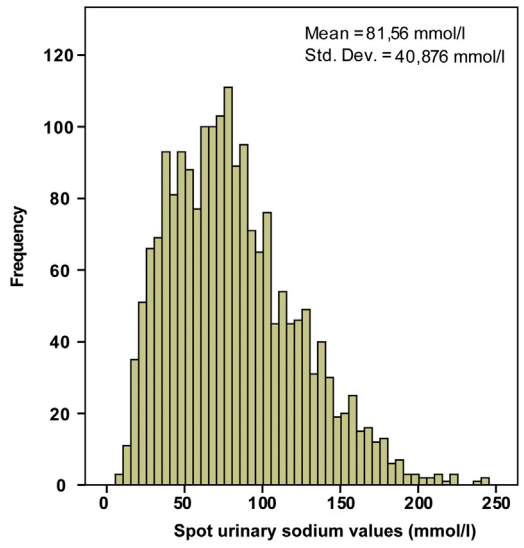
TABLE 1 Baseline Characteristics of the Entire Study Population

	Total Population (N = 80)	Low Sodium Excreters (n = 41)	High Sodium Excreters (n = 39)	p Value
Demographics				
Age, yrs	71 ± 11	73 ± 10	69 ± 12	0.069
Males	70 (88)	34 (83)	36 (92)	0.205
Heart failure type				
HFrEF	69 (86)	32 (78)	37 (95)	0.029
HFpEF	11 (14)	9 (22)	2 (5)	0.029
Heart failure cause if HFrEF				0.173
Ischemic	47 (59)	22 (69)	25 (68)	
Nonischemic	22 (31)	10 (31)	12 (32)	
Physical features				
Systolic blood pressure, mm Hg	118 ± 13	117 ± 14	120 ± 11	0.283
Diastolic blood pressure, mm Hg	69 ± 10	68 ± 11	70 ± 8	0.427
Weight, kg	82 ± 17	78 ± 16	86 ± 18	0.035
BMI, kg/m^2	27 ± 5	27 ± 5	28 ± 6	0.411
Heart rate, beats/min	65 ± 8	66 ± 11	64 ± 7	0.233
Comorbidities				
Atrial fibrillation	32 (40)	18 (44)	14 (36)	0.465
COPD	8 (10)	4 (10)	4 (10)	0.941
Hypertension	58 (73)	30 (73)	28 (72)	0.890
Dyslipidemia	65 (81)	35 (85)	30 (77)	0.445
Diabetes	13 (16)	4 (10)	9 (23)	0.106
Laboratory analysis				
Sodium, mmol/l	139 ± 2	140 ± 3	140 ± 2	0.718
Potassium, mmol/l	4.7 ± 0.5	4.6 ± 0.5	4.8 ± 3.9	0.067
Hemoglobin, g/dl	13.9 ± 1.3	13.9 ± 1.3	14.0 ± 1.4	0.753
Estimated GFR, ml/min	54.7 ± 19.4	54 ± 21	55 ± 18	0.850
NT-proBNP, ng/l	771 (221–1,906)	784 (257–2,924)	783 (228–1,752)	0.908
NYHA functional class				0.553
II	72 (90)	37 (90)	35 (90)	
III	8 (10)	4 (10)	4 (10)	
Echocardiography				
LVEF, % (if HFrEF)	33 ± 7	32 ± 8	34 ± 6	0.327
LVEDD, cm (if HFrEF)	6.3 ± 1.2	5.6 ± 1.4	6.4 ± 1.2	0.010
LVESD, cm (if HFrEF)	5.3 ± 1.4	4.6 ± 1.5	5.5 ± 1.3	0.005
E/e′ (all)	11.6 ± 4.7	13.2 ± 5.0	12.2 ± 6.2	0.410
TAPSE, cm (all)	1.9 ± 0.8	1.9 ± 0.6	2.0 ± 0.7	0.683
Guideline-directed HF therapy				
ACE inhibitor (if HFrEF)	44 (64)	20 (63)	24 (65)	0.839
ARB (if HFrEF)	22 (32)	11 (34)	11 (34)	0.680
Beta-blocker (if HFrEF)	67 (97)	31 (97)	36 (97)	0.917
CRT or ICD (all patients)	58 (73)	26 (63)	32 (81)	0.062
Aldosterone antagonist (all patients)	65 (81)	32 (78)	33 (85)	0.452
Loop diuretics (all patients)	29 (36)	15 (37)	14 (36)	0.949

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; E/e′ = early mitral inflow velocity-to-mitral annular early diastolic velocity ratio; GFR = glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; TAPSE = tricuspid annular plane systolic excursion.

