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Changes in Brain Natriuretic Peptide Levels and Bioelectrical Impedance Measurements After Treatment With High-Dose Furosemide and Hypertonic Saline Solution Versus High-Dose Furosemide Alone in Refractory Congestive Heart Failure

A Double-Blind Study

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OBJECTIVES The aim of this study was to evaluate the effect of a new treatment for refractory congestive heart failure (CHF) on brain natriuretic peptide (BNP) plasma levels and hydration station.

BACKGROUND The study was aimed at evaluating the effects of the combination of high-dose furosemide and small-volume hypertonic saline solution (HSS) in refractory CHF patients.

METHODS A total of 94 patients (34 women/60 men) with refractory CHF (age 55 to 80 years) were enrolled. They had to have an ejection fraction <35%, serum creatinine <2 mg/dl, blood urea nitrogen <60 mg/dl, a reduced urinary volume, and a low natriuresis (<500 ml/24 h and <60 mEq/24 h, respectively). Patients were divided (double-blind) into two groups: group 1 (18 women/30 men) received an intravenous furosemide (500 to 1,000 mg) plus HSS twice a day in 30 min. Group 2 (16 women/30 men) received an intravenous bolus of furosemide (500 to 1,000 mg/twice a day) alone, for four to six days. At entry, body weight, blood pressure, heart rate, and laboratory parameters were checked during hospitalization; BNP levels were measured on admission, 6 and 30 days after discharge, while on admission and 6 days after, impedance plethysmography was performed. The HSS group received 120 mmol of Na intake versus 80 mmol in non-HSS group. Fluid intake of 1,000 was given to both groups.

RESULTS The groups were similar for clinical characteristics. A significant increase in daily diuresis and natriuresis was observed in HSS group, $p < 0.05$. The BNP values showed significant intragroup and intergroup differences, 6 and 30 days after treatment. The patients from the HSS group reached a better hydration state than the non-HSS group after six days. In addition, the HSS group showed a significant reduction in hospitalization time and readmission rate.

CONCLUSIONS Our data show that the HSS group reached dry weight more rapidly, a significantly faster reduction in BNP levels, shorter hospitalization stay, and lower incidence in readmissions in the 30-day study period. (J Am Coll Cardiol 2005;45:1997–2003) © 2005 by the American College of Cardiology Foundation

Despite recent advances in the treatment of congestive heart failure (CHF) and the results in randomized trials, many patients continue to present with signs and symptoms that are refractory to treatment with digoxin, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and other vasodilators, and the prevalence and incidence of CHF is increasing progressively worldwide (1–3). The management of patients with advanced CHF classically consists in sodium intake restriction together with physical activity and treatments that include digitalis, diuretics, and ACE inhibitors (4). Diuretics, particularly potent loop diuretics, have long been accepted as first-line treatment of patients with severe CHF and extreme fluid retention (5,6). However, a lack of response to diuretics is a common event, particularly in elderly patients with advanced disease. When diuretic resistance occurs, proposed therapeutic options include higher doses or constant diuretic infusion (7), concomitant dopamine infusion to increase renal blood flow, potentiating diuretic activity (8), and a combination of different classes of diuretics, providing synergistic effects (9–11). Previously, we showed the safety and tolerability of

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BIA = bioelectrical impedance analysis
BNP = brain natriuretic peptide
BW = body weight
CHF = congestive heart failure
HSS = hypertonic saline solution
NYHA = New York Heart Association

the combination of high-dose furosemide associated with small-volume hypertonic saline solution (HSS) infusion plus normosodic diet (12,13) and that this combination in comparison with an intravenous high-dose infusion of furosemide as bolus plus iposodic diet in patients with severe CHF determined a significant reduction of hospitalization time, the maintenance of the achieved New York Heart Association (NYHA) functional class at discharge, the reduction of readmissions to hospital for CHF worsening (14), and a significant mortality rate reduction (55% survival after 48 months) (15). Because natriuretic peptides have been shown to be a useful part of epidemiological studies and clinical trials in advanced heart disease (16–19), and these peptides have been shown to be very powerful prognostic markers (7,20–26), we performed a randomized double-blind study to verify the effects of HHS treatment plus high-dose furosemide on brain natriuretic peptide (BNP) plasma levels at entry, 6 days, and 30 days after treatment and on hydration state at entry and 6 days after in patients with advanced CHF (NYHA functional class IV) in comparison with an intravenous high-dose infusion of furosemide as bolus.

