Original Article

Sodium Effects on Pulmonary Capillary Wedge Pressure in Compensated Heart Failure Patients During 12 Months of Follow-Up: A Randomized and Double-Masked Study

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Abstract

Background: Few studies compared different sodium (Na) diets associated with high furosemide doses (FHD) and fluid intake restriction (FIR) on the PCWC in compensated heart failure (HF) patients.

Objectives: The study was aimed to verify FHD effects, 120 mmol/Na/day and FIR (1.000 ml day) vs FHD, FIR, and 80 mmol/Na/day on the PCWP, during 12 months of follow-up.

Methods: 289 patients with HF were randomized: Group A (n =146) received 120 mmol Na/day, FIR, and 125-250 mg bid of furosemide. Group B (n = 143): 80 mmol Na/day, FIR and 125-250 mg bid of furosemide. Clinical and laboratory assessments were evaluated at baseline, every week for the 1st month, every 2 weeks for the next 2 months, and then every month. Patients performed echocardiograms at entry, at 6 and 12 months.

Result: Group A, during 12 months, maintained diuresis as at baseline, whereas Group B showed a significant reduction, as well as for natriuresis and serum Na; renal function did not show a substantial difference in Group A. PCWP was stable in Group A, whereas it increased in Group B. Readmissions and mortality showed 22 and 11 patients in Group A versus 63 and 27 deaths in Group B (p< 0.001, p <0.004)

Conclusion: Our data suggest that a moderate Na diet combined with FHD and FIR have beneficial effects on the PWCP and clinical outcomes. Readmissions and mortality were considered exploratory variables; in fact, the study was underpowered to analyze the prognosis, and results had to be considered with caution. NCT01738659.

Keywords: Diuretics; Heart Failure; Sodium.

Introduction

The restriction of dietary Na and diuretics has long been accepted as first-line treatment for patients with severe heart failure (HF) and fluid retention.[1,2] Further, we observed that the patients receiving a moderate restriction of Na diet (120 mmol/d), compared with patients receiving a low-Na diet (80 mmol) combined with furosemide high doses (FHD) and water intake restriction (1,000 mL/d), after discharge were less likely to require subsequent hospitalization and more likely to be alive. The moderate Na restriction combination was also effective in reducing neurohormonal activation (BNP, plasma renin activity, and aldosterone) compared to a low-sodium diet.[3-5] Relief of symptoms and a reduction in pulmonary capillary wedge pressure (PCWP) is generally considered one of the main therapeutic targets in HF to verify compensation and to monitor the disease. The echocardiographic estimation of PCWP (echo-PCWP) is deemed to be an interesting, noninvasive, and repeatable parameter for exploring central hemodynamics. The study was aimed to verify, in a randomized, double-masked study, including compensated HF patients (NYHA class II) associated with FHD, moderate Na restriction intake compared with FHD with a restricted Na diet on the PCWP during 12 months of follow-up. Moreover, we also investigated the incidence of readmissions and mortality.

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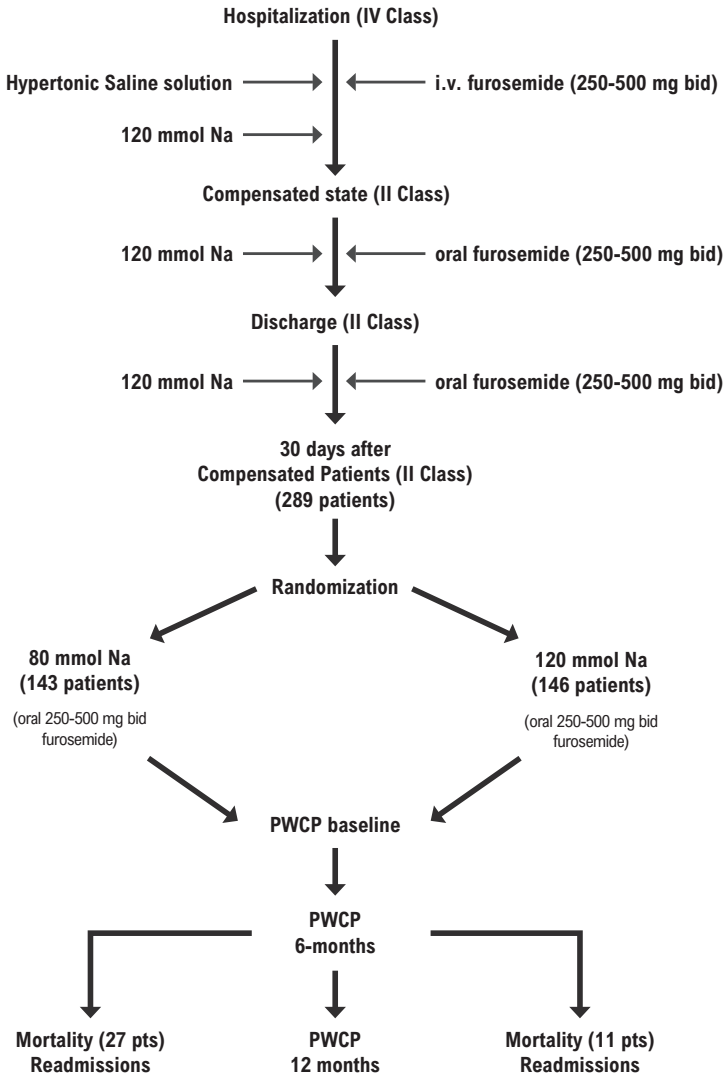
Central Illustration: Sodium Effects on Pulmonary Capillary Wedge Pressure in Compensated Heart Failure Patients During 12 Months of Follow-Up: A Randomized and Double-Masked Study



