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FRACTIONAL SODIUM EXCRETION AND ITS RELATION TO IN-HOSPITAL MORBIDITY AND MORTALITY IN PATIENTS ADMITTED WITH DECOMPENSATED HEART FAILURE

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All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: We aimed to correlate between urinary fractional sodium excretion as a marker of diuretic resistance in patients admitted with congestive heart failure and its impact on length of hospital stay together with in-hospital morbidity and mortality.

Methodology: Total 46 decompensated heart failure patients were enrolled in this study. We decided that the urine sample from which we can calculate the FENa level will be a 24-hour sample in an attempt to decrease the variability of FENa levels.

$$FENa = \frac{100 \times Na(urinary) \times creatinine(plasma)}{Na(plasma) \times creatinine\ (urinary)}$$

Intravenous furosemide was started on admission either as a continuous infusion or shots.

Results: The median age was 59 years;the majority were of male gender {n=41(89%)} .NYHA heart failure class on admission revealed that 8(17.4%) patients had NYHA class III and 38(82.6%) patients had a NYHA class IV . There was no correlation between FENa and NYHA class on admission (r = -0.09. p=0.51) or with the left ventricular ejection fraction(LVEF) (r = -0.04. p=0.77).Also no correlation was found between FENa and the total furosemide dose per day (r = -0.07, p=0.64).

FENa results came out with a median value of 1.5% with minimum and maximum FENa results equal to 0.05% and 5.2% respectively. The only three variables that contributed significantly to the prediction of hospital stay were Hb, LVEF, and FENa.

Conclusion: FENa can be used upon the patient's admission to guide therapy with combination therapies with other classes of diuretics in attempt to reduce the hospital stay.

Key Words: Fractional sodium excretion, Heart failure, Diuretic resistance.

INTRODUCTION

A variety of factors can account for persistent fluid retention in heart failure patients, including inadequate diuretic dose, excess sodium intake, delayed intestinal absorption of oral diuretics, decreased diuretic excretion into the urine, and increased sodium reabsorption at sites in the nephron other than those inhibited by the diuretic.[1-3]

Although difficult to quantify, diuretic resistance is thought to occur in one of three patients with CHF. In moderate and severe CHF patients, diuretic resistance occurs more frequently and often becomes a clinical problem.[4]

Despite its frequency, the term "diuretic resistance" remains inadequately defined. In general, failure to decrease the extracellular fluid volume despite liberal use of diuretics is often termed diuretic resistance. In clinical settings, diuretic resistance in edematous patients has been defined as a clinical state in which sodium intake and excretion are equalized before adequate elimination of fluid occurs.[4] More technically, diuretic resistance has been expressed as a FENa of <0.2%. FENa represents the amount of sodium excreted (mmol/time) as a percentage of filtered load.[5]

Characteristically ,loop diuretics produce marked water diuresis and natriuresis in heart failure patients in the first 6 hours after the intravenous dose; during this period, FENa can peak at approximately 20% to 25%.[6]

However in another study it was found that following a single dose of furosemide (1 mg/kg), peak FENa was achieved 30 minutes following injection in the younger patients (17 to 40 years old) and 120 minutes following injection in older patients (75 to 80 years old). Thus, timing of urine sample may lead to variability in the measurement of FENa.[7]

METHODOLOGY

46 patients admitted with a primary diagnosis of decompensated heart failure were enrolled in this study [stage C HF according to the AHA/ACC classification] of whatever cause.

Exclusion criteria involved the following:

-Patients with normal left ventricular ejection fraction.

-Mild symptoms not necessitating adding or increasing the dose of diuretics.

-Patients with chronic kidney disease (i.e GFR <60ml./min/1.73 m^2).

1-Full history and clinical examination.

2-Twelve lead electrocardiogram

3-Chest X-ray

4-Echocardiography: Left ventricular systolic functions were assessed by measuring the LVESD, left ventricle end diastolic dimension LVEDD by M-mode at the parasternal long axis then re assessed by parasternal short axis view upon which ejection fraction was calculated. Ejection fraction was assessed by Simpson's method in patients with segmental wall motion abnormalities.