METHODS

The rationale and design of the HHS study have been reported previously (12–15).

Patient population. From January 2000 to January 2002, 94 patients were consecutively admitted to hospital with NYHA functional class IV refractory CHF.

Eligibility criteria. Patients had to have, according to the definition of refractory CHF (1) and according to Framingham criteria and NYHA functional classification for CHF (2), uncompensated CHF (dyspnea, weakness, lower limb edema, or anasarca), NYHA functional class IV that was unresponsive to treatment with oral high doses of furosemide up to 250 to 500 mg/day and/or combinations of diuretics (thiazide, loop diuretic, and spironolactone), ACE inhibitors (captopril 75 to 150 mg/day), digitalis, beta-blockers, and nitrates and to be under this therapy at least two weeks before the study and 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, despite the increase of furosemide and the combination of other diuretics. Additionally, they had to have a left ventricular ejection fraction <35%, serum creatinine <2 mg/dl, blood urea nitrogen ≤60 mg/dl, a reduced urinary volume (<500 ml/24 h), and a low natriuresis (<60 mEq/24 h) despite receiving the established treatments. None of the patients were taking nonsteroid anti-inflammatory drugs. Each patient provided written informed consent before starting the study.

Randomization. Baseline characteristics of the study subjects are shown in Tables 1 and 2.

Double-blind randomization was carried out using a preliminary computer algorithm, and the assignment of patient was decided at the time of admission by an independent physician, before performing complete clinical examination and laboratory measurements. The solutions were prepared before by an independent nursing team directed by an independent physician. The solutions contained different concentrations of NaCl and two different doses of furosemide (250 or 500 mg). These infusions were numbered and were blinded to physicians treating the patients. The same smaller doses were prepared without NaCl addition and numbered as in the previous group. In addition, the nursing team prepared a bolus of furosemide (500 or 1,000 mg) or placebo, which was also numbered. When randomization was decided, the treating physicians received the solutions without any identification sign. The double-blind was revealed only when randomization was finished. The randomization staff, in this way, gave the treatment according to baseline characteristics of patients, and according to the protocol of treatment previously reported, without informing about solution composition to the physicians performing the study. The final data and clinical results were collected by another independent physician and, after analysis, were given to the appropriate person. All patients included in the study, after randomization, underwent 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 blood pressure (mean of three measurements), and heart rate. Fasting blood samples were drawn to determine serum Na, K, Cl, bicarbonate, albumin, uric acid, creatinine, urea, and glycemia on a daily basis during hospitalization and continuing until a clinically compensated state was obtained. The total daily output of urine was

Table 1. Clinical Characteristics and Etiology of CHF

		Furosemide Without HSS	Furosemide With HSS
Patient number	94	46	48
Gender, F/M	34/60	16/30	18/30
CHF etiology			
CAD	46	22	24
HHD	27	13	14
DCM	21	11	10
AF	15	8	7

AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; DCM = dilatative cardiomyopathy; HHD = hypertensive heart disease; HSS = hypertonic saline solution.

Table 2. Clinical and Laboratory Parameters Before (at Entry) and After Six Days of Treatment

