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NORMAL SODIUM DIET VERSUS LOW SODIUM DIET IN COMPENSATED CONGESTIVE HEART FAILURE: IS SODIUM AN OLD ENEMY OR A NEW FRIEND ?

Running Title: Normal sodium diet vs low sodium diet in CHF.

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ABSTRACT

The study evaluated the effects of a normal (120 mmol Na) versus a low sodium diet (80 mmol Na) on readmissions for HF during six months of follow-up in compensated congestive heart failure (CHF) patients. 232 (88 F/144 M) compensated CHF pts (from IV to II Class NYHA) aged 55 to 83 years, with EF <35% and serum creatinine <2 mg/dl were randomized in 2 groups: group 1: 118 pts (45 F/73 M) received a normal sodium diet plus oral furosemide (250-500 mg bid); Group 2: 114 pts (43 F/71 M): received a low sodium diet plus oral furosemide (250-500 mg bid), and the treatment received after discharge (30 days) and for 180-days after, associated with a drink intake of 1000 ml daily. Signs of CHF, BW, BP, HR, laboratory parameters, ECG, echocardiogram, BNP; Aldosterone values and plasma renin activity (PRA) were examined at baseline, and 180 days after. Normal sodium group showed a significant reduction ($p < 0.05$) in readmissions. BNP values were lower in normal sodium group (685 ± 255 pg/ml vs 425 ± 125 pg/ml; $p < 0.0001$) than low sodium group. The aldosterone and PRA showed significant increase ($p < 0.0001$) in low sodium group during follow up, while normal sodium showed a little significant reduction ($p = 0.039$) in aldosterone levels and not significant difference in PRA levels. After 6 months of follow up, aldosterone and PRA were ($p < 0.0001$) significantly higher in low sodium group. Normal sodium group showed a lower incidence of re-hospitalization during the follow up and a significant reduction in BNP, aldosterone plasma levels and PRA. Our data show that a normal sodium diet improves outcome and sodium depletion has detrimental renal and neurohormonal effects with worse clinical outcome in compensated HF patients. Further studies are required to determine if this is due to high dose diuretic or low-sodium diet.

Key words: Furosemide, normosodic diet, hyposodic diet, congestive heart failure.

INTRODUCTION

The management of patients with advanced CHF classically consists in sodium restriction, moderate physical activity and a tailored treatment that include digitalis, diuretics and ACE-inhibitors [1]. Diuretics, particularly loop diuretics, have long been accepted as first-line treatment of patients with severe CHF and important fluid retention [2,3]. However, a lack of response to diuretic therapy is a common event particularly in elderly patients with advanced disease. Previously we reported the safety and tolerability of the combination of high dose furosemide associated with small-volume hypertonic saline solution (HSS) i.v. infusion [4,5,6], in patients with refractory CHF, and this combination in comparison with an i.v. high dose infusion of furosemide as bolus, determined a significant reduction of hospitalization time. In addition, we observed that patients receiving a normal sodium diet maintained the achieved NYHA functional class at discharge, a reduction of hospital readmissions for worsening CHF (7,8), and a significant mortality rate reduction (55% vs 13% survival after 48 months) [9,10]. Successively, systematic data on BNP plasma levels changes and bioelectrical variables occurring in HF patients before and after treatment showed that patients receiving HSS reached their dry weight more rapidly than those not receiving HSS solution [11,12]. The study was evaluating the effects of a normal sodium diet (120 mmol Na) versus low sodium diet (80 mmol), with high-dose furosemide and severe fluid restriction (1.000 ml/day), in patients compensated after recently decompensated CHF, on readmissions for worsening HF (primary endpoint). In addition, were also evaluated the combination of readmissions and mortality (secondary endpoint), and BNP, ALD plasma levels and plasma renin activity (PRA) during six months of follow up.

MATERIALS AND METHODS

Patient population: From January 2000 to May 2005, 1244 patients were consecutively admitted to hospital with worsening HF.

Eligibility criteria We included into the study only compensated patients who previously were hospitalized (previous 30 days) for recently decompensated CHF with the following characteristics: patients had to have, according to the definition of refractory CHF [13] and according to Framingham criteria and New York Association Functional classification for congestive heart failure [14], uncompensated CHF (dyspnoea, weakness, lower limbs oedema or anasarca), NYHA IV functional class that was unresponsive to treatment with oral high doses of furosemide up to 250-500 mg/day and/or combinations of diuretics (thiazide, loop diuretic and spironolactone), ACE-inhibitors (captopril 75-150 mg/day), digitalis, beta-blockers and nitrates and to be under this therapy at least 2 weeks before hospitalization. The patients were judged unresponsive when they showed, during the treatment as above reported, a reduction of urine volume and constant increase of body weight (BW) and impairment of clinical signs of CHF as above reported, in spite the increase of furosemide and the combination of other diuretics (including thiazide). Additionally, they had to have a left ventricular ejection fraction (EF) <35%, serum creatinine <2 mg/dl, BUN \leq 60 mg/dl, a reduced urinary volume (<500 ml/24h) and a low natriuresis (<60 mEq/24h) despite receiving the established treatments. None of the patients had to take non-steroid anti-inflammatory drugs (NSAID). All patients received high dose furosemide (250-1000 mg bid), hypertonic saline solution, a normal sodium diet (120 mmol), and a

reduced drink fluid intake (1000 ml/day) during hospitalization..When compensated state was achieved (II NYHA Class) patients received oral furosemide (250-500 mg/bid), normal sodium diet (120 mmol Na), and a drink fluid intake of 1000 ml daily according to our previous reports. [4-11] and the treatment was continued after discharge. Patients were considered clinically compensated when they reached a change in NYHA functional class to at least II and the accomplishment of ideal BW, calculated by the Lorenz formula. and bioelectrical impedance measurements [11] Diuretic doses ranged from 250 to 500 mg/bid because these doses allowed maintenance of body weight and water balance. The diuretic doses were titrated according to the doses used during hospitalization. In addition, after discharge patients received tailored therapy (ACE-inhibitors, digitalis, antialdosterone, beta-blockers and nitrates) too. Only patients in II NYHA class 30 days after discharge were included into the study and randomized.