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Study flowchart.

Methods

Patient population

Of the 354 patients who were discharged in a compensated state, 289 were randomized.

Inclusion criteria

The study included compensated HF (II NYHA class) patients hospitalized in the previous 30 days for recently decompensated congestive HF (IV NYHA Class). They had to have a suitable echocardiographic window (for PWCP calculation). Patients were considered clinically compensated if they showed NYHA Class II, and the compensation fluid balance was determined by a tetra polar impedance plethysmography (BIA-101, Akern, Firenze, Italy).

At discharge, all the patients underwent a complete physical and laboratory examination and echocardiography. Diuretic doses were 125 to 250 mg bid because these doses allowed maintenance of BW and water balance during hospitalization and after discharge.

Exclusion criteria

Patients with unsuitable echocardiographic windows, cerebral vascular disease, dementia, cancer, uncompensated diabetes, severe hepatic disease, and alcoholic habits were excluded. Patients were also excluded if they declined to take part in the study protocol, were unable to follow the assigned treatment, or did not attend the scheduled clinical visits. In addition, patients with side effects of angiotensin-converting enzyme inhibitor treatment (cough), even if these patients were given angiotensin II-receptor blockers, were also excluded.

Pre-randomization and study protocol (Central Illustration)

After discharge, all the patients suitable for the study (NYHA Class II) carried out clinical evaluations as outpatients every week for the first 30 days, and 30 days after the discharge, those who met the eligibility criteria (NYHA Class II and dry weight) were included in the study. During the 30 days after discharge, an expert independent team, according to clinical variables, BIA parameters, and abdominal ultrasound findings (pleural or abdominal effusion) titrated the medical treatment (Table 1). For this reason, it was not necessary to correct the assigned treatments during the next follow-up. In fact, all of the enrolled patients were stable in NYHA Class II and received the best treatments, and they were able to maintain the dry profile. The ambulatory expert team used the same clinical and instrumental items, including BIA,[6] of congestion and clinical stability and were blinded to evaluated parameters. During the follow-up, other treatments were not added except for readmitted patients, who received treatment correction. A preliminary computer algorithm was applied for the patients' assignment at the baseline (30 days after discharge) and before performing clinical and laboratory measurements. We obtained 2 groups: Group A (n 146): 1000 mL/day of fluid intake combined with 120 mmol (2.8 g) Na/day and 125 to 250 mg bid of furosemide. Group B (n 143): 1000 mL/day of fluid intake combined with 80 mmol (1.8 g) Na/day and 125 to 250 mg bid of furosemide. Written informed consent was obtained from each patient before starting the study. The local ethics committee approved the protocol.

Baseline characteristics of the study subjects are shown in Tables 1 and 2. After randomization (double-masked), patients were evaluated every week for the first month, every 2 weeks for the next 2 months, and then every month for the remainder of the study period. A complete physical examination, with a careful assessment of signs and symptoms of congestive HF, including measurement of BW (in the morning before breakfast), supine and standing arterial blood pressure (mean of 3 measurements), heart rate, and BIA evaluation, was performed at every follow-up assessment. At baseline (before receiving the scheduled treatments), fasting blood samples were drawn to determine serum laboratory parameters, urinary Na excretion, diuresis volume, BNP, and BIA. A chest x-ray, electrocardiogram, and echocardiogram were also evaluated at baseline and 180 days and 1 year of follow-up in both groups.