FIGURE 2 Histogram of All Spot Urinary Sodium Values



proportion of patients functioning in NYHA functional class II and NT-proBNP concentration of 777 (IQR: 221 to 1,906) ng/l. Patients with HFrEF were optimally treated with guideline-recommended HF therapies as illustrated by the ubiquitous use of renin-angiotensin-aldosterone blockers and beta-blockers and the high use of cardiac resynchronization therapy and implantable cardioverter-defibrillators. Online Table 1 illustrates baseline physical examination features assessing congestion states in the entire population and after subdivision according to baseline loop diuretic use, indicating that most patients had few signs of congestion at baseline.

LONGITUDINAL SPOT URINE CONCENTRATION IN THE ENTIRE POPULATION. By the 30-week follow-up, a total of 1,970 individual urine samples had been collected. A total of 34 patients collected consecutive urine samples only during the first 12 weeks, as they expressed their desire to discontinue further sample collection at the first follow-up. The remaining patients collected samples for the entire 30-week follow-up. Mean U_{na} concentration was 81.6 ± 41 mmol/l. A histogram documenting the distribution of all spot U_{na} concentrations analyzed is shown in **Figure 2**. **Figure 3A** illustrates the repeated measurements of U_{na} concentration with corresponding 95% confidence interval (CI) for the entire patient population. In the entire patient population, U_{na} concentration remained stable throughout the study, as illustrated by the nonsignificant time effect ($p = 0.663$). However, visual inspection of all individual urinary profiles indicates interindividual differences (Online Figure 2). Post hoc *t*-test results of the slope and the intercept of the curve of the linear mixed model divided patients into chronically high and low sodium excretion (**Figure 3B**). Baseline characteristics of high and low sodium excreters are listed in **Table 2**, illustrating a high resemblance in baseline characteristics. Additionally, in the high sodium excreters group the slope of the individual U_{na} concentration curve remained stable in 30 of the 39 patients (77%) and significantly dropped over time in 9 patients (23%). In the low sodium excreters group, the U_{na} concentration remained stable in fewer patients (26 of the 41 patients or 63%), whereas 15 patients (37%) exhibited a decline in sodium output over time. Binary regression analysis, carried out to determine what clinical, biochemical, and echocardiographic factors were associated with being a high sodium excreter, are shown in **Table 3**, indicating that only younger age was an independent predictor of being a high sodium excreter (odds ratio [OR]: 0.91; 95% CI: 0.83 to 1.00; $p = 0.045$ per year).

URINARY SODIUM IN RELATION TO OUTCOME. During a mean follow-up of 587 ± 54 days, a total of 21 individual patients developed the endpoint of AHF hospitalization. Follow-up was complete in all patients. Three patients who had an AHF episode subsequently died, all after the period of actively collecting urine samples. The median time to the first AHF hospitalization was 129 days (range: 71 to 248 days). **Table 3** shows the baseline characteristics of the patients with or without an AHF hospitalization. Patients who had AHF hospitalization during follow-up had lower blood pressure, a lower level of hemoglobin, lower estimated glomerular filtration rate (eGFR), higher NT-proBNP, and poorer right ventricular and left ventricular systolic function and indices of higher filling pressures (E/e′ and right ventricular systolic pressure).