Exclusion criteria: Patients with concomitant other important co-morbidity, cerebral vascular disease, dementia, cancer, uncompensated diabetes, inability to give informed consent, severe and hepatic disease, and inability to follow the assigned treatment. Patients requiring pace-maker implantation and alcoholic habit, who did not follow the protocol of treatment, programmed clinical visits, drink fluid intake of 1.000 ml day, and reduction or discontinuation of prescribed treatments. In addition, patients with side effects for ACE-inhibitors (cough), even if these patients were given angiotensin-2 blockers, to obtain as more homogeneous as possible treatments were excluded too.

Protocol of the study and follow up (figure 1):

Pre-randomization evaluation: After discharge (first 30 days) the patients were controlled with clinical and laboratory evaluations, as outpatients every week for the first 30 days and those who just 30 days after the discharge meet the eligibility criteria were included into the study. During 30-days period after discharge, the treatments (where necessary) were corrected according to clinical status and laboratory measurements (reduction and/or increase of diuretics, ACE-inhibitors, digitalis, antialdosterone, beta-blockers and nitrates), in this way, during the follow up it was not necessary to correct the assigned treatments. In fact, all the enrolled patients were stable and receiving the best treatments which were able to maintain the compensated state obtained after discharge and before randomization During the follow-up period, other treatments were not added to those administered. Corrections of therapy were carried out only in readmitted patients

Randomization: Only patients judged compensated in II NYHA Class, by an independent external team (at least two) of blinded physicians about study protocol, were included into the study and randomized in two groups: a group received 120 mmol Na and continued oral furosemide (250-500 mg bid) and a group received 80 mmol Na and continued oral furosemide (250-500 mg bid), associated with the above reported therapy. Both groups received a drink fluid intake of 1000 ml daily. Randomization was carried out using a preliminary computer algorithm and the assignment of all patients was decided at the baseline (just 30 days after discharge) before performing clinical and laboratory measurements Written informed consent was obtained from each patient before starting the study The protocol was approved by local ethical committee. Baseline characteristics of the study subjects are shown in **tables 1 and 2.**

After randomization evaluation: After randomization (just after the first 30 days from discharge) and after the baseline clinical and laboratory assessments, the patients were evaluated every week for the first 1 month, every two weeks for the subsequent two months and every month for the subsequent periods. A complete physical examination, with a careful check of CHF signs and symptoms, including measurement of BW (in the morning before breakfast), supine and standing arterial blood pressure (BP) (mean of 3 measurements) and heart rate (HR) was performed at every follow up assessment. At baseline (before receiving treatments) fasting blood samples were drawn to determine serum Na, K, Cl, bicarbonate, albumin, uric acid, creatinine, urea and glycaemia. Aldosterone, plasma renin activity (PRA) and BNP plasma levels were also controlled. Chest-x ray, ECG and echocardiogram (to obtain EF according to the modified Simpson' rule, which uses 2 cross section views (4 and 2 chamber apical views) were also evaluated. All these parameters, and BNP plasma levels, were also obtained at 90 and 180 days of follow up, while plasma aldosterone and PRA were measured by radioimmunoassay in core laboratories at baseline and after 6 months of follow-up in both groups. In addition, all the patients with diabetes were receiving insulin therapy, oral anti-diabetes drugs were discouraged also after discharge and follow up. All patients after randomization received multiple written standard diets with a Na amount of 80 mmol and prepared preliminarily by our dietitians. The 120 mmol group received the same diets with the addition of 40 Na mmol/day. In this way, all patients received the same amount in saturated fat, fruit, vegetable and etc. In addition, patients were also contacted every week during follow up by physicians and dietitians for a telephone interview to control the adherence to reduced fluid intake as well as the prescribed diet. Other informations were also obtained from a systematic contact with family doctors, who were informed about the study end points. Any of the patients experiencing worsening HF according to family doctors were invited to attend hospital for evaluation. Two blinded physicians performed the evaluations to verify the clinical status and if worsening HF were present.

Statistical analysis

We performed a multiple regression sample size calculating basing on a β value of 0.10 (90% power) and α value of 0.05. Therefore the sample size obtained was 67 for group and this number was assumed as minimum one for this study patients. We estimate a 20% of reduction in readmissions for worsening HF, on the basis of the data from our previous reports (9). Analysis was by intention to treat and according to absolute risk reduction; we calculated the number needed to treat (NNT) to prevent one event. We calculated event distributions with the Kaplan-Meier method and compared them by log-rank analysis. Data were analysed using the two-tailed t-test to identify differences between groups and analysis of variance (ANOVA) for repeated measures with Bonferroni post hoc test correction for intra-group data. Nominal data was analysed by the Chi-square test and $p < 0.05$ was assumed as statistically significant. All calculations were done with SPSS statistical software and the results are expressed as mean \pm SD.