After randomization, all patients received multiple written standard diets containing 80 mmol of Na prepared by our dieticians and also received a diary where they had to report the amount of daily fluid intake and diet variation. In the case of diet variation, patients had to report the amount of the changed or added food (patients were also given a list of equivalent food in sodium they could use as a substitute). At every programmed control, blinded physicians received the diary, and a new diary was given to patients.[6] Group A and B received the same diets (80 mmol of Na), but Group A received the addition of 40 mmol/Na/day to obtain a 120 mmol of Na diet, whereas Group B received 80 mmol of Na and placebo addition to administer only 80 mmol of Na diet. In this way, all patients received the same amount of saturated fat, fruit, and vegetables. In addition, the patients were contacted every week during follow-ups by physicians and dieticians for a telephone interview to determine their adherence to the study protocol. Other information was also obtained by regular contact with family doctors, who were informed about the endpoints of the study. The patients experiencing worsening congestive HF, according to their family doctor, were invited to attend the hospital for evaluation and hospitalized again if indicated.

Echocardiographic study design

Echocardiographic data were collected at entry (just after randomization), 6, and 12 months after.

Transthoracic echocardiography

A 2-dimensional echocardiographic examination was performed with a commercially available system (Vivid Seven Dimension; General Electric). Images were acquired in the left lateral decubitus position with a phased-array transducer in the standard parasternal and apical views. Standard 2-dimensional and Doppler data, triggered to the QRS complex, were digitally stored in a cine-loop format.

Echocardiographic analysis

The analyses were performed offline by two independent investigators experienced in echocardiographic measurements, who were blinded to clinical data and randomization. All reported echocardiographic measurements were averaged from three consecutive cycles. In case of any discrepancy, the echocardiographic images were reviewed again and a decision was made by consensus. The inter-observer and intra-observer coefficients of variation were 4% and 3%, respectively. LV volumes, LVEF, mitral regurgitation, and left atrial maximum volume were assessed, as recommended by the American Society of Echocardiography.[7,8] The following formulas to calculate PCWP were used: PCWP = 1.21 (E/Ea) + 1.91 (for patients with sinus rhythm);[9] and PCWP = 0.821 (E/Ea + 6.489 (for patients with atrial fibrillation).[10-16]

Endpoints

The primary endpoint was PCWP changes, and exploratory secondary endpoints were death or first hospitalization for worsening HF for cardiac causes.

Table 1 – Clinical Characteristics and etiology of chronic heart failure. Data are expressed as mean ± SD

	Total cohort	Group A (120 mmol/day)	Group B (80 mmol/day)	p<
Patients No.	289	146	143	
Age (years)	74.9±11	75.5±11	74.4±12	0.41
Sex Female	110	54 (37.0%)	56 (39.2%)	0.7
Diabetes		45 (30.8%)	47 (32.9%)	0.7
Captopril (75-150 mg day)		146 (100%)	143 (100%)	ns
Carvedilol (6.25-25 mg bid)		88 (60.3%)	86 (60.1%)	0.98
Digitalis (0.125-0.25 day)		31 (21.2%)	28 (19.6%)	0.72
Furosemide (125 mg bid)		101 (69.2%)	97 (67.8%)	0.80
Furosemide (250 mg bid)		45 (30.8%)	46 (32.2%)	0.80
Spironolactone (25 mg day)		103 (70.5%)	105 (73.4%)	0.58
CHF Etiology				
CAD	146	75 (51.4%)	71 (49.7%)	0.77
HHD	101	49 (33.6%)	52 (36.4%)	0.61
DCM	42	22 (15.1%)	20 (14.0%)	0.79
AF	65	34 (23.1%)	31 (21.7%)	0.76

CHF: chronic heart failure; CAD: coronary artery disease; HHD: hypertensive heart disease; DCM: dilative cardiomyopathy; AF: atrial fibrillation.