Figure 3C illustrates the longitudinal U_{na} profile of patients with or without AHF hospitalization. Patients with AHF hospitalization had a lower longitudinal U_{na} concentration compared with patients without AHF hospitalization ($F_{[1.80]} = 24.063$; $p < 0.001$). Both the time effect and the interaction between time and development of AHF hospitalization were nonsignificant ($p = 0.612$ and $p = 0.634$, respectively), indicating that patients who develop AHF during follow-up exhibit their own statistically lower U_{na} trajectory. Intercept analysis indicates that these curves are differentiated from one and another from the beginning ($p < 0.001$). In an additional sensitivity analysis including NT-proBNP and eGFR as random-effects, patients with an AHF episode still exhibited a lower U_{na} concentration ($p = 0.041$).

Because 34 of the patients collected samples only during the first 12 weeks, a sensitivity analysis restricted to the 46 remaining patients with a complete 30-week collection was also performed, using the same fixed and random effects in the linear mixed model. Similarly, the sensitivity analysis revealed that patients with AHF hospitalization also had a significantly lower U_{na} concentration ($F_{[1.46]} = 5.071$; $p = 0.027$). An additional sensitivity analysis restricted to HFrEF patients indicated similar results ($F_{[1.218]} = 20$; $p < 0.001$), as did a sensitivity analysis restricted to patients not taking loop diuretics at baseline ($F_{[1.203]} = 11$; $p < 0.001$). Online Table 2 illustrates baseline characteristics according to the presence of baseline loop diuretic use, whereas Online Figure 3 illustrates the longitudinal U_{na} concentration according to baseline loop diuretic use.

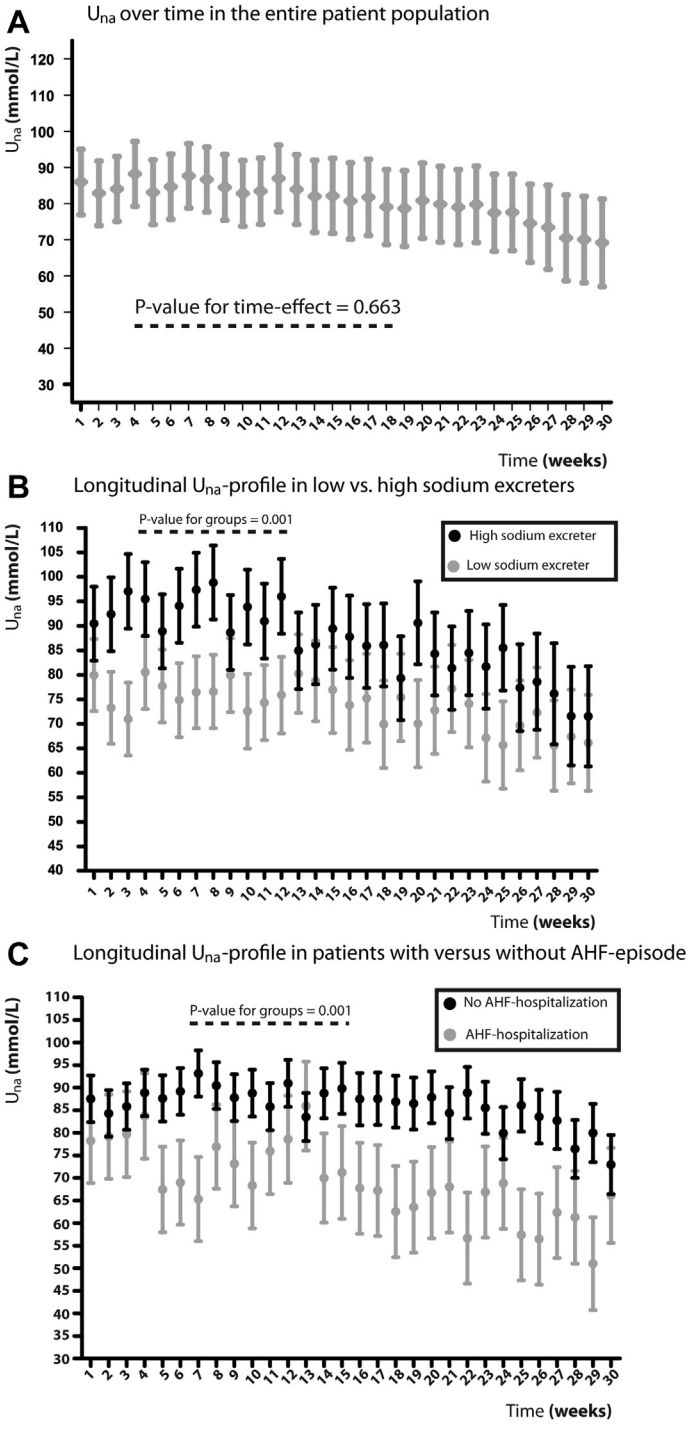
A total of 16 patients developed AHF hospitalization during the period of actively collecting weekly urine samples. To further assess temporal changes in U_{na} concentration preceding and following AHF hospitalization, the urine samples preceding and following the week of HF hospitalization are plotted in the **Central Illustration**. Additionally, longitudinal weight changes and changes in the VAS scale in relation to the development of AHF are also illustrated in the **Central Illustration**, showing that the U_{na} concentration significantly dropped in the week preceding AHF hospitalization. This decline in U_{na} concentration could not be identified over longer periods before decompensation (e.g., −2 weeks or −1 week). Interestingly, in comparison to U_{na} concentration changes, early changes in weight and VAS dyspnea scoring were not apparent. Additionally, none of the patients indicated on the biometric evaluation form that their food pattern changed or became diminished (Online Table 3). After the AHF hospitalization, the U_{na} concentration returned to a similar value as before the AHF hospitalization.