RESULTS

Of the 1244 patients admitted in hospital for worsening HF, 76 did not show reduced urinary volume (<500 ml/24h) and a low natriuresis (<60 mEq/24h), 92 were with severe co-morbidity (see exclusion criteria), 25 with side effects for ACE-inhibitors, 58 were requiring pace-makers, 18 were with alcoholic habit, 136

showed creatinine > 2.0 and/or BUN > 60 mg, (on hospital admission) and 451 were classified as NYHA Class III on hospital admission. In addition, 79 patients refused consent to participate to study either after discharge and 30 days after discharge, 54 patients during the 30 days period after discharge did not follow the prescribed limited drink fluid intake (1000 ml), and were also excluded from the study, but they accepted to be controlled as those included into the study. Twenty three patients classified as NYHA class III after hospital discharge were also excluded from the study. We obtained 232 (female/male: 88/144) compensated HF patients (NYHA class II) of different etiologies (110 coronary artery disease (CAD), 76 hypertensive heart disease (HHD), 46 dilatative cardiomyopathy (DCM), aged 53 to 85 years, who met the entry criteria and agreed to be enrolled and were randomized in two groups: Group 1 (118 pts) receiving normal sodium diet (120 mmol Na) and Group 2 (114 pts) receiving low sodium diet (80 mmol Na). (**Table 1**). The 120 mmol Na group maintained during the follow up daily diuresis as at baseline, whereas 80 mmol Na group showed a significant reduction in daily diuresis compared with baseline and with 120 mmol Na group. The same result was observed for natriuresis as well as serum Na. Serum K decreased significantly but the value remained in the normal range in both groups (**Table 2**). In addition, the renal function parameters controlled after 3 and 6 months in 120 mmol groups did not show significant differences from baseline values in contrast with increased creatinine and BUN values in 80 mmol group (**Table 2**). The 120 mmol group showed no significant variation in BW weight. In both groups systolic and diastolic values of BP were decreased without important clinical manifestations (**Table 2**). A significant ($p < 0.001$) intergroup difference was observed in BNP plasma levels at the end of the study. These differences were significantly favorable in normal sodium group but with lower values at 90 (525 ± 215 pg/ml vs 415 ± 115 pg/ml; $p < 0.001$) and 180 days (685 ± 255 pg/ml vs 425 ± 125 pg/ml; $p < 0.0001$) in comparison with low sodium group (**Figure 2**). In the 80 mmol group, aldosterone (normal value 7-150 pg/ml) (baseline, 188 ± 171 pg/mL) increased at 6 months (296 ± 224 pg/ml, $p < 0.0001$), while in the 120 mmol group, showed a little but significant ($p = 0.002$) reduction (baseline, 192 ± 160 pg/ml versus 152 ± 102 pg/ml) at 6 months. The PRA (normal value 0.2-0.8 ng/ml/h) showed not significant difference ($p = 0.6$) between baseline (3.91 ± 3.71) and at 6 months (3.65 ± 3.28) of follow up in 120 mmol group, while showed a significant ($p = 0.039$) increase (3.98 ± 3.68 vs 5.74 ± 4.12) in 80 mmol group. The baseline values were similar in both groups, while after 6 months of follow up the values in ALD and PRA levels were significantly higher ($p < 0.0001$) in 80 mmol than 120 mmol group (**Figure 3**).

Follow up: The 120 mmol group showed a significant reduction ($p < 0.05$) in readmission rate (primary endpoint) in comparison with 80 mmol group (**figure 4, table 3**), and a significant reduction ($p < 0.001$) in combined mortality and readmissions (secondary endpoint) (**figure 5, table 3**). During the 180 days follow-up period 9 patients from 120 mmol group were readmitted for worsening HF (III-IV NYHA Class) and six patients died (1 sudden death and 5 irreversible HF). The 80 mmol group showed 30 patients readmitted to the hospital for clinical signs of HF and they presented at entry higher functional class than at discharge (III/IV NYHA Class), Fifteen patients died during the 180 days study period in 80 mmol group, (4 sudden death and 9 irreversible HF and 2 other causes, (neoplastic disease and stroke)) (**Table 3**). **Figure 4-5** show the Kaplan-Meier cumulative event curves for primary end point (hospital readmission) and combined readmissions and

mortality (secondary endpoint) in the two groups during 180 days follow-up. Curves analysis show an evident early (first 30 days) beneficial effects of a normal sodium intake that was more consistent during the subsequent months. In 80 mmol group 26.32 % of patients had an adverse outcome in comparison with only 7.63% in 120 mmol group. The Absolute Risk Reduction was 18.69%.(CI 9.29-28.08) and numbers of patients needed to treat to reduce a readmission ranges from 3.6 to 10.8 (NNT=6). No patients were receiving beta-blockers at time of the admission in hospital. Beta-blockers were also started when patients were compensated during hospitalization and after discharge, but only 18 patients (from both groups) tolerated beta-blockers (carvedilol), while the other patients showed signs of HF worsening and beta blockers were discontinued All patients continued ACE-inhibitors as previously reported (captopril 75-150 mg/day). No patient of both groups during follow up was excluded from the study for renal deterioration (creatinine > 2.0 mg) but the readmitted patients. Echocardiographic data during follow up showed a significant slight improvement of EF in 120 mmol patients. All the enrolled patients showed a good compliance with the prescribed treatments, only 21 patients (12 from 120 mmol group and 9 from 80 mmol group) during the first month (during summer) increased drink fluid intake (1.500 ml) and this violation of the protocol was corrected at subsequent control (7 days after). In addition, **tables 4-5-6** show the clinical characteristics, laboratory parameters and results of CHF patients who refused consent but continued the prescribed treatments, and who did not follow the prescribed fluid intake (1000 ml day) after discharge, but they continued oral furosemide (250-500 mg bid) and normal sodium intake (120 mmol). These patients were not analyzed because they were not randomized and because the study was not aimed to study the effects of free fluid intake, but they were also controlled subsequently. The patients assuming a drink fluid intake > 1.000 ml (1.500-2000 ml/day) showed a high incidence of readmissions for HF worsening (30%) (16 patients) in the first 6 months. We also observed that the refused consent group showed similar results to those randomized to normal sodium diet (120 mmol), while the free fluid intake group (1.500-2000 ml/day) showed a increase in readmissions similar to patients with low sodium diet.