Statistical analysis

We performed a multiple regression sample size calculation based on a b value of 0.10 (90% power) and a p-value of 0.05. Therefore, the sample size obtained was 67 for each group, and this number was assumed as a minimum for this study. We estimated a 20% reduction in readmissions for worsening congestive HF based on findings from our previous study. Analysis was by intention to treat and according to absolute risk reduction. Event distributions were calculated with the Kaplan-Meier method and compared by log-rank analysis. Univariate and multivariate analyses were performed to determine the independent predictors of readmission rate. The results were expressed as hazard ratio and their 95% confidence interval. Nominal data were analyzed using the chi-square test, and p-values <0.05 were considered statistically significant. All calculations were done using PASW Statistics version 18.0 (SPSS, Inc., Chicago, Illinois), and the results are expressed as mean ±SD.

Results

Of the 354 acute HF patients discharged in compensate state and dry profile,18 patients refused to consent to participate in to study after discharge, 31 showed unsuitable echocardiographic window for PCW calculation, and 18 patients during the 30 days after discharge did not follow the prescribed limited drink fluid intake (1000 mL) and were also excluded from the study. We obtained 289 (female/male: 110/179, mean age 74.9 years) compensated congestive HF patients (NYHA Class II) and dry weight of different etiologies (146 coronary artery disease, 101 hypertensive heart disease, 42 dilatative cardiomyopathy) and were randomized in 2 groups:

Group A (146 patients) received moderate Na restriction (120 mmol), and Group B (143 patients) received a low-sodium

Table 2 – Clinical and laboratory parameters at entry (before treatment). Data are expressed as mean ± SD

	A (120 mmol/day)	B (80 mmol/day)	p<
Patients No.	146	143	
HR	72±11	73±12	0.46
Body Weight (Kg)	87.1±15	85.2±14	0.20
Diuresis (ml/24h)	2410±350	2225±250	0.0001
Serum Na (mEq/L)	140±4	141±5	0.061
Serum K (mEq/L)	3.8±0.2	3.9±0.3	0.0009
Urinary Na (mEq/24h)	103.1±13	106.4±11.4	0.023
BUN (mg/dl)	63±4	61±3	0.0001
Serum Creatinine (mg/dl)	1.44±0.3	1.41±0.2	0.31
Uric Acid (mg/dl)	7.3±2.1	7.6±2.2	0.29
GFR	55±4	56±3	0.017

HR: heart rate; GFR: glomerular filtration rate.

diet (80 mmol) in combination with 1000 mL/day of fluid intake and 125 to 250 mg bid of furosemide in both groups.

Clinical characteristics

Table 1 shows that both groups were homogeneous and well-matched in general characteristics, clinical and laboratory parameters, and HF etiology. All the patients maintained the prescribed treatments as well as the Na diet and the daily fluid intake assigned during the follow-up. No corrections in treatments were required after randomization and at the assigned visits. During the run-in period, no patient required admission for HF worsening. The analysis (performed at the end of the study) of diaries given to patients showed good compliance with assigned diet and fluid intake. The range of 95-110 mmol Na/day and 65-70 mmol Na/day was observed in groups assigned to moderate and low sodium restriction, respectively. The range of 1000 to 1150 mL/day in fluid intake was observed in both groups. All patients continued the tailored treatments obtained during hospitalization and run-in period, as indicated in Table 1. No patient in either group was excluded during follow-up for renal deterioration (creatinine >2.0 mg), but only a readmitted patient had an increase in plasma creatinine levels >2.0 mg.

Laboratory parameters

Tables 2, 3 and 4 show the baseline clinical and laboratory values after 12 months of follow-up. Group A maintained during the follow-up daily diuresis as at baseline, whereas Group B showed a significant reduction in daily diuresis compared with baseline. The same result was observed for natriuresis as well as serum Na. Serum K values remained in the normal range in both groups. Group A did not show a significant difference in renal function after 12 months, in contrast with the increase in creatinine and BUN values in Group B. Both groups group showed a substantial reduction in BW, but Group A had a more important decrease in BW. In both groups, systolic and values of blood pressure were decreased without important clinical manifestations, whereas diastolic values were stable in Group A and increased in Group B.

The BNP values showed a significant intra-group increase in Group B, whereas Group A did not show considerable variation, and the comparison after 12 months evidenced a substantial reduction in Group A in comparison with Group B ($p < 0.0001$).

Echocardiography

Table 4 shows that PCWP was stable during follow-up in Group A, whereas this parameter increased significantly in Group B as well as the end-diastolic volume, respectively. In addition, EF showed an increase in both groups, but Group A showed a more significant improvement.

