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Can fractional excretion of sodium predict worsening of renal function, in-hospital mortality, and length of hospital stay in acute decompensated heart failure?

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Original Article

Abstract

BACKGROUND: Fractional excretion of sodium (FENa), the reflection of sodium (Na) handling by the kidney during natriuresis, is influenced by exo- and endogenous factors that have a powerful impact on renal function. We performed this study to define the correlation between FENa and worsening renal function (WRF) and assess the value of FENa in the length of hospital stay and in-hospital mortality in the patients with acute decompensated heart failure (ADHF).

METHODS: This prospective observational study was performed in two tertiary governmental heart centers located in Ahvaz, Iran, from March 2019 to March 2020. Any individual suffering from ADHF who had no renal failure, received only loop diuretics, and was on a low Na diet was eligible for recruitment in this study. The urine sample used to calculate FENa was a 24-hour sample.

RESULTS: Over the one year, 56 patients met the inclusion criteria. The total study population had a mean age of 61.46 ± 14.22 years with the dominance of women (51.8%). The mean age of men and women was 58.59 ± 14.35 and 64.13 ± 13.80 years, respectively. During hospitalization, 13 (23.2%) patients experienced WRF. In patients who experienced WRF during hospitalization, FENa of < 1% was mostly observed compared to FENa of 1%-2% (42.9% vs. 0%, P < 0.05). Post-hoc test of data on mean hospitalization days indicated that those with lower FENa had longer admission periods than those with other FENa groups (< 1%: 3.04 ± 1.02 days vs. 1%-2%: 1.58 ± 0.66 days, P < 0.001 and < 1%: 3.04 ± 1.02 days vs. > 2%: 2.30 ± 0.92 days, P = 0.02). There was no significant relation in terms of in-hospital death across different categories of FENa (P = 0.69).

CONCLUSION: Our data suggested that FENa less than 1% was associated with WRF and could be associated with a longer hospitalization period. We did not find any association between FENa and in-hospital mortality. Further studies with a larger number of patients are required to determine the cut-off value.

Keywords: Sodium; Heart Failure; Kidney; Hospitalization

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Introduction

Heart failure (HF) is a clinical syndrome in which the heart cannot respond appropriately to the body's metabolic needs.[1] HF is a prevalent disorder worldwide that over 5.8 million in the United States of America (USA) and 23 million worldwide suffer from it.[2]

Several studies have shown that patients with HF frequently suffer from comorbid diseases, which are common and pose excess mortality risk independently.[3,4] The most prevalent comorbid

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disease is renal impairment (RI), as in different types of cardio-renal syndromes (CRS).[5,6]

With the onset of cardiac dysfunction, left ventricular ejection fraction (LVEF) decreases and leads to worsening renal function (WRF), decrease in diuretic response, and finally, volume overload by interfering of at least renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and anti-diuretic hormone (ADH).[7-9]

WRF, defined as a 0.3 mg/dl increase in the serum creatinine (Cr) level during the hospitalization period, is considered a sensitive marker of RI, which is a marker of poor prognosis for HF in hospitalization and after discharge periods.[10-12]

Fractional excretion of sodium (FENa), the product of net sodium (Na) filtration and absorption, reflects Na handling by the kidney.[13] According to several studies, pretreatment FENa lower than 1% in patients with HF was associated with pre-renal azotemia.[14-16]

Because the mentioned factors play a crucial role in the pathophysiology of WRF and have a direct effect on FENa and besides, WRF is related to the HF prognosis, we performed this study to define the correlation of FENa and WRF and assess the value of FENa in the length of hospital stay and in-hospital mortality in the patients with acute decompensated HF (ADHF).

Materials and Methods

This observational study was performed in two tertiary governmental heart centers (Imam Khomeini Hospital and Golestan Hospital) in Ahvaz, Iran. From March 2019 to March 2020, any individual suffering from ADHF who met inclusion criteria was eligible for recruitment in this study.

Diagnostic criteria were based on American College of Cardiology (ACC), American Heart Association (AHA), and New York Heart Association (NYHA) guidelines with signs and symptoms of fluid retention such as peripheral edema and dyspnea.[17]

Inclusion criteria were as follows: 1) primary diagnosis of ADHF at admission (AHA/ACC C, D; NYHA III, IV), 2) Cr level lower than 2 mg/dl (176 mmol/l), 3) loop diuretic monotherapy, 4) being on 2 g Na diet daily since admission, and 5) daily administration of at least 40 mg intravenous (IV) furosemide.

