ELSEVIER

European Journal of Heart Failure 2 (2000) 305–313

The European Journal of Heart Failure

www.elsevier.com/locate/heafai

Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure

Salvatore Paterna[a], Pietro Di Pasquale[b,*], Gaspare Parrinello[a], Piera Amato[a], Antonella Cardinale[a], Giuseppe Follone[a], Alfonso Giubilato[b], Giuseppe Licata[a]

[a] *Department of Internal Medicine, University of Palermo, Palermo, Italy*
[b] *Division of Cardiology, 'Paolo Borsellino', G. F. Ingrassia Hospital, Palermo, Italy*

Received 20 February 2000; received in revised form 24 April 2000; accepted 23 May 2000

Abstract

Background: Diuretics, have been accepted as first-line treatment in refractory heart failure, but a lack of response is a frequent event. A randomised single blind study was performed to evaluate the effects of the combination of high-dose furosemide and small-volume hypertonic saline solution (HSS) infusion in the treatment of refractory NYHA class IV congestive heart failure (CHF). *Materials and methods:* Sixty patients (21 F/39 M) with refractory CHF (NYHA class IV) of different etiologies, unresponsive to high oral doses of furosemide, ACE-inhibitors, digitalis, and nitrates, aged 65–90 years, were enrolled. They had to have an ejection fraction (EF) $< 35\%$, serum creatinine < 2 mg/dl, BUN ≤ 60 mg/dl, a reduced urinary volume and a low natriuresis. The patients were randomised in two groups (single blind): group 1 (11 F/19 M) received an i.v. infusion of furosemide (500–1000 mg) plus HSS (150 ml of 1.4–4.6% NaCl) b.i.d. in 30 min. Group 2 (10 F/20 M) received an i.v. bolus of furosemide (500–1000 mg) b.i.d., without HSS, during a period lasting 6–12 days. Both groups received KCl (20–40 mEq.) i.v. to prevent hypokalemia. All patients underwent at entry a physical examination, measurement of body weight (BW), blood pressure (BP), heart rate (HR), evaluation of signs of CHF, and controls of serum Na, K, Cl, bicarbonate, albumin, uric acid, creatinine, urea and glycemia and daily during hospitalization, as well as the daily output of urine for, Na, K and Cl measurements. Chest X-ray, ECG and echocardiogram were obtained at entry during and at the discharge. During the treatment and after discharge the daily dietary Na intake was 120 mmol with a drink fluid intake of 1000 ml daily. An assessment of BW and 24-h urinary volume, serum and urinary laboratory parameters, until reaching a compensated state, were performed daily, when i.v. furosemide was replaced with oral administration (250–500 mg/day). After discharge, patients were followed as outpatients weekly for the first 3 months and subsequently once per month. *Results:* The groups were similar for age, sex, EF, risk factors, treatment and etiology of CHF. All patients showed a clinical improvement. Six patients in both groups had hyponatremia (from 120 to 128 mEq./l) at entry. A significant increase in daily diuresis in both groups was observed (from 390 ± 155 to 2100 ± 626, and from 433 ± 141 to 1650 ± 537 ml/24 h, $P < 0.05$). Natriuresis (from 49 ± 15 to 198 ± 28 mEq./24 h) was higher in group 1 vs. group 2 (from 53.83 ± 12 to 129 ± 39 mEq./24 h, $P < 0.05$). Serum Na (from 135.9 ± 6.8 to 142.2 ± 3.8 mEq./l, $P < 0.05$) increased in the group 1 and decreased in the group 2 (from 134.7 ± 7.9 to 130.1 ± 4.3 mEq./l). Serum K was decreased (from 4.4 ± 0.6 to 3.9 ± 0.6, and 4.6 ± 9 to 3.6 ± 0.5 mEq./l, $P < 0.05$) in both groups. BW was reduced (from 73.8 ± 9.1 to 63.8 ± 8.8, and from 72.9 ± 10.2 to 64.5 ± 7.5 kg, $P < 0.05$) in both groups. Group 2 showed more patients in NYHA class III than group 1 (18 vs. 2 patients, $P < 0.05$). Group 2 showed an increase of serum creatinine. Serum uric acid increased in both groups. BP values decreased, and HR was corrected to normal values in both

* Corresponding author. Chief Division of Cardiology, 'Paolo Borsellino', Via Val Platani 3, 90144, Palermo, Italy. Tel. : +39-091-524181; fax: +39-091-7033742.