	Furosemide Without HSS			Furosemide With HSS		
	Entry	6 Days	p Value	Entry	6 Days	p Value
Patient number	46	46		48	48	
Age (yrs)	74.5 ± 6	—		74.7 ± 8	—	
SBP (mm Hg)	146 ± 22	118 ± 11	<0.0001	145 ± 21	115 ± 11	<0.0001
DBP (mm Hg)	82 ± 14	77 ± 11	<0.06	80 ± 13	75 ± 11	<0.045
HR (beats/min)	83 ± 15	82 ± 11	<0.7	83 ± 12	78 ± 8	<0.01
Ejection fraction	30.2 ± 3	31.1 ± 4	<0.22	30.1 ± 3	32 ± 5	<0.026
Body weight (kg)	75.8 ± 15	67.1 ± 14	<0.006	76.0 ± 16	65.8 ± 15	<0.002
Diuresis (ml/24 h)	425 ± 129	1,660 ± 515*	<0.0001	410 ± 141	2,250 ± 652*	<0.0001
Serum Na (mEq/l)	134.9 ± 7	130.1 ± 3*	<0.0001	133.8 ± 6	142.3 ± 3.4*	<0.0001
Serum K (mEq/l)	4.8 ± 0.6	3.5 ± 0.4*	<0.0001	4.4 ± 0.4	3.9 ± 0.3*	<0.0001
Urinary Na (mEq/24 h)	54.5 ± 12.4	129 ± 32*	<0.0001	49.1 ± 12	197 ± 22*	<0.0001
Urinary K (mEq/24 h)	59 ± 29	96 ± 35	<0.0001	64 ± 21	86 ± 22	<0.0001
Serum glucose (mg/dl)	91 ± 21	96 ± 24	<0.29	97 ± 23	95 ± 22	<0.66
BUN (mg/dl)	56.1 ± 3.5	99 ± 11*	<0.0001	62 ± 4	64 ± 9.5*	<0.18
Serum creatinine (mg/dl)	1.55 ± 0.05	1.98 ± 0.2*	<0.0001	1.51 + 0.1	1.45 + 0.05*	<0.0001
Uric acid (mg/dl)	6.6 ± 2.1	9.8 ± 3.7	<0.0001	6.8 ± 2.8	9.6 ± 3.2	<0.0001
Serum albumin (g/dl)	4.2 ± 0.7	4.18 ± 0.6	<0.88	3.9 ± 0.5	3.8 ± 0.5	<0.33
Hospitalization (days)	10.5 ± 2.6			6.57 ± 2.3		<0.0001
Weight (kg) lost	8.1 ± 2.4			10.9 ± 4.1		<0.0001

Data are expressed as mean ± SD. *$p < 0.0001$, differences between the two groups six days after the treatment.
BUN = blood urea nitrogen; DBP = diastolic blood pressure; HSS = hypertonic saline solution; HR = heart rate; SBP = systolic blood pressure.

collected for Na, K, and Cl measurements. Chest X-ray, electrocardiogram, and echocardiogram (to obtain ejection fraction according to the modified Simpson's rule, which uses two cross-section views (four- and two-chamber apical views) were obtained before the beginning of the therapy and again at the time of hospital discharge and 30 days after. The BNP plasma levels were measured on admission, 6 days, and 30 days after discharge. The evaluation of the hydration state was performed on admission and six days after. The compensation fluid balance was detected by a tetrapolar impedance plethysmography (BIA-101, Akern, Firenze, Italy). The bioelectrical parameters of resistance and reactance were measured using an electric alternating current flux of 800 μA and an operating frequency of 50 kHz. The accuracy was checked with a calibration circuit of known impedance (R = 380 Ω, Xc = 47 Ω, 1% error; where R = resistance and Xc = reactance). Whole body impedance measurements were taken by using a standard position of outer and inner electrodes on the right hand and foot. The entire procedure was performed according to the indications of the National Institutes of Health technology assessment conference statements (27). For each patient a database was created that included anthropometric data (height, weight, and body mass index). Bioelectrical impedance analysis (BIA) evaluates some basic properties of the body by measuring resistance, reactance (reactance is a form of opposition that electronic components exhibit to the passage of alternating current because of capacitance or inductance; in some respects, reactance is like an alternating current counterpart of direct current and indicates an absolute amount of body cell mass), and phasic angle (phase angle is an indicator of cellular health and integrity; a low phase angle is consistent with an inability of cells to store energy and an indication of breakdown in the selective permeability of cellular membranes; a high phase angle is consistent with large quantities of intact cell membranes and body cell mass; phase angle is proportional to the ratio of reactance and resistance; the range of phase angle in the human body is 1° to 20°). In healthy and ill individuals total body water and fat-free mass can be estimated using formulas that include BIA variables and often also individual's general characteristics. As an alternative, BIA values are evaluated, as such, in comparison to reference values obtained in the general population (as resistance and reactance percentiles, or bivariate resistance-reactance confidence limits). It is well known that BIA reflects variation in total body water and the ratio between extracellular water and total body water; BIA is used to estimate the volumes of body fluid compartments. Electrical current is conducted by body water, and impeded by other body components. The opposition to flow of electrical current is called impedance. Impedance is proportional to the length of the conductor, and inversely proportional to the cross-sectional area. Because volume is simply length multiplied by area, impedance is directly related to the volume of the body fluid. Fluid compartment volume measures are a useful part of body composition assessment for several reasons. Estimates of extracellular fluid volume together with total body water volume allow calculation of intracellular fluid volume. Intracellular fluid volume correlates strongly with body cell mass. The recruited patients were randomized into two groups (double-blind fashion): group 1 received an intravenous 30-min infusion of furosemide (500 to 1,000 mg) plus HSS (150 ml of 1.4% to 4.6% NaCl) twice a day, and maintained a normosodic diet (120 mEq NaCl); group 2 received an intravenous infusion of furosemide (500 to