5-Laboratory investigation: Complete blood count. Full kidney functions test (serum creatinine, potassium, urea and sodium levels).

Full Liver functions test.

Full lipid profile.

Fasting and post-prandial blood sugar.

Fractional excretion of sodium (FENa)

Thus, we decided that the urine sample from which we can calculate the FENa level will be a 24-hour sample in an attempt to decrease the variability of FENa levels between the different timings of the urine sample collection.

It was calculated from spot creatinine and sodium(Na) levels from a 24-hour urine sample along with serum levels of sodium and creatinine in the same 24-hour period; it's calculated as follows[8]:

The 24-hour urine collection was started as follows where the patient discards the 1st urination in early morning then

$$\text{FENa} = \frac{100 \times \text{Na(urinary)} \times \text{creatinine(plasma)}}{\text{Na(plasma)} \times \text{creatinine (urinary)}}$$

starts to collect urine in a specially designed metered container for the next 24-hours till the 1st urination of the next day and by this the collection process is completed.

Glomerular filtration rate was estimated by the Cockcroft-Gault equation:

6-In-hospital management: The patients were given a standard diet, receiving a defined fluid (1.5L./day) and a low salt (no more than 2.5 gm/day) intake.

$$\text{Ccr (mL/min)} = \frac{(140 - \text{Age}) \times \text{lean body weight [kg]} \times 0.85 \text{ (if female)}}{\text{Serum Creatinine [mg/dL]} \times 72}$$

The patients were started on anti-failure medications including ACEI/ARBs, spironolactone, BB and positive inotropic agents if low cardiac output signs and symptoms were present.

Intravenous furosemide was started on admission either as a continuous intravenous infusion or in the form of intravenous shots.

The patients were followed-up during the hospital stay for the following:

In-hospital mortality and occurrence of malignant arrhythmias (recurrent sustained ventricular tachycardia and torsades de pointes ventricular tachycardia in the long

QT syndrome), duration of hospital stay.

RESULTS

Of the 46 patients enrolled in this study ; the median age was 59 years;the majority were of male gender {*n=41(89%)*} . Prevalence of Diabetes mellitus {*n=30(65.2%)*}, hypertension {*n=30(65.2%)*}, dyslipidemia {*n=28(60.9%)*}, coronary artery disease {*n=34(73.9)*} and history of smoking was reported {*n=31(67.4%)*} (Table1).

NYHA heart failure class on admission revealed that 8(17.4%) patients had NYHA class III and 38(82.6%) patients had a NYHA class IV classification.

The mean systolic blood pressure on admission was 98±19.2mmHgand the mean diastolic blood pressure was 64±11.4mmHg with a mean pulse rate of 103.4±12.7 beats per minute.

The electrocardiogram revealed that 36 (71.3%) patients were in sinus rhythm while 10(21.7%) had atrial fibrillation. Also 8(17.4%) patients had left bundle branch block.

Their echocardiography showed an EF with a median of 28%. The left LVEDD had a median of 68mm. while the median of LVESD was 55mm. and finally the RVSP had a median of 50mmHg.

Laboratory workup revealed Hb with a median of 12.2gm/dl and a median for serum potassium level (K+) measuring 3.8mg/dl. The median creatinine clearance was 106ml/min/1.73m^2 while the median of serum levels of creatinine (S.Cr) and sodium (S.Na) were 0.8mg/dl and 138mmol/L. respectively. Also the medians for urinary excretion of creatinine and sodium were 55mg/dl and 83mmol/L. respectively. The daily urine volume had a median of 2100 ml./day.

FENa results came out with a median value of 1.5% with minimum and maximum values equal to 0.05% and 5.2% respectively.