DISCUSSION

To our knowledge, this is the first investigation to assess the outcome response to different dose of Na intake in medically treated patients with compensated HF. In the present study we randomized low sodium (80 mmol Na) vs normal sodium (120 mmol Na) diet in compensated HF patients receiving the same treatment during hospitalization and 30 days after discharge. In this way, this criterion allowed us to evaluate the effects of normal sodium versus low sodium diet in the follow up period in patients matched for clinical characteristics and treatments. We choose 120 mmol of Na because epidemiological studies showed that in Europe and Italy it was estimated an assumption of a mean of 3.5 g (150 mmol) Na/day [15,16] Our data suggests that a normal sodium diet with a limited drink fluid intake (1 litre) associated with loop diuretic is able to reduce both hospital readmission for worsening of HF (primary endpoint) and neurohormonal activation (BNP,PRA and ALD plasma levels) after six months of follow up. The beneficial effects obtained with this association suggest that low sodium diet and free water intake usually recommended in clinical practice [17-19] could not be the best treatment for these patients and merits further investigations. In addition, more recently, the accepted link between Na intake and cardiovascular events was not confirmed. In fact, it was evidenced that

high Na intake does not induce total body water storage but induces a relative fluid shift from the interstitial into the cardiovascular space [20]. Conversely, revised NHANES II study showed an inverse association of Na with cardiovascular mortality [21] while other papers refuted this link [22]. Unfortunately, the two studies included different populations, a general population in the NHANES II study and a selected population of pre-hypertensive patients in the TOHP study [23], while compensated heart failure patients were included in the present paper. These data does not allow conclusive considerations about the management of Na in cardiovascular diseases. Our results indicate that renal hemodynamic and neurohormonal responses in Na intake were tolerated without any excessive Na and water retention and were associated with lower hospital readmissions for worsening HF. In the arm receiving 120 mmol of Na, only 9 patients were readmitted during the follow-up period in comparison with 30 patients readmissions in the arm receiving 80 mmol of Na. These findings oppose the results of previous studies, in which untreated and conventionally treated patients with HF have been shown to accumulate Na and water in excess during dietary Na loading [24-28]. In view of these clinical data, we hypothesized that normal Na intake maintains a suitable arterial blood volume that per se inhibits the neurohormonal activation observed during low sodium diet, and improve both renal and hormonal alterations. In fact, the maintained plasma volume expansion determines an increased diuresis and natriuresis associated with reduced levels of AVP, plasma renin activity or ang II, and ALD [29,30]. These data could explain that despite the small difference (27 mmol Na) in urinary sodium between the two groups, probably the observed large difference in PRA could be due to the additive or synergistic effects of reduction in plasma volume and Na plasma levels in 80 mmol Na group with a subsequent RAAS stimulation. On the contrary, the additive or synergistic effects of plasma volume expansion and the normal Na plasma levels observed in 120 mmol Na group determine an inhibition of RAAS. system [31]. In addition, the difference in natriuresis confirmed that all patients followed the assigned diets. Maintenance of normal blood volume depends upon a balance between Na intake and renal excretion. The reduced tissue perfusion, operating in CHF patients, stimulate the proximal tubule avidly reabsorption of Na and water, limiting the amount of dilute urine that can be generated and excreted. Thus, given the well-documented influence of the renal blood supply on Na handling and the reversal of the antinatriuresis when renal perfusion is increased in these patients, it seems likely that the renal vascular response participates in the Na retention in patients with advanced HF [31]. Recently, it was showed that altered Na intake elicited the same absolute and relative hemodynamic responses in HF patients as healthy controls. In addition, a suppression of vasoconstrictor hormones was determined in HF compensated patients receiving high Na intake [32-34]. It is possible that regular Na administration is able to restore fluid balance and to inhibit vasoconstrictor systems. These results suggest that Na combined with appropriate diuretic therapy and fluid intake might be beneficial to maintain a good intravascular volume and thereby to improve cardiac and renal blood flow. On the contrary, during Na restriction, Na and water retaining hormonal systems are activated and cardiac forward flow is impaired [33-35]. In addition it has been demonstrated that intravascular volume depletion induced by low Na intake can compromise renal function, especially if associated with ACE-inhibitors or diuretics [36,37]. Thus not only neuroendocrine activation but also a compromised cardiorenal function could result from intravascular volume depletion induced by low Na

intake. Worsening indices of renal function limit symptomatic and neurohormonal therapy, lead to longer hospital stay, and predict higher rate of early readmissions and death. [38-40] The marked increase and/or normalization in serum Na levels, observed in patients receiving normal Na intake, is consistent with vasopressin and RAAS inhibition [41]. Probably, the association of high diuretic dose did not allow excessive increases in plasma volume, and the normal Na intake maintained normal Na plasma levels avoiding the effects of hyponatremia and stimulation of RAAS system. The effects on hyponatremia is very important, because it has long been associated with worse outcome [42,43]. It is possible that the intensity of diuretic therapy created an opportunity for protective benefit from higher Na intake that would not be realized with lower diuretic doses. In addition, it was shown that furosemide at therapeutic concentrations exerts a direct venodilator effect [24,44]. The normosodic diet and oral dose of furosemide enough to maintain a stable body weight may explain the significant reduction in BNP, ALD and PRA plasma in comparison with hyposodic group [45]. The little variation in ALD and PRA plasma levels suggest that a normosodic diet, fluid restriction and oral dose of furosemide enough to maintain a stable body weight did not allow a further stimulation of the RAAS system which maintained similar values to those observed at baseline. However, it is possible that the therapeutic effects of this treatment are not only mediated by the direct effects on renal hemodynamics, but also by neurohormones modulation [34,46,47]. It is possible that the Na intake (120 mmol) allowed a continue response to diuretics also by a reduction of intrarenal PGE2 inactivation, and an improvement of medullary microcirculation with reduction of hyper-osmolality and a vasopressin inhibition PGE2-induced. [48]. These last mechanisms could also justify the maintenance of the reduction in BNP levels observed after 90 and 180 days. The data obtained from patients who refused consent and continued the treatments (even if not randomized) were similar to those randomized to 120 mmol Na diet while those who assumed a higher fluid intake (1.500-2000 ml/day) and 120 mmol Na diet showed similar results to those randomized to 80 mmol of Na (perhaps for dilutional mechanism). These results confirm that the combination of reduced fluid intake (1000 ml/day) and a normal sodium diet (120 mmol) is able to explain the reduction both hospital readmissions and in PRA, ALD, and BNP levels. Before planning the present study, we evaluated in two groups (15 patients for group) of compensated (II Class NYHA) patients (similar to those included into the study) the effects of lower doses of furosemide (100-250 mg/day) after discharge associated with normal sodium diet (120 mmol) or with low sodium diet (80 mmol) and a reduced fluid intake (1 litre). We observed that the group receiving normal sodium diet showed a rapid worsening of HF within the first two weeks from discharge (10 patients were readmitted for HF worsening), and the group with low sodium diet showed a dramatic rapid worsening of HF within the first week from discharge (11 patients were readmitted for HF worsening) (unshown data). These data suggested us that higher doses of loop diuretics needed to maintain body weight and water balance and determined the diuretic dose of the present study. Further studies comparing a normal sodium diet plus free fluid intake versus a normal sodium diet plus reduced fluid intake are necessary. In conclusion, the present investigation suggests a surprising efficacy of a new strategy to improve chronic diuretic response by Na intake increase and limited drink fluid intake (1000 ml daily). Our study shows that the use of high doses of loop diuretics were not detrimental also in the long term, as previously reported [9]. The difference between our