PII: S1388-9842(00)00094-5

groups. Group 2 showed a longer hospitalization time than group receiving HHS infusion (11.67 ± 1.8 vs. 8.57 ± 2.3 days, $P < 0.001$). In the follow-up (6–12 months), none of the patients from group 1 were readmitted to the hospital and they maintained the NYHA class achieved at the discharge. Group 2 showed 12 patients readmitted to hospital and a higher class than at discharge. *Conclusion:* Our data suggest that the combination of furosemide with HSS is feasible and it appears that this combination produces an improvement of hemodynamic and clinical parameters, reduces the hospitalization time and maintains the obtained results over time in comparison with those receiving high-dose furosemide as bolus.

Keywords: Furosemide; Hypertonic saline solution; Refractory congestive heart failure

1. Introduction

Despite recent advances in the treatment of congestive heart failure (CHF), many patients continue to present signs and symptoms that are refractory to the treatment with digoxin, diuretics, ACE-inhibitors and other vasodilators [1]. Since the prevalence and incidence of CHF is increasing progressively worldwide [2,3], new strategies are needed for the management of patients with refractory CHF, a major therapeutic challenge defined as the condition in which patients with New York Heart Association (NYHA) functional class III–IV present symptoms that have not improved, or have actually worsened, following recent attempt escalate therapy [1]. The management of patients with advanced CHF, classically consists in sodium intake restriction, physical activity together 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 important fluid retention [5,6].

However, a lack of response to furosemide is a common event particularly in elderly patients with advanced disease. The age-related renal impairment of renal function, the concomitant therapies that may affect renal function [7,8], the changes induced by CHF on the gastrointestinal absorption and motility, the reduced splanchnic blood flow [9–11], contribute to this resistance. When diuretics resistance occurs, proposed therapeutic options include higher doses or constant furosemide infusion [12], concomitant dopamine infusion to increase renal blood flow, potentiating diuretics activity [13], and combination of different classes of diuretics, providing synergistic effects [14].

Hemodynamic alterations operating in CHF entail an expansion of extracellular fluid volume (total blood volume and interstitial volume) and a reduction of arterial blood volume with a consequent regional blood flow alteration. These alterations with associated hormonal pattern modifications are responsible of a relevant hydrosaline retention with signs and symptoms of peripheral and central congestion and an important reduction in renal blood flow [15,16].

Several studies have demonstrated the efficacy of hypertonic saline solution (HSS) infusion in conditions in which regional organ blood flow is impaired [17,18]. As such, HSS was first applied for the primary treatment of severe hemorrhagic and traumatic shock and this therapy promptly restored central hemodynamics and peripheral blood flow [19]. The suggested mechanisms were a direct myocardial stimulation with high cardiac output maintenance, increase of intravascular volume, and subsequent peripheral arterial vasodilatation (effect of hyperosmolality and plasma volume), reduction of tissue edema (shifting of tissue water along the osmotic gradient) [20], increased renal blood flow, reduced sympathetic tone [21].

HSS therapy has been the object of several experimental studies evaluating the effects of small-volume in resuscitation, in sepsis and multiple organ failure [20,22,23]. In view of the above facts, we hypothesize that the combination of high-dose loop-active diuretic and small-volume HSS through an i.v. infusion could be effective in the treatment of patients with refractory CHF and previously we showed the safety and tolerability of this combination [24]. A randomised single blind study was performed to evaluate the efficacy of high-dose furosemide associated with small-volume hypertonic saline solution (HSS) infusion in comparison with an i.v. high-dose infusion of furosemide as a bolus, in hospitalized patients with severe CHF refractory (NYHA class IV) to conventional therapy.

2. Materials and methods

2.1. Patient population and eligibility criteria

From January 1996 to June 1998, 754 patients were consecutively admitted to hospital with CHF. To be eligible to enter the trial, patients had to have, according to the definition of refractory CHF [1] and according to the Framingham criteria and New York association functional classification for congestive heart failure [1], uncompensated CHF (dyspnea, weakness, lower limbs edema or anasarca), NYHA

functional class IV 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, and nitrates and to be under this therapy at least 2 weeks before the study and before hospitalization.