1,000 mg) as bolus twice day, without HSS, and maintained an iposodic diet (80 mEq NaCl) for a period of four to six days. Daily dosage of furosemide was defined considering diuretics, urinary volume, blood pressure values, and severity of signs and symptoms of congestion. The dose of HSS was determined in each patient (first group) according to the following schedules: for serum Na values <125 mEq/l HSS, concentration was 4.6%. For serum Na values between 126 mEq/l and 135 mEq/l HSS, concentration was 3.5%, and, for serum Na values >135 mEq/l, HSS concentration varied between 1.4% and 2.4%. KCl (20 to 40 mEq) intravenous was administered to prevent hypokaliemia. During the study period, the patients received ACE inhibitors, digitalis, nitrates, and beta-blockers (when possible) as previously reported. During the treatment and after hospital discharge, the daily dietary sodium intake was 120 mEq for the first group and 80 mEq for the second group, with a fluid intake of 1,000 ml daily in both groups. An accurate assessment of BW (in the morning before breakfast) and 24-h urinary volume was performed every day. Serum and urinary laboratory parameters were measured daily until reaching a clinical compensated state, considered as a change in NYHA functional class to at least IIb and the accomplishment of ideal BW, calculated by the Lorenz formula. Once the clinical compensated state was reached, the intravenous administration of furosemide (both groups) and HSS was stopped (first group) and replaced with oral furosemide administration (250 to 500 mg/twice a day) and oral KCl supplementation and the best therapy continued without changes after the discharge along with the standard therapy (ACE inhibitors [captopril 75 to 150 mg/day], digitalis [0.125 to 25 mg/day], antialdosterone, beta-blockers, and nitrates) in both groups. The double-blind aspect of the study was continued at discharge and for the subsequent 30 days. During the study period, other treatments were not added to those administered.

Statistical analysis. The results are expressed as mean values ± SD. The statistical analysis was performed using the two-tailed *t* test to identify differences between the groups and analysis of variance for repeated measures with Bonferroni correction for intragroup data. The number of comparisons included in the Bonferroni correction was three for each group. Nominal data were analyzed by chi-square test; a p value <0.05 was considered to be significant.