studies and those reported in literature, probably are due to association of the normal sodium diet and higher diuretic dose. In fact, the studies reporting detrimental effects of long-term treatment with loop diuretics were performed in CHF patients receiving low sodium diet and different diuretic doses [34,49,50]. In addition, all the readmitted patients were treated with HSS solution and high dose of loop diuretics which determined rapid compensation (<6 days), especially the patients from low sodium group. To date, this counterintuitive approach underlines the need for better understanding of factors that regulate Na and water handling in chronic CHF. The observation that a normosodic diet improves outcome in compensated CHF patients and that high dose of loop diuretics if associated with normosodic diet do not determine detrimental effects in renal function suggest that Na depletion has detrimental renal and neurohormonal effects with worse clinical outcome in patients with compensated CHF. Further studies are required to determine if this is due to the high dose diuretic or low sodium diet.

Limits of the study: the more important limit was the brief follow-up, but the interim analysis (by ethical committee) after six months of follow up showed a significant reduction in readmissions rate and recommended the discontinuation of the study. These data were sufficient to suggest that a normosodic diet and a reduced drink fluid intake associated with a tailored therapy with furosemide may improve outcome in compensated HF patients. Another important limit was the unblinded design, but we attempted to perform a double blinded study but it was not possible because the patients receiving the prescribed diets perceived the difference in salt amount. In addition, to reduce bias, the randomization was performed by an external team of physicians blinded to the study, and other different blinded physicians performed evaluation in the programmed controls and evaluated the readmitted HF patients during follow up. The laboratory and neurohormonal controls were also performed by blinded physicians. The adherence to diet, fluid intake and doses of furosemide were also controlled by two blinded physicians. All these physicians communicated the results of controlled data to responsible of research after the conclusion of the study. Another limit was the low rate of beta-blocker therapy but the enrolled patients were compensated CHF (from advanced IV to II class NYHA): unresponsive, before hospitalization, to best conventional treatment (high doses of furosemide, combination of diuretics, beta-blockers, ace-inhibitors, etc), and in previous hospitalizations beta-blocker treatment was discontinued for repeated episodes of pulmonary oedema. This low rate of beta-blocker treatment did not influence the outcome of patients. It is also possible that the intensive follow up may have affected the outcome, but this intensive follow up was mandatory because of novelty of the study.

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Table 1: Clinical Characteristics and ethiology of CHF.

| | | 80 mmol Na | 120 mmol Na |
|-----------------------------|--------|-------------------|--------------------|
| Patient No. | 232 | 114 | 118 |
| Age (years) | | 73.3±9 | 72.1±7 |
| Sex F/M | 88/144 | 43/71 | 45/73 |
| Diabetes | 55 | 25 | 30 |
| Captopril (75-150 mg day) | 232 | 114 | 118 |
| Carvedilol (6.25-25 mg bid) | 18 | 10 | 8 |
| digitalis (0.125-0.25 day) | 47 | 23 | 24 |
| Furosemide (250 mg bid) | 142 | 73 | 69 |
| Furosemide (500 mg bid) | 90 | 46 | 44 |
| Spiroinolattone(25 mg day) | 202 | 99 | 103 |
| <u>CHF Ethiology</u> | | | |
| CAD | 110 | 53 | 57 |
| HHD | 76 | 37 | 39 |
| DCM | 46 | 24 | 22 |
| AF | 51 | 26 | 25 |

CAD=Coronary Artery Disease;HHD= Hypertensive Heart Disease; DCM= Dilatative

Cardiomyopathy; A.F=Atrial fibrillation.