Follow-up Characteristics: In-hospital follow-up for morbidity and mortality showed that there were no mortalities and 3 patients had sustained ventricular tachycardia that required DC shock. Only 2(4.3%) patients had symptoms and signs of low cardiac output state, while the rest 41(89%) patients had an event-free hospital stay (Figure1).

The mean hospital stay was *8 ±4.2*days with a minimum of 4 days and a maximum of 22 days.

Correlation between the fractional excretion of sodium (FENa) with different clinical variables: The correlation between the hospital stay and the log of the FENa percentage was r = -0.489 with p=0.0006. This result is with the outlier excluded, but when the outlier is included, Pearson's correlation drops to -0.33, but the p-value is still significant at p=0.021. Therefore there is a significant inverse correlation between FENa and hospital stay (Figure 2).

There was no correlation between FENa and NYHA class on admission (r = -0.09. *p=0.51*) or with the left ventricular ejection fraction (LVEF) (r = -0.04. *p=0.77*).Also no correlation was found between FENa and the total furosemide dose per day (r = -0.07, *p=0.64*).

A multiple regression model was run with the dependent variable log (FENa), predicted by the independent variables: Diabetes Mellitus (DM), Hypertension (HTN), Dyslipidemia, and Coronary Artery Disease (CAD). None of these variables showed a significant relation to FENa.

As a way to identify the independent predictor(s) of length of hospital stay, a multiple linear regression analysis was done putting in the model the different clinical variables such Hb, serum sodium level, Left ventricular ejection fraction (LVEF), Heart Failure classification, and FENa.

The only three variables that contributed significantly to the prediction of hospital stay were Hb, LVEF, and FENa; with the latter variable showing the most significant relation (Table 2).

DISCUSSION

Table 1: Demographic and risk factors of the Studied group

Parameter	
Age (Years) Range (min-max)	29-79
Gender Male/ Female n(%)	41/ 5 (89.1%/ 10.9%)
DM	65.2%
HTN	65.2%
DUSLIP.	60.9%
Smoking	67.4%
Coronary Artery Disease	73.9%

* Data are expressed as number(%)

Table2: Independent Predictors of Length of Hospital Stay

Independent Predictor of length of hospital stay	p-value
Hb	0.01Signif.
Serum Na+	0.1 NS
LVEF	0.003Signif.
Lasix dose /day	0.4 NS
NYHA classif.	0.4 NS
Log (FENa)	0.00005Signif.

Figure 1: In Hospital Outcome

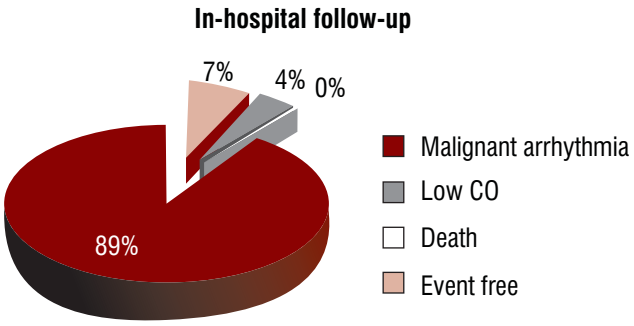
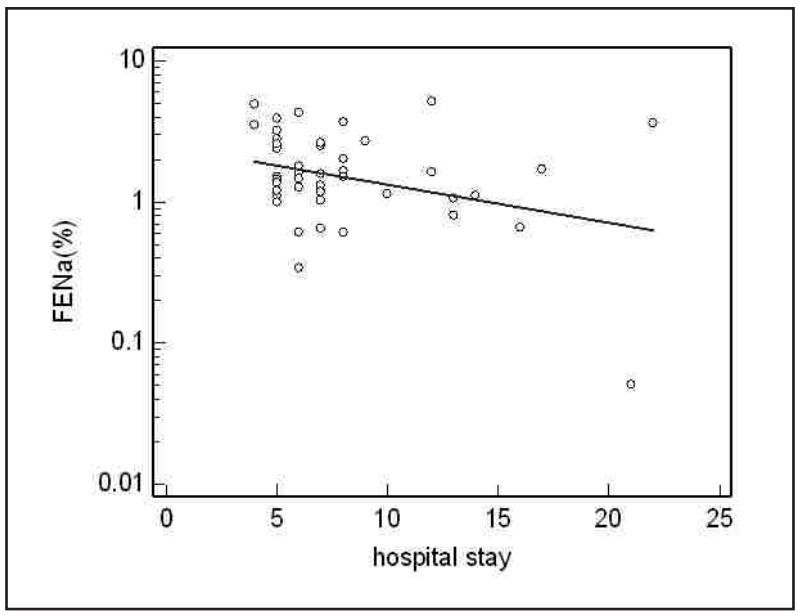