SPOT SAMPLES VERSUS CONTINUOUS COLLECTION. Online Figure 4 shows an analysis of the relationship between the correlation of the averaged spot U_{na} concentration and averaged 24-h U_{na} concentration in patient populations with or without AHF hospitalization. Patients with AHF hospitalization had both lower spot and continuous collection U_{na} concentrations, but the strength of the correlation did not differ from patients without an AHF episode (R-to-Z Fisher transformation $p = 0.960$).

DISCUSSION

The current study is the first to provide insight in the longitudinal U_{na} profiles in stable HF patients,

FIGURE 3 Longitudinal U_{na} Values for the Entire Population, High- and Low-Sodium Excreters, and Patients With or Without AHF Hospitalization



Bars indicate mean with standard deviation. **(A)** Repeated U_{na} measurements in the entire population. **(B)** U_{na} profile of low and high sodium excreters. **(C)** U_{na} profile of patients with or without HF admission. AHF = acute heart failure; U_{na} = urinary sodium; other abbreviation as in **Figure 1**.

TABLE 2 Multivariate Binary Regression Analysis of Clinical, Biochemical, and Echocardiographic Associates of High Sodium Excreters

	Odds Ratio	Lower 95% CI Boundary	Upper 95% CI Boundary	p Values
Age, yrs	0.91	0.83	1.00	0.045
Males	1.04	0.12	8.75	0.972
NYHA functional class (II = reference)	0.25	0.05	1.39	0.113
Dyslipidemia	0.38	0.06	2.30	0.291
RAS blocker	2.53	0.17	37.96	0.501
Beta-blocker	2.40	0.03	175.81	0.689
MRA	0.99	0.15	6.73	0.990
Loop diuretic	0.47	0.09	2.46	0.368
BMI, kg/m^2	1.01	0.87	1.17	0.930
SBP, mm Hg	1.05	0.98	1.12	0.168
Hemoglobin, g/dl	0.74	0.43	1.26	0.265
Plasma sodium, mmol/l	0.94	0.73	1.22	0.647
eGFR, ml/min per 1.73 m^2	1.01	0.96	1.06	0.816
Plasma NT-proBNP, ng/l	1.00	1.00	1.01	0.143
Plasma osmolality, mOsm/l	1.00	0.99	1.01	0.595
Plasma aldosterone, ng/l	1.00	1.00	1.00	0.318
PRA, µg/l/h	1.00	0.98	1.02	0.849
EDV, ml	0.96	0.29	3.25	0.950
ESV, ml	2.16	0.71	6.58	0.177
LVEF, %	1.01	0.93	1.09	0.796
E/E′	1.00	0.87	1.14	0.938
RVSP, mm Hg	0.99	0.92	1.06	0.757
TAPSE, cm	0.28	0.08	1.05	0.059