Table 2: Clinical and laboratory parameters at entry and after 90 and 180 days. Data are expressed as mean \pm SD.

| | 80 mmol Group | | | | 120 mmol group | | | |
|--------------------------|-----------------|----------------|-----------------|--------|----------------|----------------|-----------------|--------|
| | Entry | 90 days | 180 days | P< | entry | 90 days | 180 days | P< |
| Patients No | 114 | 106 | 99 | | 118 | 114 | 112 | |
| SBP (mmHg) | 126 \pm 15 | 116. \pm 11 | 107 \pm 13 | 0.001 | 125 \pm 15 | 114 \pm 11 | 111 \pm 11 | 0.01 |
| DBP (mmhg) | 82. \pm 13 | 76. \pm 11 | 77 \pm 9 | 0.001 | 83 \pm 14 | 78 \pm 12 | 75 \pm 11 | 0.001 |
| HR (beats/min) | 85 \pm 14 | 83 \pm 11 | *82 \pm 12 | ns | 84 \pm 11 | 76 \pm 9 | *72 \pm 8 | 0.0001 |
| Ejection Fraction | 29.3 \pm 5 | 30.1 \pm 6 | 30.2 \pm 6 | ns | 29.5 \pm 4 | 32.2 \pm 6 | 32.5 \pm 5 | 0.001 |
| Body Weight (Kg) | 76.9 \pm 15 | 79.1 \pm 13 | *80.2 \pm 13 | 0.001 | 75.2 \pm 14 | 74.8 \pm 15 | *75.3 \pm 10 | ns |
| Diuresis (ml/24h) | 2560 \pm 425 | 1580 \pm 555 | *1525 \pm 565 | 0.0001 | 2495 \pm 635 | 2250 \pm 565 | *2150 \pm 480 | 0.048 |
| Serum Na (mEq/L) | 138.3 \pm 5 | 132.3 \pm 4 | *132.1 \pm 5 | 0.001 | 138.7 \pm 7 | 140.4 \pm 3 | *139.5 \pm 6 | 0.001 |
| Serum K (mEq/L) | 4.6 \pm 0.8 | 3.7 \pm 0.4 | 3.6 \pm 0.8 | 0.0001 | 4.7 \pm 0.5 | 3.9 \pm 0.4 | 3.7 \pm 05 | 0.0001 |
| Urinary Na (mEq/24h) | 102 \pm 11 | 77 \pm 9 | * 76 \pm 7 | 0.01 | 105 \pm 14 | *106 \pm 12 | *103 \pm 11 | ns |
| BUN (mg/dl) | 56.5 \pm 3.6 | 101 \pm 12 | *105 \pm 5.8 | 0.0001 | 58.5 \pm 7 | 67 \pm 9 | *68.4 \pm 7.2 | 0.001 |
| Serum Creatinine (mg/dl) | 1.55 \pm 0.05 | 1.89 \pm 0.3 | *2.1 \pm 0.5 | 0.001 | 1.56 \pm 0.2 | 1.48 \pm 0.3 | *1.45 \pm 0.4 | 0.01 |
| Uric Acid (mg/dl) | 6.7 \pm 2.1 | 9.8 \pm 3.5 | 10.2 \pm 2.3 | 0.0001 | 6.6 \pm 2.5 | 9.8 \pm 3.5 | 9.9 \pm 4.3 | 0.0001 |

(*) = p < 0.001, differences between the two groups : 80 mmol versus 120 mmol after 180 days .

Table 3: Results of the study (180 days): Readmissions and Mortality.

| | 80 mmol Na | 120 mmol Na | ARR (95% CI) | P< |
|-----------------------------------|--------------------|--------------------|---------------------|--------------|
| Patient No. | 114 | 118 | | |
| Sex F/M | 43/71 | 45/73 | | |
| Readmissions | 30 (26.32%) | 9 (7.63%) | 18.69% | 0.05 |
| Mortality | 15 (13.15%) | 6 (5.08%) | 8.07% | ns |
| sudden death | 4 | 1 | | |
| Irreversible HF | 9 | 5 | | |
| other causes | 2 | - | | |
| Readmissions and Mortality | 45 (39.47%) | 15 (12.71%) | 26.76% | 0.001 |

Table 4: Clinical Characteristics and ethiology of CHF patients receiving normal sodium diet (120 mmol Na), who refused consent and patients excluded for protocol violation (fluid intake > 1000 ml/die).

| Patient No. | Refused Consent 79 | Fluid intake violation 54 | p< |
|-----------------------------|-----------------------|------------------------------|----|
| Age (years) | 75.4±13 | 71.2±11 | ns |
| Sex F/M | 33/46 | 23/31 | ns |
| Diabetes | 21 | 14 | ns |
| Captopril (75-150 mg day) | 79 | 54 | ns |
| Carvedilol (6.25-25 mg bid) | 7 | 3 | ns |
| digitalis (0.125-0.25 day) | 29 | 14 | ns |
| Furosemide (250 mg bid) | 68 | 49 | ns |
| Furosemide (500 mg bid) | 11 | 5 | ns |
| Spironolactone (25 mg day) | 64 | 51 | ns |
| <u>CHF Ethiology</u> | | | |
| CAD | 50 | 35 | ns |
| HHD | 22 | 13 | ns |
| DCM | 7 | 6 | ns |
| AF | 37 | 21 | ns |

CAD=Coronary Artery Disease;HHD= Hypertensive Heart Disease; DCM= Dilatative Cardiomyopathy; A.F=Atrial fibrillation.

Table 5: Results (180 days) in readmissions and mortality of CHF patients receiving 120 mmol Na and who refused consent and patients excluded for protocol violation (fluid intake > litre).

| | Refused consent | Fluid intake violation | P< |
|------------------------|------------------------|-------------------------------|--------------|
| Patient No. | 79 | 54 | |
| Readmissions | 7 | 16 | 0.019 |
| Mortality | 5 | 10 | 0.098 |
| Sudden death | 1 | 3 | ns |
| Irreversible HF | 2 | 6 | ns |
| Other causes | 2 | 1 | ns |

Table 6: Clinical and laboratory parameters at entry and after 180 of CHF patients receiving 120 mmol Na. who refused consent and patients excluded for protocol violation (fluid intake > 1 L). Data are expressed as mean \pm SD.