Bioelectrical data

In Table 4, the bioelectrical data resistance and reactance showed that Group A maintained during follow-up the dry state reached at discharge and during the run-in period. In contrast, Group B showed a significant reduction in data resistance and data reactance ($p < 0.0001$), respectively.

Clinical outcomes

During follow-up, Group A showed a significant reduction in readmissions ($p< 0.001$) and mortality ($p<0.004$) in comparison with Group B. During the follow-up, 22 patients from Group A were readmitted for worsening HF (NYHA Class III-IV), and 11 patients died (4 sudden death, 7 irreversible HF). Group B showed 63 patients readmitted for clinical signs of HF (NYHA Class III/IV), and 27 patients died (8 sudden death, 19 irreversible HF) (Table 5). Figure 1 shows the Kaplan-Meier cumulative event curves for readmissions and mortality during 12 months of follow-up in both groups. In addition, the number of patients needed to be treated to reduce readmission and mortality (NTT) resulted in 3 (95% CI 3 to 5) and 9 (95% CI 5 to 28), respectively. Cox regression analysis with an unadjusted hazard ratio for one year of hospital readmission in patients allocated to the low-sodium diet arm was statistically significant. In the final adjusted model, the following covariates were included: furosemide dose, age above 80 years, diabetes, and sex. After adjustment, a low sodium diet remained a significant risk factor (HR = 3.169, 95% CI, 2.003 to 5.014, $p< 0.001$). The furosemide lower dose (125 mg) resulted in a risk factor for readmission (HR = 5.419; 95% CI, 1.359 to 21.602, $p = 0.017$) - the protective influence FHD is just a non-significant trend (HR = 0,498, 95% CI, 0,245 to 1,011, p=0 0.052), age above 80 years was also a significant risk factor for readmission (HR 1.708, CI 95% 1.085 to 2.689, $p= 0.021$) on the other hand diabetes and sex does not influence the outcomes in our study (table 6).

Table 3 – Clinical and laboratory parameters after 12 months. Data are expressed as mean ± SD

	A (120 mmol/day)	B (80 mmol/day)	p <
Patients No	132	116	
HR	73±6	86±11	0.0001
Body Weight (Kg)	77.2±9	81.8±12	0.0001
Diuresis (ml/24h)	2150±450	1450±350	0.0001
Plasma Na	139±5	132±4	0.0001
Plasma K	3.8+0.3	3.6±0.3	0.0001
Urinary Na (mEq/24h)	108±9	65±8	0.0001
BUN (mg/dl)	63±7	105±12	0.0001
Serum Creatinine (mg/dl)	1.5±0.2	2.1±0.4	0.0001
Uric Acid (mg/dl)	10.3±2.7	9.9±3.3	0.26
GFR (ml/min)	54±6	45.6±4	0.0001
Hospitalization Time	6.5±2	11.5±4	0.0001

HR: heart rate; GFR: glomerular filtration rate.

Table 4 – Clinical, echocardiographic, and BIA data during the study period

	Baseline	6 months	12 months	p<	
Patients No.	146	138	132		A (120 mmol Na/Day)
Patients No.	143	127	116		B (80 mmol Na/day)
SBP	118±11	115±12	116±12	0.09	A (120 mmol Na/Day)
SBP	121+13	118±14	112±11	0.0001	B (80 mmol Na/day)
p<	0.035	0.062	0.007		
DBP	71±6	72±7	72±6	0.39	A (120 mmol Na/Day)
DBP	72±7	80±11	78±9	0.0001	B (80 mmol Na/day)
p<	0.25	0.0001	0.0001		
PCWP	13.1±2	13.07±1.5	13.5±1.7	0.80	A (120 mmol Na/Day)
PCWP	13.5±3	16.3±2.5	18.7±3.5	0.0001	B (80 mmol Na/day)
p<	0.18	0.0001	0.0001		
EDV/ml/m^2	101±13	103±12	104±11	0.10	A (120 mmol Na/Day)
EDV/ml/m^2	99±11	109±15	115±14	0.0001	B (80 mmol Na/day)
p<	0.159	0.0001	0.0001		
EF	34.5±5	38.6±5	38.4±4	0.0001	A (120 mmol Na/Day)
EF	35.1±4	36.6±4	36.5±5	0.007	B (80 mmol Na/day)
p<	0.26	0.0001	0.001		
W-Body R	565±33	555±31	544±23	0.0001	A (120 mmol Na/Day)
W-Body R	570±32	478±28	467±21	0.0001	B (80 mmol Na/day)
p	<0.19	0.0001	0.0001		
W-Body Xc	56.4±5	55.2±6	53±7	0.0001	A (120 mmol Na/Day)
W-Body Xc	55.8±5	44.9±5	42±4	0.0001	B (80 mmol Na/day)
p<	0.30	0.0001	0.0001		
BNP	375±125	385+105	405±135	0.11	A (120 mmol Na/Day)
BNP	381±132	505+115	655±145	0.0001	B (80 mmol Na/day)
p<	0.62	0.0001	0.0001		