E/E′ = mitral peak velocity of early filling (E)-to-early diastolic mitral annular velocity (E′) ratio; EDV = end diastolic volume; ESV = end systolic volume; MRA = mineralocorticoid receptor antagonist; PRA = plasma renin activity; RAS = renin-angiotensin system; RVSP = right ventricular systolic pressure; other abbreviations as in Table 1.

offering novel insights into the potential contributing mechanism of developing AHF. Main findings may include the following. 1) Stable HF patients overall exhibited a relatively stable U_{na} concentration over time, although great interindividual differences exist. 2) Patients who developed AHF hospitalization exhibited a significantly lower U_{na} concentration overtime. 3) Shortly before the AHF hospitalization, the U_{na} concentration further dropped and returned to baseline after decongestive therapy. 4) A significant amount of stable HF patients excreted high concentrations of sodium without developing overt decompensation, and Un_a profiling may help to identify such patients.

Increasing data are pointing out that a higher U_{na} concentration during diuretic treatment for AHF is associated with a higher odds of achieving euvolemia and a lower risk of HF readmissions and cardiovascular mortality (6,7,9). However, no data are available for chronic renal sodium excretion during a phase of clinical stability. Therefore, the present study expands the field of spot U_{na} concentration measurements to patients with stable HF, indicating that chronic HF patients exhibit a relative stable U_{na} profile over longer time periods, excreting relative similar amounts of U_{na} concentrations on consecutive weeks. Interestingly, differences in LV function; use of medications, including diuretics; renal function; and residual neurohormonal activation or natriuretic peptides did not account for different patterns of U_{na} concentration. Nevertheless, significant differences were seen between patients, with some patients excreting higher concentrations of sodium and other patients excreting lower concentrations of sodium. Intriguingly, these patients are ostensibly similar in terms of baseline characteristics, perhaps suggesting that sampling of the U_{na} concentration can offer unique information.

Furthermore, patients who developed AHF hospital admission exhibited a significantly lower U_{na} concentration. Additionally, the present prospective data indicate a temporal relationship between a declining U_{na} concentration and the development of an AHF admission, which may suggest that, in the vicinity of clinical decompensation, the renal natriuretic excretion drops further. Importantly, patients did not indicate that they altered their food pattern over the weeks before decompensation. These data may be important as they provide further insight into potential mechanisms to explain why stable HF patients decompensate. Aside from pathways related to the heart (e.g., triggering factors such as ischemia, arrhythmia, or acute blood pressure changes) (14), data from patients with implantable hemodynamic monitors have illustrated that subtle rises in filling pressures precede the AHF hospitalization by numerous days (15). The present data now supplement this finding by illustrating that alterations in the renal pathway (e.g., loss of natriuretic capacity) probably contribute to and precede the development of AHF. Indeed, more sodium retention will lead to enhanced vasoreactivity and plasma volume, thereby further contributing to the occurrence of AHF (3). Interestingly, temporal changes in weight and the VAS-dyspnea score were not as apparent early on as changes in U_{na} concentration. Indeed, it is well known that significant weight gain during the week before AHF admission only has a 6% sensitivity, underscoring the need for more sensitive tools to detect decompensation (16).

Several reasons may explain the relationship between a low U_{na} concentration and the observed poor clinical outcome. First, it is clear that the present study cannot account for differences in the amount of ingested sodium. Therefore, it may be possible that patients who require AHF hospital admission have a lower sodium intake than patients without decompensation as a result of more