RESULTS

Ninety-four (female/male: 34 to 59) with refractory CHF of different etiologies (46 coronary artery disease, 27 hypertensive heart disease, 21 dilated cardiomyopathy, aged 55 to 81 years, met the entry criteria and continued the study in accordance with the study protocol (Table 1). The patients showed at entry: 94 orthopnea, 94 extreme fatigue on effort, 94 third heart sound, 94 marked peripheral edema, 94 hepatic enlargement, 94 bronchial rales, 79 pleural effusions, 31 pericardial effusion, 48 ascites. A prominent improvement in clinical parameters such as dyspnea, lower limb edema, anasarca, and weakness was obtained in all patients studied. In fact, patients from the two groups and patients in anasarca (ascites, pleural, and pericardial effusion) experienced complete resolution of this state (evaluated clinically and by X-ray and echocardiography) after the treatment that resulted in the rapid relief of dyspnea, weakness, and fatigue. Before the study, natriuresis was low in most patients despite that they were receiving high oral doses of furosemide and/or combinations of diuretics, suggesting the presence of a resistance to furosemide action. A significant increase was observed in daily diuresis in both groups. The natriuresis was increased in both groups as well as serum Na. Serum K was decreased significantly, but the value remained in the normal range in both groups (Table 2). In addition, the renal function was controlled also after discharge did not show significant differences with those obtained after six days of treatment (Table 3). The HSS group showed a higher amount of Na excreted (approximately 200 mEq Na/24 h vs. 130 mEq Na/24 h in non-HSS group, p = 0.001). The amount of Na administered intravenously each day ranged from approximately 1.6 g (300 ml/day of 1.4% hypertonic saline) to 5.4 g (300 ml/day of 4.6% hypertonic saline) for HSS group plus 2.8 g (120 mEq) Na/24 h (normosodic diet) versus 1.8 g (80 mEq) Na/24 h (iposodic diet) in non-HSS group. Body weight was reduced, and the reduction was proportional to increased urinary volume. As previously reported (14,15), the changes in NYHA functional class, with most study patients going from class IV to class II, was evidenced in both groups. The serum creatinine and serum uric acid concentrations significantly increased after therapy in both groups. The patients did not complain of any major discomfort during treatment and tolerated well the intravenous infusion. No side effects of this therapy, in particular hearing loss or tinnitus were observed in HSS patients. In both groups, systolic and diastolic values of blood pressure were decreased without important clinical manifestations, and HR was corrected to normal values (Tables 2 and 4). Table 5 shows the changes of BNP plasma levels in both groups. The BNP values showed significant intragroup differences (values on admission vs. 6 days and 30 days after). In addition, we observed that plasma levels of

Table 3. Laboratory Parameters of Renal Function at Discharge

	Furosemide Without HSS	Furosemide With HSS	
	Discharge	Discharge	p Value
Patient number	46	48	
Diuresis (ml/24 h)	1,550 ± 355	2,180 ± 545	<0.0001
Urinary Na (mEq/24 h)	119 ± 21	188 ± 25	<0.0001
Urinary K (mEq/24 h)	93 ± 29	87 ± 23	<0.26
BUN (mg/dl)	98 ± 12	65 ± 10	<0.0001
Serum creatinine (mg/dl)	1.97 ± 0.2	1.55 ± 0.05	<0.001
Uric acid (mg/dl)	10.8 ± 4.3	10.3 ± 3.7	<0.54

Data are expressed as mean ± SD.
BUN = blood urea nitrogen; HSS = hypertonic saline solution.

Table 4. Results of the Study (30 Days): Side Effects, Readmissions, and Mortality

	Furosemide Without HSS	Furosemide With HSS	p Value
Patient number	46	48	
Gender, F/M	16/30	18/30	
Side effects (tinnitus)	11	0	<0.05
Readmissions	12	0	<0.05
Mortality	3	0	
Sudden death	2	0	

HSS = hypertonic saline solution.

BNP were significantly lower in HSS group in comparison with non-HSS group, 6 days and 30 days after treatment. The evaluation of hydration state evidenced that patients from HSS group reached, after 6 days, a better hydration state in comparison with non-HSS group. Tables 6 and 7 show the BIA variables that were very stable, the coefficient of variation on serial measurements being 1.7% for resistance and 2.1% for reactance, which increased after treatment, especially in the HSS group; phase angle, which also increased after treatment, showed a mean coefficient of variation of 1.2% and a maximum variation of 0.3°. Patients were discharged from the hospital after 6 to 12 days. The HSS group showed a significant reduction in hospitalization time and readmission rate in agreement with our previous results (14,15).