| | Refused Consent | | p< | Fluid intake violation | | |
|--------------------------|-----------------|-----------------|--------|------------------------|----------------|--------|
| | Entry | 180 days | | entry | 180 days | p< |
| Patients No | 79 | 74 | | 54 | 44 | |
| SBP (mmHg) | 128 \pm 17 | 119. \pm 14 | 0.0001 | 131 \pm 11 | 124 \pm 16 | 0.012 |
| DBP (mmhg) | 85. \pm 15 | 76. \pm 11 | 0.0001 | 83 \pm 14 | 78 \pm 12 | 0.064 |
| HR (beats/min) | 88 \pm 14 | 83 \pm 11 | 0.016 | 84 \pm 11 | 91 \pm 9 | 0.0001 |
| Ejection Fraction | 27.2 \pm 7 | 29.5 \pm 4 | 0.015 | 29.5 \pm 4 | 28.2 \pm 4 | ns |
| Body Weight (Kg) | 76.9 \pm 15 | 77.1 \pm 12 | ns | 74.9 \pm 11 | 78.7 \pm 9 | 0.068 |
| Diuresis (ml/24h) | 2560 \pm 425 | 2585 \pm 675 | ns | 2465 \pm 435 | 2125 \pm 665 | 0.003 |
| Serum Na (mEq/L) | 138.3 \pm 5 | 141.3 \pm 5 | 0.0001 | 138.7 \pm 7 | 132.3 \pm 4 | 0.0001 |
| Serum K (mEq/L) | 4.8 \pm 0.7 | 3.7 \pm 0.3 | 0.0001 | 4.6 \pm 0.7 | 3.5 \pm 0.4 | 0.0001 |
| Urinary Na (mEq/24h) | 107 \pm 13 | 102 \pm 17 | ns | 104 \pm 14 | 101 \pm 15 | ns |
| BUN (mg/dl) | 55.7 \pm 3.7 | 61.4 \pm 12 | 0.0001 | 58.5 \pm 7 | 67 \pm 9 | 0.0001 |
| Serum Creatinine (mg/dl) | 1.52 \pm 0.06 | 1.49 \pm 0.07 | ns | 1.66 \pm 0.5 | 1.71 \pm 0.7 | ns |

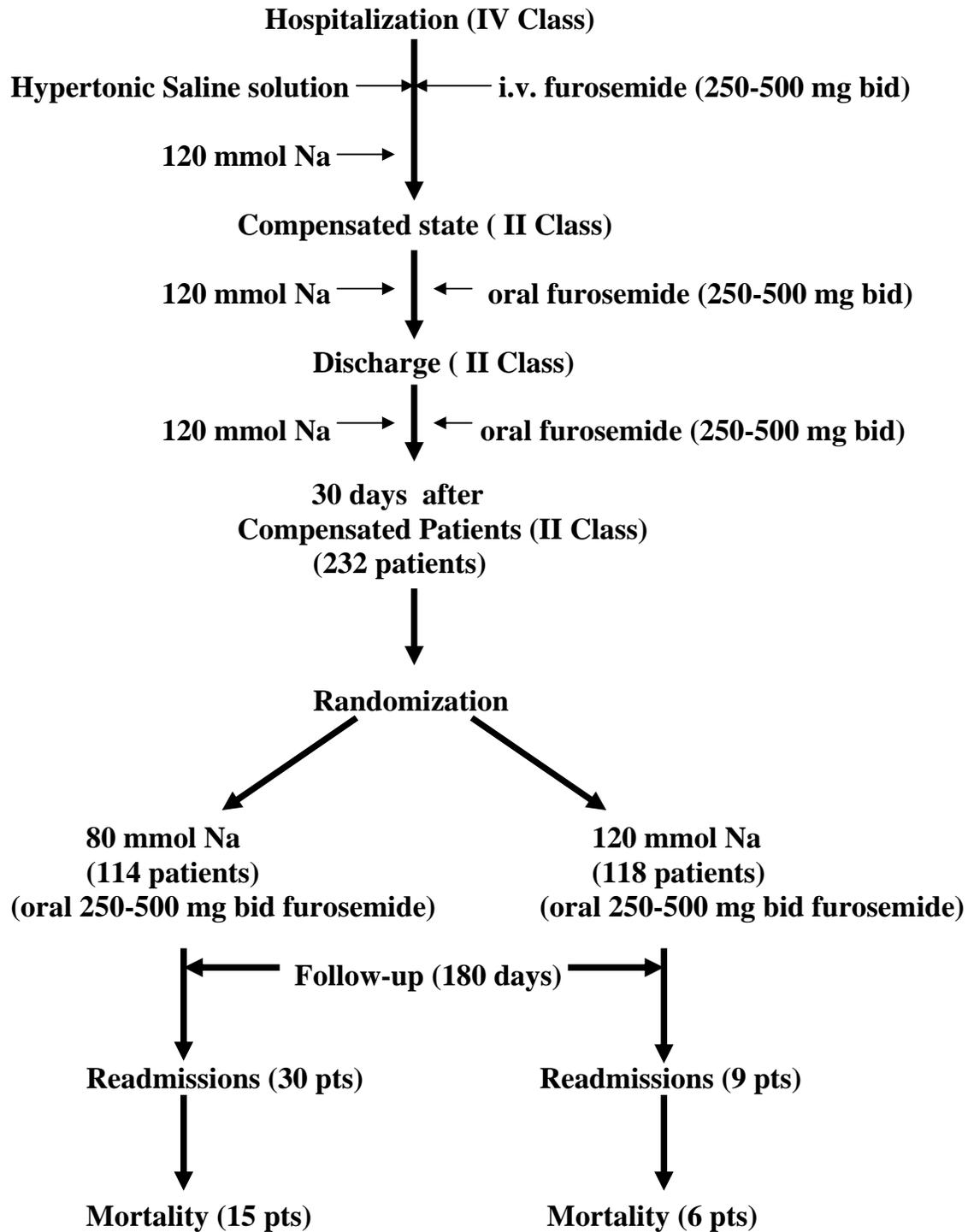
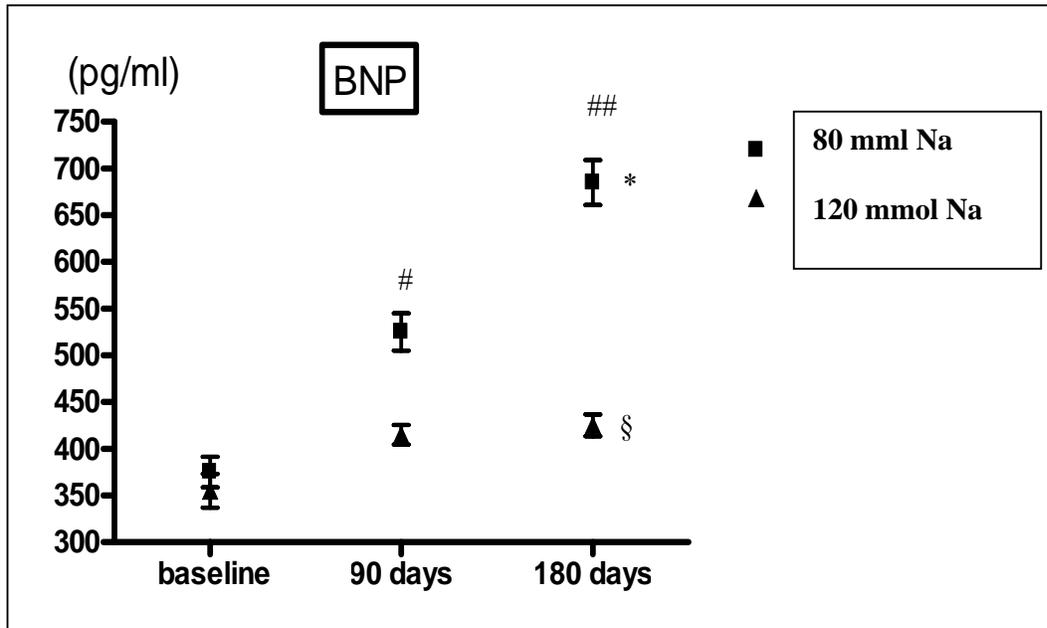