Each patient was evaluated based on chest X-ray, 12-lead electrocardiography (ECG), and echocardiography. All admitted patients were treated daily with a loop diuretic, furosemide. IV doses of the furosemide could vary between 40 to 160 mg/day based on the physician's discretion. An oral form of the remedy was considered equivalent to a one-half dose of IV form because of its 50% bioavailability.[18]

The patient's 24-hour urine was collected in a metered container and changed at each patient's specific time of day. Then, for the calculation of FENa, both urine spot samples from the container and serum samples during the same 24 hours were taken to measure Cr and Na levels in each. The calculation of FENa is as follows:

$$\text{FENa} = \frac{\text{Serum (Na)} \times \text{Urine (Cr)}}{\text{Serum (Cr)} \times \text{Urine (Na)}} \times 100$$

The patients were followed up during the admission period to reach the NYHA functional class II.

Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (ID: IR.AJUMS.REC.1399.201). This article is the result of a residency course thesis with the number 9905.

Statistical analysis: We used the SPSS software (version 22, IBM Corporation, Armonk, NY, USA) for data analysis. Categorical and continuous variables were reported as frequency (percentage) and mean ± standard deviation (SD). Normality assumption was performed using the Shapiro-Wilk test. Chi-square test (or Fisher's exact test) was used to evaluate any differences between categorical variables. A post-hoc test with Bonferroni correction was implemented to examine the potential differences between each pre-defined group. The correlation between hospitalization stay and FENa was assessed through Pearson/Spearman correlation according to normality status of data. We considered all P-values < 0.05 as statistically significant.

Results

The total study population had a mean age of 61.46 ± 14.22 years, and more than half were women (51.8%). The mean age of men and women was 58.59 ± 14.35 and 64.13 ± 13.80, respectively. The continuous variables had abnormal distributions. The mean LVEF and serum Cr were 20.80 ± 8.93% and 1.08 ± 0.20 mg/dl, respectively. During hospitalization, 13 (23.2%) patients experienced WRF. The frequencies of FENa according to pre-defined classification were as the following: < 1%: 21 (37.5%), 1%-2%: 12 (21.4%), > 2%: 23 (41.1%). 17 out of 56 (30.4%) patients

died during hospitalization due to multiorgan failure. The differences between cardiac parameters and WRF, according to FENa groups, are shown in table 1. Our findings revealed some differences in terms of right ventricular dysfunction (RVD), tricuspid regurgitation (TR), and WRF (P = 0.02, P = 0.04, and P = 0.01, respectively). Moderate to severe RVD was more prevalent among patients with FENa of < 1% compared to those with FENa of 1%-2% (71.4% vs. 16.7%, P < 0.05). Likewise, the lowest group of FENa had significantly higher percentages of WRF rather than patients in the middle group (FENa: 1%-2%) (42.9% vs. 0%, P < 0.05). On the other hand, individuals with FENa of 1%-2% suffered more from mild TR than those with FENa of less than 1%.

Data on mean mortality and hospitalization days indicated that those with the lowest FENa had a more extended admission period than those with the other FENa categories (< 1%: 3.04 ± 1.02 days vs. 1%-2%: 1.58 ± 0.66 days, P < 0.001 and < 1%: 3.04 ± 1.02 days vs. > 2%: 2.30 ± 0.92 days, P = 0.02). There were no significant differences in terms of death across different categories of FENa.

Regarding the correlation between FENa and hospitalization length, although increasing FENa was associated with a shorter hospital stay, this correlation was not statistically significant (r = -0.239, P = 0.07).

Discussion

FENa has been used in several studies to assess the effectiveness of diuresis in patients with HF. As a result of these studies, a baseline FENa of less than 1% is associated with pre-renal azotemia caused by renal hypoperfusion.[14-16] This study aimed to figure out whether there was a correlation between FENa and WRF.

FENa, the reflection of net Na filtration and absorption from different nephron segments, is influenced by endo- and exogenous factors.[13] Diuretics, one of the exogenous factors, block Na absorption from different segments of the nephron in a way that loop diuretics, the most abundant used diuretic agents in patients with ADHF,[19] produce marked diuresis and natriuresis, which can reach approximately 20%-25% in the first 6 hours after IV injection followed by minimal diuresis till 24 hours.[20] Moreover, because of the age variation of reaching the peak time of FENa, we decided to calculate FENa based on a 24-hour urine spot sample.[21] We excluded patients with high salt intake because of being an exogenous factor leading to natriuresis and subsequently altering FENa.[22] Hypoperfusion caused by a decrease in renal blood flow in severe HF may involve Na reabsorption from different segments of nephrons, being one of the endogenous factors in altering FENa.