Figure 2: Correlation Between FENa and Length of Hospital Stay



Fractional excretion of sodium (FENa) was used in various previous studies to assess the effectiveness of diuresis in heart failure. Data included in these studies showed that baseline FENa in these patients is approximately less than 1% indicating indicating pre-renal azotemia due to renal hypoperfusion.[9-11] In a subset group of these patients a baseline pre-treatment FENa of less than 0.2% were considered to have diuretic resistance.[1]

The aim of this study was to find out if there was a correlation between FENa and in-hospital morbidity and mortality.

As regards the in-hospital duration of stay there was a significant inverse correlation between both variables (p=0.0006).

FENa reflects net sodium filtration and reabsorption from multiple nephron segments; loop diuretics block sodium reabsorption on the loop of Henle, while having no effect on the proximal tubule. Decreased renal blood flow in severe systolic heart failure may promote sodium reabsorption from this segment, thus decreasing FENa. In our study, we didn't find a significant correlation between FENa (calculated from a 24-h. urine sample) and ejection fraction ($r = -0.04$; $p = 0.7$).This was discordant with previous studies that have noticed a strong correlation between the cardiac index of heart failure patients measured by the thermo-dilution method, and their FENa calculated before starting the loop diuretic piretanide ($r = 0.85$; $P < 0.01$).[12] While other studies correlated FENa with the ejection fraction where FENa was calculated at least 6 hours after the administration of intravenous loop diuretics and again there was a significant correlation between both variables ($r = 0.48$, $p = 0.015$).[13]

Also we couldn't find a significant correlation between the total diuretic dose per day and FENa values.

The median length of hospital stay was 7 days in comparison with 5 days for patients in American hospitals in the past few years.[14]

A multivariate regression model with other variables that might have influence on hospital-stay (including low ejection fraction, Hb, serum sodium level, HF classification on admission, furosemide dose per day and FENa was done. When the histogram of hospital stay was plotted, we noticed that the highest probability of stay is the shortest possible, and that higher numbers of days were of gradually lower probability. This is quite similar to a Poisson distribution; therefore the model was fit, assuming this distribution. The results revealed a significant impact of Hb($p = 0.01$), LVEF ($p = 0.003$)and FENa ($p = 0.00005$) on length of hospital stay with the latter variable having the strongest impact by an increase in the length of stay.

Furthermore, Harjal et al found a significant inverse correlation between FENa and LVEF.[15] The same goes for the decrease in Hb count that's associated with an increased stay.[16]

In our study we didn't find any association between NYHA class and the length of stay which was consistent with another trial that showed no association.[17]

Maybe the only contradicting result was that of the admission serum sodium level that had no correlation with the length of stay and this was against the data posted by Callahan et al. that found that low sodium level was a significant predictor of increased hospital stay.[18]

The significance of FENa level as a predictor of hospital stay was quite remarkable although it wasn't the only predictor of hospital stay but was certainly the most significant.

CONCLUSION

The fractional excretion of sodium test was proved to have the strongest impact on hospital stay among other determinants such as low haemoglobin level and low ejection fraction. Larger number of patients is needed to detect cut-off values for FENA to determine diuretic resistant patients.

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