The patients were judged unresponsive when they showed during the treatment as above reported an reduction of urine volume and constant increase of body weight and impairment of clinical signs of heart failure as reported, in spite of the increase of furosemide and the combination of other diuretics. Additionally, they had to have a left ventricular ejection fraction (EF) $< 35\%$, serum creatinine < 2 mg/dl, BUN ≤ 60 mg/dl, a reduced urinary volume and a low natriuresis despite receiving the established treatments. None of the patients had to take non-steroid anti-inflammatory drugs.

Baseline clinical characteristics of the study subjects are shown in Tables 1 and 2. Each patient provided written informed consent before starting the study. Randomization (single blind) was carried out by sequentially numbered boxes and was decided at entry, before performing complete clinical examination and laboratory measurements. 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 (BP) (mean of three measurements) and heart rate (HR). Fasting blood samples were drawn to determine serum Na, K, chloride, bicarbonate, albumin, uric acid, creatinine, urea and glycemia in a daily basis during hospitalization and continued until a clinical compensated state was obtained. The total daily output of urine was collected for creatinine, Na, K and Cl measurements.

Chest X-ray, ECG and echocardiogram (to obtain EF 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. Two observers blinded to the clinical data evaluated the two-dimensional echocardiographic images. The recruited patients were divided in two groups (single blind fashion), the first group received an i.v. 30 min, infusion of furosemide (500–1000 mg) plus HSS (150 ml of 1.4–4.6% NACI) b.i.d., and the second group received an i.v. infusion of furosemide (500–1000 mg) as a bolus b.i.d., without HSS, for a period of 6–12 days. Furosemide daily dosage was definite 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 (20–40 mEq.) i.v. was administered to prevent hypokaliemia.

Table 1
Clinical characteristics and ethiology of CHF (first group, patients receiving HSS)[a]

Patient *n*	Sex	Age (years)	CHF ethiology	EF%	Diuresis (ml/24 h)	NaU (mEq./24 h)
1	F	68	CAD + AF	35	450	45
2	F	72	CAD + AF	30	500	40
3	M	69	CAD + AF	32	350	55
4	F	85	HHD	35	450	65
5	M	84	CAD	27	350	45
6	M	82	HHD	35	500	60
7	M	60	CAD	35	850	85
8	F	84	HHD	35	500	50
9	F	71	CAD	30	400	60
10	F	84	CAD + AF	35	350	55
11	M	76	CAD	35	400	40
12	M	65	CAD	27	300	30
13	M	78	HHD	24	350	35
14	F	73	DCM	26	250	25
15	F	90	DCM	23	300	30
16	M	70	CAD	22	300	60
17	F	67	DCM	35	400	40
18	F	62	DCM	35	350	55
19	M	62	CAD	35	750	75
20	M	85	CAD	35	400	30
21	M	79	DCM	24	300	65
22	M	68	DCM	35	300	50
23	M	70	HHD	27	250	25
24	M	72	DCM	20	200	40
25	M	80	CAD	25	300	40
26	F	69	HHD	35	300	45
27	M	74	CAD	35	250	55
28	M	71	DCM	35	750	75
29	M	73	DCM	26	300	45
30	M	64	CAD	21	250	55

[a]*Abbreviations:* CAD, coronary artery disease; HHD, hypertensive heart disease; DCM, dilatative cardiomyopathy; AF, atrial fibrillation; and EF, left ventricular ejection fraction.

During the period of study the patients received, ACE-inhibitors, digitalis, and nitrates, as previously reported. During the treatment and after hospital discharge the daily dietary sodium intake was 120 mmol with a drink fluid intake of 1000 ml daily. An accurate assessment of body weight (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 [Male body weight = (height in cm-100) − ≪ height in cm-150)/4.9); Female, body weight = (height in cm-100) − ≪ height in cm 150)/2.5)].