adherence to instructions to sustain to a low sodium diet. More recent iterations of HF guidelines recognize that the evidence for sodium restriction is scarce, of low methodological quality, and often conflicting (12). Indeed, some observational data even suggest that low sodium intake (typically <3 g/day) may be associated with compensatory neurohormonal and sympathetic activation (17,18). Second, it can be hypothesized that patients with a chronically lower U_{na} concentration exhibit a higher risk for AHF due to an inability to excrete sufficiently high concentrations of sodium to sustain euvolemia (4). Although some chronic sodium retention may initially be compensated for by increased nonosmotic interstitial sodium buffering, it seems that this compensatory pathway also falls short in the long run (3,19). The close temporal relationship between the further drop in U_{na} concentration and the development of AHF may suggest an inability to buffer any additional retained sodium, leading to overt clinical decompensation. In addition, decompensation predominantly occurred in patients who already had a lower U_{na} concentration, which may suggest the role of intrinsic renal adaptations favoring chronic tubular sodium retention (1,2). Third, it could be hypothesized that patients with an AHF episode, have mechanisms in place that result in more fluctuation in the U_{na} concentration throughout the day, favoring a lower U_{na} in the morning. For instance, sicker patients often manifest enhanced nocturnal diuresis, which could lower the morning U_{na} concentration in comparison to a continuous collection. However, our data argue against this as an explanation for why HF patients with an AHF episode have a chronically lower spot U_{na} concentration, as there was no difference in the strength between the correlation of spot versus continuous collection U_{na} concentration in patients with or without a HF episode, perhaps arguing against more fluctuation in U_{na} concentration due to enhanced nocturnal free water clearance in the sicker patients. However, to finitely determine whether intrinsic changes in renal sodium excretion or enhanced nocturnal free water diuresis is at the basis of the lower U_{na} concentration we would have needed 24-h urine samples instead of U_{na} spot samples. However, collecting longitudinally almost 2,000 urine collections is not practically feasible. Nevertheless, regardless of the mechanism that lowers U_{na} concentration in patients who develop AHF, the U_{na} spot samples offered novel prognostic information, even in addition to data from established biomarkers such as NT-proBNP and eGFR, potentially even detecting imminent decompensation.

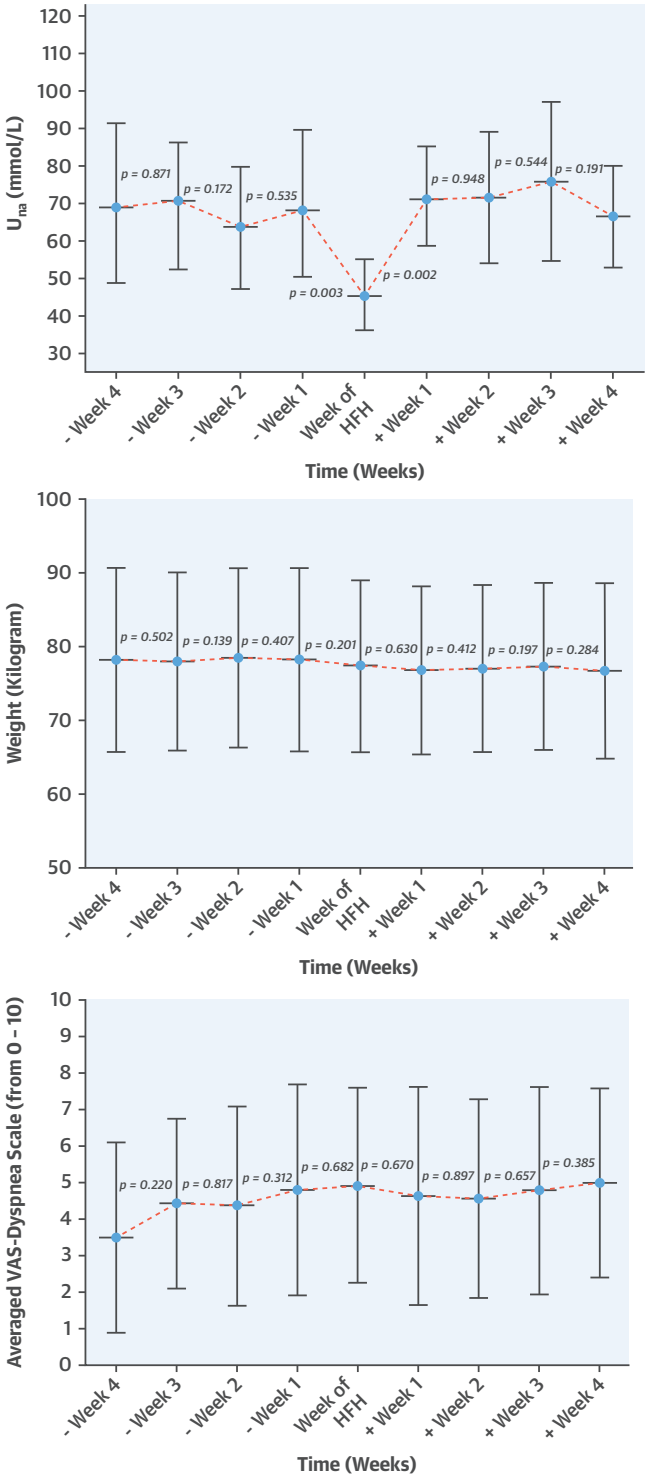
Equally interesting in the present study is the finding that a large number of patients consumed and excreted high concentrations of sodium. This may