Follow up. During the 30-day double-blind follow-up period, no patients from the first group were hospitalized or died, while 12 patients from the second group were readmitted to the hospital for clinical signs of heart failure, and they presented, at entry, higher functional class than at discharge (NYHA functional class III), while the remaining patients maintained the same NYHA functional class achieved at the time of hospital discharge. Three patients died during the 30-day study period in the second group (sudden death and irreversible heart failure). Only six patients received beta-blockers (carvedilol) in both groups. All patients continued ACE inhibitors as previously reported (captopril 75 to 150 mg/day). During the follow-up, the outpatients were controlled, and the treatments (where necessary) were corrected according to clinical status and laboratory measurements (reduction and/or increase of diuretics, fluid intake, and Na/K intake, BNP levels, and BIA parameters). No correction of therapy was carried out in all patients but in readmitted patients who received open treatments after readmission. Echocardiographic data during follow-up showed a nonsignificant slight improvement in ejection fraction in all patients.

Table 5. Changes in BNP Levels During the Study Period (30 Days)

	BNP Values (pg/ml)		
	Furosemide Without HSS	Furosemide With HSS	p Value
Admission	1,265 ± 515*	1,212 ± 491*	<0.6
6 days	468 ± 251*†	343 ± 196*†	<0.008
30 days	552 ± 284*†	312 ± 165*†	<0.0001
p value	<0.0001	<0.0001	

Data are expressed as mean ± SD. Differences between groups were performed by *t* test. *p < 0.0001, differences between the results obtained on admission vs. 6 days and 30 days after treatment in each group; †p = NS, differences between 6 days vs. 30 days after treatment in both groups (analysis of variance).

BNP = brain natriuretic peptide; HSS = hypertonic saline solution.

Table 6. Bioimpedance Analysis Parameters in Decompensated Heart Failure Patients Before and After Intravenous Treatment With HSS Plus Furosemide

	Admission	6 Days After	p Value
Weight	76.08 ± 16.67	65.82 ± 15.38	<0.002
BMI	29.12 ± 5.2	26.92 ± 5.05	<0.038
Resistance (Ω)	409.9 ± 112.4	503.6 ± 114	<0.0001
Reactance (Ω)	27.2 ± 15.6	40.4 ± 16.7	<0.0001
Ph.A	3.59 ± 1.2	4.45 ± 1.42	<0.002
R/h	259.4 ± 81.6	317.8 ± 80.5	<0.0001
Xc/h	17.2 ± 9.9	25.6 ± 11.1	<0.001

Values are expressed as mean ± SD.

BMI = body mass index; HSS = hypertonic saline solution; Ph.A = phase angle; R/h = resistance/height ratio; Xc/h = reactance/height ratio.

DISCUSSION

The mechanism(s) explaining the efficacy of the proposed combined infusion in the treatment of severe and refractory CHF may comprise the instantaneous mobilization of extravascular fluid into the intravascular space through the osmotic action of HSS (12–15,28,29) and the rapid excretion of this volume by the action of extracellular fluid expansion itself and by the action of intravenous furosemide infusion. Further, HSS, by a demonstrated increase in renal blood flow (30), may facilitate the action of diuretics and help overcome an established diuretic resistance, frequently observed in these patients, related to CHF itself (24–26) or to age-associated decrease in renal function (22,23). Regarding the kidney and its circulation, patients with CHF reveal a picture that strikingly resembles that defined in response to hemorrhage. 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 disease (31); HSS infusion determines a

Table 7. Bioimpedance Analysis Parameters in Decompensated Heart Failure Patients Before and After Intravenous Treatment With Furosemide Without HSS

	Admission	6 Days After	p Value
Weight	75.85 ± 15.78	67.12 ± 14.18	<0.006
BMI	29.6 ± 5.9	27.71 ± 5.81	<0.125
Resistance (Ω)	411.1 ± 117.5	483.4 ± 116.2	<0.004
Reactance (Ω)	28.2 ± 16.3	38.6 ± 13.7	<0.001
Ph.A	3.61 ± 1.3	4.15 ± 1.32	<0.051
R/h	261.2 ± 83.4	298.7 ± 76.3	<0.027
Xc/h	17.7 ± 10.2	23.6 ± 10.1	<0.006

Data are expressed as mean ± SD.