Table 2
Clinical characteristics and ethiology of CHF (second group, patients without HSS)[a]

Patient *n*	Sex	Age (years)	CHF ethiology	EF%	Diuresis (ml/24 h)	NaU (mEq./24 h)
1	M	70	CAD	35	350	85
2	M	70	CAD	35	450	50
3	M	71	CAD	30	450	60
4	M	79	HHD	30	500	55
5	F	83	CAD + AF	25	350	60
6	F	81	HHD	32	800	30
7	M	65	CAD	35	550	45
8	F	82	HHD	33	600	40
9	M	73	CAD	35	500	55
10	M	83	CAD	30	450	65
11	F	71	CAD	25	350	45
12	M	67	CAD + AF	25	350	60
13	F	79	DCM	30	450	65
14	M	76	DCM	34	500	55
15	M	70	DCM	30	350	60
16	F	75	CAD	35	400	30
17	M	73	DCM	25	450	45
18	M	66	HHD	35	550	45
19	M	72	CAD	30	450	35
20	F	75	CAD + AF	25	500	70
21	M	73	HHD	27	600	60
22	F	78	DCM	35	450	60
23	M	77	CAD	30	250	45
24	M	79	DCM	25	200	60
25	M	75	CAD + AF	27	300	40
26	M	85	CAD	30	300	55
27	F	64	DCM	30	250	45
28	M	81	HHD	33	750	55
29	M	70	CAD	27	300	65
30	F	66	DCM	30	250	75

[a]*Abbreviations:* CAD, coronary artery disease; HHD, hypertensive heart disease; DCM, dilatative cardiomyopathy; AF, atrial fibrillation; EF, left ventricular ejection fraction.

Once the clinical compensated state was reached, the i.v. administration of furosemide (both groups) and HSS (first group) was stopped and replaced with oral furosemide administration (250–500 mg/day) and oral KCl supplementation and the best therapy continued without changes after the discharge along with the standard therapy (ACE-inhibitors, digitalis and nitrates) in both groups. During the study-period and follow-up other treatments were not added to those administered (beta-blockers, Ca + antagonists, angiotensin II receptor antagonists, etc.).

No patients received inotropic drugs i.v. during the study period. After the discharge, patients were followed on a weekly basis with clinical and laboratory evaluation for the first 3 months and later they were evaluated once per month in the day-hospital of the clinic for a further 12 months.

2.2. Statistical analysis

The results are expressed as mean values ± S.D. The statistical analysis was performed using the two-tailed *t*-test to identify differences between the groups and analysis of variance (ANOVA) for repeated measures with the Bonferroni correction for intragroup data. Nominal data were analyzed by the χ^2-test, a P value < 0.05 was considered to be significant.

3. Results

Sixty patients (female/male, 21:39) with refractory CHF of different etiologies: 31 coronary artery disease (CAD), 12 hypertensive heart disease (HHD), 17 dilatative cardiomyopathy (DCM), aged 65–90 years, met the entry criteria and continued the study in accordance with the study protocol (Tables 1 and 2). The patients showed at entry: 60 orthopnea, 60 extreme fatigue on effort, 60 third heart sound, 60 marked peripheral edema, 60 hepatic enlargement, 60 bronchial rales, 51 pleural effusion, 25 pericardial effusion, 23 ascites.

A prominent improvement in clinical parameters such as dyspnea, lower limb edema, anasarca and weakness was obtained in all 60 patients studied. In fact, 12 patients (from first group) and 9 patients (from second group) 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 (mean ± S.D., 49 ± 15 and 53.83 ± 12 in both groups, mEq./24 h) despite all patients were receiving high-oral doses of furosemide and/or combinations of diuretics, suggesting the presence of a resistance to furosemide action. Six patients in both groups had hyponatremia (from 120 to 128 mEq./l) prior to the beginning of the combined therapy.