SBP: systolic blood pressure; DBP: diastolic blood pressure; PCWP: pulmonary capillary wedge pressure; EDV: end-diastolic volume/m^2; EF: ejection fraction; W-Body R: whole body resistance; W-Body Xc: whole body reactance; BNP: brain natriuretic peptide.

No patient of either group during follow-up was excluded from the study for renal deterioration (creatinine > 2.0 mg) but the readmitted patients. All patients showed good compliance with the prescribed treatments; only 19 patients (8 from Group A and 11 from Group B) during the first month increased drinking fluid intake (1.500 mL); this violation of the protocol was corrected at subsequent control (7 days after).

Discussion

To our knowledge, this is the first investigation to assess the effects of 2 different sodium diets in compensated HF and dry weight on PWCP during 12 months of follow-up. Furthermore, this study has demonstrated in the long term for the first time the cross relationships occurring between echo-PCWP, BNP plasma levels, and BIA parameters, thus confirming a strict correlation between fluid accumulation, clinical compensation, and body hydration in HF. Group A showed a significant reduction in mortality and readmissions in comparison to Group B. In agreement with these results, Group A showed no significant variations in PCWP, while Group B showed a significant increase during follow-up. This finding suggests that patients from Group B had a higher incidence of congestion. In addition, the renal function parameters in Group A did not show significant differences from baseline values, in contrast with increased

creatinine and BUN values in Group B. These data suggest that a moderate Na restriction may be able to maintain the plasma volume and impede neurohormonal activation.[9,17-19] This also could improve long-term diuresis and natriuresis in patients with chronic HF. A moderate Na restriction was likely able to maintain fluid balance and inhibit vasoconstrictor systems.[3,5,18,20] In fact, Na and water-retaining hormonal systems are activated in HF, and cardiac forward flow is impaired during Na restriction.[19,21] The marked increase and/or normalization in serum Na levels observed in patients with normal Na intake is consistent with vasopressin and RAAS inhibition.[19,21] The origins of HF are rooted in a salt-avid state largely mediated by the RAAS system, whose activation is based on reduced renal perfusion. Stimuli that normally lead to RAAS activation keep working in patients with HF. Treatments that minimize, interfere with, or reverse RAAS activation are integral to the optimal management of HF.[22] Is salt beneficial, or is extensive use of diuretics dangerous? There is not a solely true or a solely false concept, but it is probable that the diuretics use in relation to Na intake (or Na intake in relation to diuretics use) is crucial to get adequate intravascular volumes. Our results seem to justify the effects of Na on plasma volume maintenance, RAAS inhibition, and maintenance of PCWP and clinical outcome. Plasma volume measurements during follow-up could be useful; unfortunately, such measurements are not easily feasible in large-scale studies.[21] The patients showed good compliance with the Na diet, fluid intake, and diuretic dose controlled by diary examination, family physician contacts, and 24-hour natriuresis checked at the programmed follow-up visits. In addition, at the follow-up controls, beta-blocker, ACE-inhibitor, and anti-aldosterone administration were also checked, and no significant variation in doses was observed. To date, an important controversy exists on sodium diet in the general population and patients with HF. Previous and recent studies evidenced no difference in outcome and metabolic parameters in HF patients randomized to low sodium diet and control without sodium reduction,[23] while in the previous observational study, was showed a significantly better outcome in patients receiving the usual sodium diet.[24] In agreement, another study regarding HF patients with cardiac EF preserved showed that patients treated with a low sodium diet showed an outcome worse in comparison with patients without sodium reduction,[25] as well as other reports, showed interesting results in maintaining volume balance and preserving plasmatic sodium values. In agreement, it was shown that patients maintaining middle sodium values had a better outcome[26] and showed that correct hydration was important to obtain a regular effective plasmatic volume with subsequent better outcomes, in HF patients receiving diuretic treatment. Recent studies have rekindled the debate, spotlighting a divided scientific community, while other reports showed that a low-sodium diet could be harmful in patients with HF.[3,4,27] In recent years authors have started to study to evaluate the role of sodium in HF patients,[28-32] and some studies[29-32] showed interesting results. All studies mostly evidenced the end of low sodium in HF dogma. In agreement, the recent "OSPREY-AHF" study[33] showed that increasing the oral salt intake in HF patients hospitalized undergoing aggressive diuretic therapy did not affect how much fluid they retain or their kidney function. Recent studies show that sodium loading in HF patients resulted in a significant reduction in plasma renin compared to healthy subjects, while no significant changes in skin sodium content, total glycosaminoglycan content, or sulfated glycosaminoglycan content were observed.[34] Our data suggest that a moderate Na restriction with a limited drink fluid intake (1 L) associated with loop diuretic is able to maintain a dry status associated with normal values of PWCP during 12 months of follow-up in patients compensated after recently worsened congestive HF. The beneficial effects obtained with this association suggest that a low-sodium diet and free water intake usually recommended in clinical practice may not be the best treatment for these patients. This counterintuitive approach underlines the need for a better understanding of factors that regulate Na and water handling in chronic congestive HF. Therefore it is conceivable that the combination of FHD with moderate sodium restriction maintains PWCP and may improve clinical outcome and does not determine significant detrimental effects in renal function.