BMI = body mass index; HSS = hypertonic saline solution; Ph.A = phase angle; R/h = resistance/height; Xc/h = reactance/height.

rapid elevation of extracellular NaCl concentration with a consequent rise in osmotic pressure, plasmatic volume expansion, instantaneous fluid mobilization into the vascular compartment, increased renal blood flow (32,33). Additionally, fluid shifted out of erythrocytes and endothelial cells to the extracellular space leads to a reduction in capillary hydraulic resistance (29).The rapid expansion of extracellular fluid volume is responsible for the decreased plasma and peritubular oncotic pressure that, along with an increased peritubular hydrostatic pressure, enhances the urinary Na excretion by a reduction in proximal Na reabsorption (34). The simultaneous administration of furosemide at high doses adds an important hydrosaline renal excretion, because the increment in renal blood flow allows furosemide's concentration in the Henle's loop to be optimal. In fact, HSS administration seems to potentiate the diuretic action of furosemide, and possibly to help overcome established resistance to diuretics with no need of higher doses and, consequently, limit electrolyte disturbance and other side effects (hypotension, tinnitus, etc). The most important results of our study were the rapid compensation obtained in these CHF class IV patients, and mainly the maintenance of the achieved NYHA functional class at discharge, and a reduction of readmissions to hospital for CHF worsening (12–15). The significant and rapid reduction in BNP values confirms the clinical data. In fact, the main stimulus for BNP peptide synthesis and secretion is cardiac wall stress (35). Because increased wall stress is a common denominator of many cardiac diseases, it follows that BNP levels may serve as biochemical markers of these states. Because of its fast induction and specific expression in overt heart failure, BNP seems the most promising natriuretic peptide as a marker of left ventricular dysfunction, which makes it an important component of cardiac care. The more significant and rapid BNP reduction in HSS patients is probably due to rapid and important plasmatic volume reduction and subsequent cardiac wall stress. It is possible that the therapeutical effects of this treatment are not only mediated by the direct effects on renal hemodynamics, but also by neurohormones modulation. It is possible that the strict control performed in these patients allowed us to correct the treatments, as well as the possibility that the Na intake (120 mEq) allowed a continued response to diuretics. This last mechanism could also justify the maintenance of the reduction in BNP levels observed 30 days after discharge. This hypothesis is the most probable because the conventionally treated patients, as previously reported, were strictly controlled, but readmissions were significantly higher (14,15) than normosodic diet patients. In addition, our previous reports were single-blind studies, while the present study was performed in double-blind fashion. The results of the hydration state also confirm the clinical and BNP findings. In fact, patients receiving HSS showed a more significant rapid improvement in hydration state than patients not receiving HSS and normosodic diet (36). We also used BIA because this method is a safe, noninvasive, rapid, and inexpensive technique, and is well correlated with other techniques in detecting body composition such as magnetic resonance imaging (37), deuterium dilution technique (38), and thermodilution (39,40). We think that diuretics augment natriuresis by impeding the reabsorption of Na that has filtered through the glomerulus. After a few days of once-daily dosing with a high-potency diuretic formulation, the increase in 24-h natriuresis that occurs after the first dose disappears or becomes markedly attenuated; this is usually referred to as braking phenomenon. The processes involved in the increase in Na reabsorption that account for the braking phenomenon have not been fully clarified (41,42). Our patients differed from the heart failure population reported in many heart failure studies because of the higher blood pressure, higher ejection fraction, and larger net diuresis. In conclusion, our data suggest that the combination of high doses of furosemide with HSS determines a more rapid compensation. In fact, systematic data on changes in bioelectrical variables occurring in HF patients before and after treatment show that patients receiving HSS reached their dry weight more rapidly than those not receiving HSS solution. In addition, a significantly faster reduction in BNP levels, shorter hospitalization stay, and lower incidence in readmissions in the 30-day period of study in CHF patients were also observed. All the three parameters investigated, clinical data, BNP levels, and bioelectrical variables, showed that HSS solution with a high-dose of furosemide plus a normosodic diet can obtain a significant improvement in advanced CHF patients.

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