A significant increase was observed in daily diuresis in both groups, but in the first group the diuresis was greater than group 2 (from 390 ± 55 ml/24 h to 2100 ± 626 ml/24 h, and from 433 ± 141 to 1650 ± 537 ml/24 h, $P < 0.05$). Natriuresis was greater in the first group (from 49 ± 15 to 198 ± 28 mEq./24 h) than the second group (from 53.83 ± 12 to 129 ± 39 mEq./24 h, $P < 0.05$) and serum Na (from 135.9 ± 6.8 to 142.2 ± 3.8 mEq./l, $P < 0.05$) was observed to increase in the first group, while in the second group it showed a reduction (from 134.7 ± 7.9 to 130.1 ± 4.3 mEq./l) after therapy. Serum K was decreased significantly (from 4.4 ± 0.6 mEq./l to 3.9 ± 0.6 mEq./l, and from 4.6 ± 9 to 3.6 ± 0.5 mEq./l, $P < 0.05$) but the value remained in the normal range (Table 4). BW weight was reduced (range 5–20 kg), from 73.8 ± 9.1 to 63.8 ± 8.8 kg, and from 72.9 ± 10.2 to 64.5 ± 7.5 kg, respectively, $P < 0.05$) and the reduction was proportional to increased urinary volume (Table 3).

Table 3
Clinical and laboratory parameters before (at entry) and after treatment (at discharge)[a]

	Furosemide without HSS			Furosemide with HSS		
	Before	After	$P <$	Before	After	$P <$
Patients (M/F)	20/10	/		19/11	/	
Age (years)	74.3 ± 5.86	/		73.57 ± 7.95	/	
SBP (mmHg)	145 ± 27.5	119.9 ± 13.7	0.001	142 ± 23.8	121.7 ± 12.7	0.001
DBP (mmHg)	82.1 ± 14.3	77.3 ± 11.5	n.s.	80.7 ± 13.8	73.2 ± 12.4	0.031
HR (b.p.m.)	83.9 ± 15.5	79.5 ± 11.3	0.021	82.7 ± 13.7	77.1 ± 10.2	0.078
Ejection fraction	30.27 ± 3.26	31.3 ± 5.9	n.s.	30.3 ± 5.34	32.1 ± 6.4	0.024
Body wt. (kg)	72.9 ± 9.3	64.5 ± 7.5	0.001	73.8 ± 9.1	63.8 ± 8.8	0.001
Diuresis (ml/24 h)	433 ± 141	1650 ± 537*	0.001	390 ± 155	2100 ± 626*	0.001
Serum sodium (mEq./l)	134.7 ± 7.9	130.1 ± 4.3*	0.007	135.9 ± 6.8	142.2 ± 3.8*	0.001
Serum potassium (mEq./l)	4.6 ± 0.9	3.6 ± 0.5**	0.001	4.4 ± 0.6	3.9 ± 0.6**	0.002
Urinary sodium (mEq./24 h)	53.83 ± 12.71	129 ± 39*	0.001	49.17 ± 15.09	198 ± 28*	0.001
Urinary potassium (mEq./24 h)	59 ± 33	95 ± 39	0.001	64 ± 28	85 ± 27	0.004
Scrum glucose (mg/dl)	95 ± 22.3	98 ± 26. 5	n.s.	98 ± 25.9	96 ± 23.8	n.s.
BUN (mg/dl)	58.1 ± 3.7	97 ± 13.5*	0.001	62.1 ± 4.1	70 ± 9.5*	0.001
Serum creatinine (mg/dl)	1.65 ± 0.07	1.94 ± 0.1*	0.001	1.6 ± 0.05	1.4 ± 0.07*	0.001
Uric acid (mg/dl)	6.3 ± 2.1	8.9 ± 3.4	0.001	6.7 ± 2.6	8.6 ± 3.2	0.014
Serum albumin (g/dl)	4.1 ± 0.7	4.08 ± 0.7	n.s.	3.9 ± 0.5	3.8 ± 0.5	n.s.
Hospitalization (days)	11.67 ± 2.6*			8.57 ± 2.3*		0.001
Weight (kg) lost	8.47 ± 2.61			9.9 ± 4.14		n.s.

[a] Data are expressed as mean ± S.D.
*$P < 0.001$.
**$P = 0.04$.