TABLE 3 Baseline Characteristics for Patients With or Without Heart Failure

	Total Population (N = 80)	Without HF Hospitalization (n = 61)	With HF Hospitalization (n = 21)	p Value
Demographics				
Age, yrs	71 ± 11	70 ± 12	74 ± 8	0.227
Males	70 (88)	54 (89)	18 (84)	0.620
Heart failure type				0.640
HFrEF	69 (86)	52 (85)	19 (89)	
HFpEF	11 (14)	9 (15)	2 (11)	
Heart failure cause (if HFrEF)				0.767
Ischemic	47 (59)	37 (61)	11 (53)	
Nonischemic	22 (31)	10 (39)	10 (47)	
Physical features				
Systolic blood pressure, mm Hg	118 ± 13	121 ± 12	112 ± 14	0.008
Diastolic blood pressure, mm Hg	69 ± 10	70 ± 10	65 ± 10	0.032
Weight, kg	82 ± 17	83 ± 18	80 ± 14	0.569
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5	0.824
Heart rate, beats/min	65 ± 8	65 ± 9	67 ± 10	0.330
Comorbidities				
Atrial fibrillation	32 (40)	22 (36)	10 (52)	0.198
COPD	8 (10)	5 (8)	3 (15)	0.335
Hypertension	58 (73)	43 (71)	17 (79)	0.471
Dyslipidemia	65 (81)	49 (79)	19 (90)	0.546
Diabetes	13 (16)	9 (15)	4 (21)	0.516
Laboratory analysis				
Sodium, mmol/l	139 ± 2	139 ± 3	139 ± 2	0.729
Potassium, mmol/l	4.7 ± 0.5	4.7 ± 0.5	4.7 ± 0.5	0.433
Hemoglobin, g/dl	13.9 ± 1.3	14.1 ± 1.3	13.2 ± 1.2	0.011
Estimated GFR, ml/min	54.7 ± 19.4	58.1 ± 19.4	43.5 ± 19.9	0.004
NT-proBNP, ng/l	771 (221–1,906)	549 (204–1,104)	2,859 (966–5,291)	0.001
NYHA functional class				0.353
II	72 (90)	56 (92)	18 (84)	
III	8 (10)	5 (8)	2 (16)	
Echocardiography				
LVEF, % (if HFrEF)	33 ± 7	34 ± 7	29 ± 8	0.099
LVEDD, cm (if HFrEF)	6.3 ± 1.2	5.8 ± 1.3	6.3 ± 1.5	0.217
LVESD, cm (if HFrEF)	5.3 ± 1.4	4.9 ± 1.4	5.3 ± 1.4	0.491
E/e′ (all)	11.6 ± 4.7	11.4 ± 4.6	16.8 ± 6.6	0.001
TAPSE, cm (all)	1.9 ± 0.8	2.0 ± 0.5	1.7 ± 0.5	0.019
Guideline-directed HF-therapy				
ACE inhibitor (if HFrEF)	44 (64)	33 (64)	11 (65)	0.926
ARB (if HFrEF)	22 (32)	16 (31)	6 (35)	0.728
Beta-blocker (if HFrEF)	67 (97)	50 (96)	17 (100)	0.412
CRT or ICD (all patients)	58 (73)	44 (72)	17 (74)	0.895
Aldosterone antagonist (all patients)	65 (81)	48 (79)	19 (90)	0.293
Loop diuretics (all patients)	29 (36)	20 (33)	10 (47)	0.248