Table 5 – Results of the study (12 months): Readmissions and Mortality

	A (120 mmol Na/day)	B (80 mmol Na/Day)	p <
Patient No.	146	143	
Sex F/M	54/92	56/87	
Readmissions	22 (15.1%)	63 (44.1%)	0.001
Mortality	11 (7.5%)	27 (18.9%)	0.004
Sudden death	4 (2.7%)	8 (5.6%)	0.22
Irreversible heart failure	7 (4.8%)	19 (13.3%)	0.012

Conclusions

Our data suggest that the association of moderate dietary sodium restriction associated with high doses of diuretics was probably able to maintain a compensatory state in high-risk hospitalized patients (NYHA class IV). In fact, in response to the compensatory neurohormonal activity stimulated by higher sodium restriction, we hypothesize that a moderate sodium diet allows both the maintenance of a better effective plasma volume and more efficient renal perfusion. That would lead to a reduction of the RAAS-dependent sodium avidity.

Furthermore, it is reasonable to believe that a balance between ingested and excreted liquids could be obtained and maintained; thus, the evidence of a mutual relationship between PWC and clinical course is the representation of the effects of this balance.

Our findings may not be applicable in all heart failure patients, in which comorbidities should always be considered. Further multi-center studies with larger patients' samples and a wider heart failure stages' record are needed to verify the effects of the different diuretic plus fluids' strategies on clinical endpoints.