Table 1. The relation between study endpoints according to fractional excretion of sodium (FENa)

Characteristics	FENa			P*
	< 1% (n = 21)	1%-2% (n = 12)	> 2% (n = 23)	
Age (year)	61.09 ± 16.10	62.00 ± 14.50	61.50 ± 12.70	0.980
Gender (women)	11 (52.4)	6 (50.0)	12 (52.2)	0.990
LVEF (%)	20.95 ± 10.20	20.41 ± 10.30	20.86 ± 7.10	0.980
RVD				
Normal	1 (4.8)[a]	5 (41.7)	5 (21.7)	0.020
Mild	5 (23.8)	5 (41.7)	8 (34.8)	
Moderate to severe	15 (71.4)[a]	2 (16.7)	10 (43.5)	
TR				
Normal	0 (0)	1 (8.3)	0 (0)	0.040
Mild	3 (14.3)[a]	7 (58.3)	10 (43.5)	
Moderate	14 (66.7)	3 (25.0)	10 (43.5)	
Severe	4 (19.0)	1 (8.3)	3 (13.0)	
WRF				
Yes	9 (42.9)[a]	0 (0)	4 (17.4)	0.010
No	12 (57.1)	12 (100)	19 (82.6)	
Death	8 (38.1)	3 (25.0)	6 (26.1)	0.690
Hospitalization (day)	3.04 ± 1.02[a,b]	1.58 ± 0.66	2.30 ± 0.92	< 0.001

Data are presented as mean ± standard deviation (SD) or number and percentage
*P-values resulted from Fisher's exact test (categorical variables) and Kruskal-Wallis test (continuous variables); [a]P < 0.05 compared with the FENa of 1%-2% resulted from the post-hoc test with Bonferroni correction; [b]P = 0.02 compared with the FENa of > 2% resulted from the post-hoc test with Bonferroni correction
FENa: Fractional excretion of sodium; LVEF: Left ventricular ejection fraction; RVD: Right ventricular dysfunction; TR: Tricuspid regurgitation; WRF: Worsening renal function

http://arya.mui.ac.ir 15 Nov.

Thus, we excluded patients who received diuretics with different mechanisms of action to neutralize this confounding variable. Our study indicated that there was no significant correlation between FENa and LVEF (P = 0.61). This was against Hasenfuss et al. study with 9 patients, which indicated a significant correlation between the cardiac index of patients with HF and FENa.[23]

Our study revealed that lower FENa was more prevalent among patients who suffered from WRF during admission, which can be explained by activation of neurohormonal mechanisms. This is consistent with Alattar *et al.* study with 51 patients, which indicated a correlation of FENa more than 0.4% with WRF.[24] Regardless of the cause, aggressive natriuresis may afford more RAAS and SNS activation, and decrease effective intravascular volume. Thus, WRF develops eventually.[24]

Systemic venous congestion, one of the symptoms of patients with HF, is crucial because it indicates RVD and TR. Furthermore, growing evidence emphasizes systemic venous congestion for the development of WRF during its treatment.[25] As a result, RVD and TR severity can be prognostic markers of WRF. Due to the data included in our study, the severity of TR can be a prognostic marker of WRF (P = 0.01), while RVD had no significant correlation with WRF (P = 0.07). This was against Testani et al. study with 141 patients, which demonstrated a significant correlation between RVD and WRF.[26] We speculate that this discrepancy is due to the lack of separation of RVD patients with left ventricular dysfunction (LVD) in our analysis, as what happened in Testani et al. study. Besides, we found a significant inverse correlation between FENa and admission periods (P = 0.03), which is concordant to Thabt et al. study, which emphasized FENa as a marker with a substantial impact on the length of hospital stay.[27] Likewise, we did not find a correlation between FENa and death (P = 0.62).

Our study specified a correlation between RVD and mortality as in Kjaergaard et al. study, a sub-study of Echocardiography and Heart Outcome Study (ECHOS) trial in Danish patients done by Tricuspid Annular Plane Systolic Excursion (TAPSE) method.[28] Our results are also concordant to the findings of Juilliere et al.,[29] de Groote et al.,[30] and La Vecchia et al.[31] studies performed by thermodilution techniques during a right heart catheterization techniques.

We acknowledge that our study has limitations, such as the lack of information concerning HF etiology and a relatively small number of patients.

Conclusion

Our data suggested that FENa less than 1% was associated with WRF and could be associated with a longer hospitalization period. We did not find any association between FENa and in-hospital mortality. Further studies with a larger number of patients are required to determine the cut-off value.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

FA and ET designed the study. SKM involved in the preparation of the paper and carried out all experimental work. SA and FH contributed to the analysis of the data and manuscript revision. All authors approved the final manuscript.

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