Figure 1: Flow chart of the study.

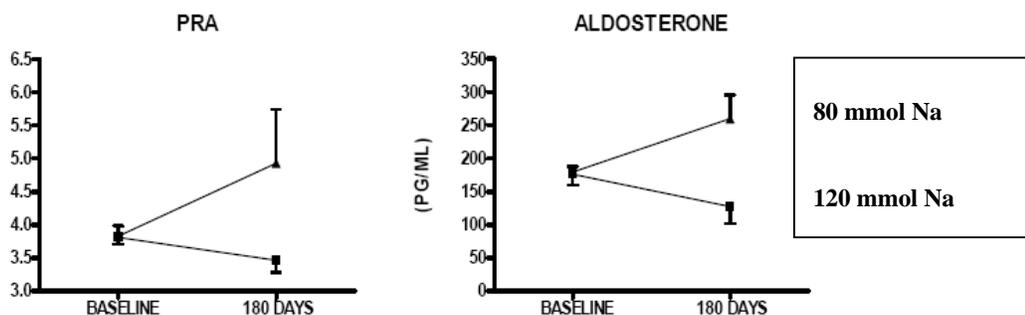
**Figure 2: Changes in BNP plasma levels in the study period. Low sodium diet =80 mmol Na;
Normal sodium diet =120 mmol Na.**



(*) $p < 0.0001$ baseline vs 180 days
(§) $p < 0.001$ baseline vs 180 days
(#) $p < 0.001$ 80 mmol vs 120 mmol (90 days)
(##) $p < 0.0001$ 80 mmol vs 120 mmol (180 days)

Figure 3: Changes in PRA (plasma renin activity and aldosterone plasma levels during the study period.

Changes in PRA ((ng/ml/h) and Aldosterone (pg/ml) levels during the study period



P<0.0001 - baseline vs 180 days aldosterone levels (80 mmol Na group)
P= 0.002 - baseline vs 180 days aldosterone levels (120 mmol Na group)
P= 0.6 - baseline vs 180 days, PRA difference (120 mmol Na group)
P=0.039 - baseline vs 180 days, PRA difference (80 mmol Na group)
P<0.0001 - difference in aldosterone and PRA between 80 mmol Na and 120 mmol Na groups at 180 days .

Figure 4: Kaplan-Meier cumulative event curves for primary end point (hospital readmissions) in the two groups during 180 days follow.up.

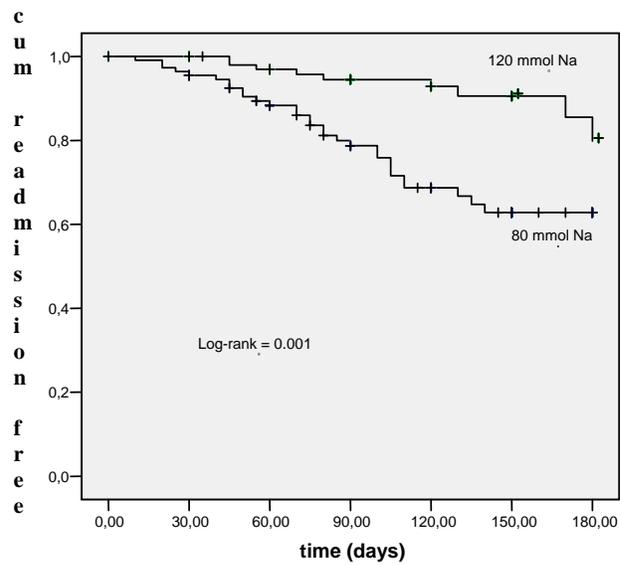


Figure 5: Kaplan-Meier cumulative event curves for combined end points (hospital readmission + mortality) in the two groups during 180 days follow-up.