Values are mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION Longitudinal U_{na} Values in Relation to HFH



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During week −1, U_{na} = 70 ± 32 mmol/l. On the week of HFH, U_{na} = 46 ± 16 mmol/l; during week +1, U_{na} = 71 ± 22 mmol/l. p Values were derived by paired *t*-test comparing the U_{na} value with the value of the preceding week. The median duration between the collection of the spot sample of the week of HFH and presentation to the hospital was 5 days (range: 4 to 7 days). HFH = heart failure hospitalization.

indicate that a subset of stable HF patients could safely ingest large quantities of sodium because they do not develop a subsequent AHF admission. Although 1 observational study in healthy individuals linked a higher U_{na} output to a higher incidence of new onset HF, this association was not statistically significant after adjusting for blood pressure (20). Our HF patients, under optimal neurohormonal blockade, did not exhibit hypertension. It is therefore questionable whether sodium restriction is truly necessary in all HF patients.

Although the present study is hypothesis generating, the data indicate that longitudinal assessment of U_{na} is feasible and may identify different subsets of stable patients. Although U_{na} concentrations were analyzed in a laboratory setting, self-measurement of U_{na} or chloride concentration is possible by using a urinary dipstick method (21). If additional studies confirm our findings, U_{na} profiling may become a tool to empower HF patients to predict imminent decompensation or to individualize dietary patterns or the diuretic regimen.

STUDY LIMITATIONS. First, this is a small study, and therefore, all results should be interpreted as exploratory and hypothesis generating. Nevertheless, the sample size of the study should be interpreted in the face of the intensive study protocol. Second, spot sodium values were used, as longitudinally collecting a large number of 24-h urine samples is impractical. However, there is increasing interest in spot U_{na} concentration, and this method can easily be integrated into clinical practice. Third, there was some subject dropout in our study (20%), which relates to the intensive study protocol. Fourth, differences in sodium intake cannot be accounted for. Fifth, dichotomizing the individual U_{na} concentration curve into high and low sodium excreters is a somewhat artificial statistical method. However, the main goal of this analysis was to determine whether different urinary phenotypes exist that may not be readily apparent when looking at baseline characteristics. Due to the small sample size, division into more groups (e.g., an intermediate group) was not possible. Finally, only a sample number of HFpEF patients were enrolled, and it is clearly not powered to assess this cohort. However, a sensitivity analysis restricted to the HFrEF cohort did demonstrate the incremental information of U_{na} concentration.

CONCLUSIONS

U_{na} concentration remains relatively consistent over time in stable, mildly symptomatic HF patients. Patients who require an HF admission exhibit a chronically lower U_{na} concentration, which further drops just before decompensation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The burden of HF readmission remains high in clinical practice. Strategies that help to understand the pathophysiology of the development of acute decompensation are necessary. The present analysis demonstrates that patients who are at risk for development of AHF chronically excrete a lower amount of sodium. Additionally, a further drop in sodium excretion precedes the development of AHF. Urinary sodium profiling may help to detect patients at risk for AHF and possibly imminent decompensation.

TRANSLATIONAL OUTLOOK: Measurement of urinary sodium in a laboratory setting is inexpensive, readily available, and may offer novel information on HF patients. However, self-measurement of urinary sodium or chloride is possible by using a dipstick method. Research is necessary to determine if this may be a tool to empower HF patients. Additionally, research is necessary to determine if tailored therapy to enhance sodium excretion is associated with a lower risk for AHF.

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KEY WORDS heart failure, outcome, salt, sodium, urinary sodium

APPENDIX For supplemental figures and tables, please see the online version of this paper.