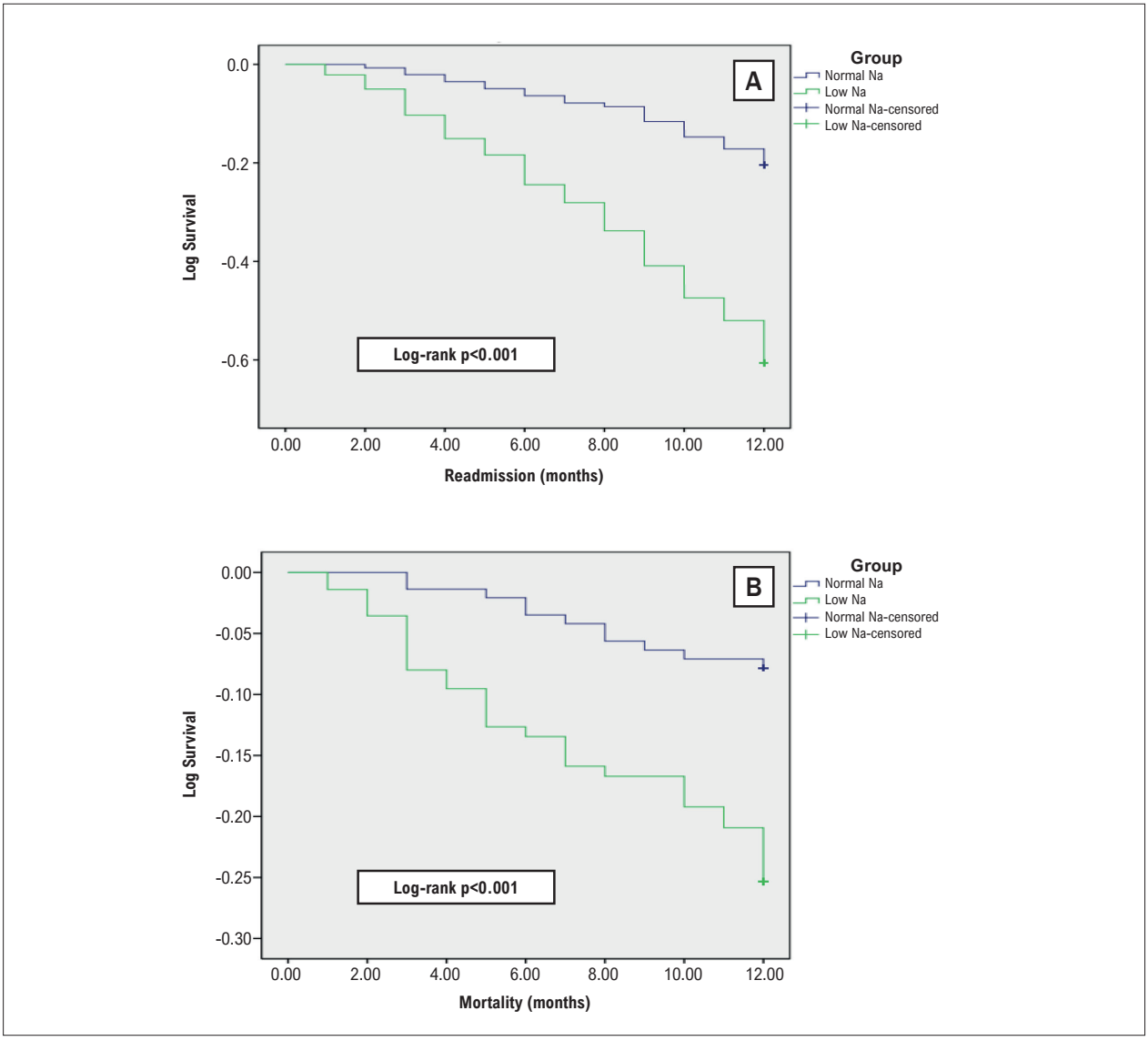

Figure 1 – *Kaplan Meier curves for hospital readmission (panel A) and mortality (panel B) in the chronic heart failure population.*

Author Contributions

Conception and design of the research: Sarullo FM, Fasullo S, Paterna S, Di Pasquale P; Acquisition of data: Sarullo FM, Fasullo S, Sarullo S, Maringhini G, Ganci F, Scalzo S, Cosenza G, Luparelli M, Vetrano G, di Francesco G, Zarcone A, Nugara C, Lo Voi A, Zerbo S, Rubino M, Paterna S, Di Pasquale P; Analysis and interpretation of the data: Sarullo FM, Fasullo S, Paterna S, Di Pasquale P; Statistical analysis: Sarullo FM, Di Pasquale P; Writing of the manuscript: Sarullo FM, Fasullo S, Zerbo S, Di Pasquale P; Critical revision of the manuscript for content: Sarullo FM, Fasullo S, Argo A, Sarullo S, Maringhini G, Ganci F, Scalzo S, Cosenza G, Luparelli M, Vetrano G, di Francesco G, Zarcone A, Nugara C, Lo Voi A, Zerbo S, Rubino M, Paterna S, Di Pasquale P.

Table 6 – Adjusted analysis of factors associated with hospital readmission in patients with heart failure

	Sig.	Exp (B)	95% CI for Exp (B)	
			Lower	Upper
Low Na	0.000	3.169	2.003	5.014
Female	0.731	1.078	0.702	1.657
Furosemide	0.036			
Furosemide (125 mg)	0.017	5.419	1.359	21.602
Furosemide (250 mg)	0.052	0.496	0.245	1.007
Diabetes	0.172	1.373	0.872	2.164
Age-above 80	0.021	1.708	1.085	2.689

CI: confidence interval.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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