Table 4
Results of combined high-dose furosemide and hypertonic saline solution i.v. infusion in patients with refractory CHF (at discharge)

Patient *n*	Furosemide (mg/b.i.d.)	HSS b.i.d.%	Weight (kg)	NYHA class	Hosp. duration (days)
1	250–500	1.4–2.4	5	IV–IIa	6
2	500–1000	1.4–3.5	15	IV–IIb	12
3	500–1000	1.4–3.5	13	IV–IIb	10
4	250–1000	1.4–2.4	20	IV–IIb	11
5	250–1000	1.4–2.4	13	IV–IIa	10
6	250–500	1.4–2.4	6	IV–IIa	6
7	250–500	1.4–2.4	13	IV–IIa	8
8	250–500	1.4–2.4	13	IV–IIb	10
9	250–500	1.4–2.4	6	IV–IIb	6
10	250–500	1.4–2.4	8	IV–IIa	7
11	500–1000	1.4–3.5	6	IV–III	6
12	250–500	1.4–2.4	5	IV–IIa	6
13	250–500	1.4–2.4	8	IV–IIb	7
14	500–1000	1.4–3.5	7	IV–III	7
15	500–1000	1.4–2.4	6	IV–IIa	6
16	250–500	1.4–2.4	8	IV–IIa	6
17	500–1000	1.4–3.5	8	IV–IIb	8
18	250–500	1.4	6	IV–IIa	6
19	500–1000	1.4–2.4	17	IV–IIa	11
20	250–500	1.4–2.4	18	IV–IIb	12
21	250–500	1.4–2.4	13	IV–IIa	10
22	250–500	1.4	7	IV–IIa	8
23	250–500	1.4	5	IV–IIa	6
24	250–1000	1.4–2.4	9	IV–IIa	8
25	250–1000	1.4–3.5	10	IV–IIb	12
26	500–2000	1.4–4.6	12	IV–IIb	12
27	250–1000	1.4–3.5	9	IV–IIb	11
28	500–2000	1.4–4.6	13	IV–IIb	12
29	250–1000	1.4–2.4	7	IV–IIa	8
30	500–2000	1.4–3.5	11	IV–IIb	9

Tables 4 and 5 show the changes in NYHA functional class with a greater improvement in patients from the first group with most of them going from class IV to class II, than the patients from the second group with most of them going from class IV to class III. Group 2 showed more patients in NYHA class III than group 2 (18 patients vs. 2 patients, respectively $P < 0.05$). The reduction in serum creatinine, observed in the first group, was possibly induced by the expansion of the extracellular fluid (ECF) volume. The second group showed an increase of serum creatinine. Serum uric acid concentrations were significantly increased after therapy in both groups, $P < 0.05$, but none of the patients developed gout symptoms. The patients did not complain of any major discomfort during treatment and tolerated the i.v. infusion well. No side effects of this therapy, in particular hearing loss or tinnitus were observed in patients receiving also HHS, while these effects were reported in six patients treated with furosemide only, without HHS. Both systolic and diastolic values of BP were decreased without important clinical manifestations, and HR was corrected to normal values (Table 3). Patients were discharged from the hospital after 8–15 days of admission. The patients not receiving HHS infusion showed a longer hospitalization in comparison with patients receiving HHS infusion (11.67 ± 1.79 vs. 8.57 ± 2.3 days, $P < 0.05$).

The patients were followed in a weekly basis for the first 3 months after discharge and later they were seen once per month in the outpatients clinic. During the follow-up period, ranging from 6 to 12 months, none of the patients (first group) was readmitted to the hospital and all the patients maintained the same NYHA functional class achieved at the time of hospital discharge. Twelve patients from the second group were re-admitted to hospital for clinical signs of heart failure and they presented at entry a higher functional class than at discharge. In the first group a total of six patients died during the follow-up period (80% survival after 12 months). Three patients died 6 and 10 months after discharge by sudden death. The other three patients died after 4–8 months after discharge, but their deaths were not attributable to cardiac causes (bladder cancer, plasma cell myeloma, femoral fracture). In the second group 11 patients died, 7 for irreversible heart failure and 4 for non-cardiac causes. No patients received beta-blockers and spironolac-

Table 5
Results of high-dose furosemide without hypertonic saline solution infusion in patients with refractory CHF (at discharge)

Patient *n*	Furosemide (mg/b.i.d.)	Weight	NYHA class (kg)	Hosp. duration (days)
1	250–500	8	IV–III	12
2	250–500	7	IV–III	14
3	250–500	8	IV–III	12
4	500–1000	11	IV–IIb	14
5	500–1000	16	IV–IIb	14
6	500–2000	10	IV–III	10
7	500–1000	7	IV–III	10
8	500–1000	6	IV–IIb	12
9	250–500	5	IV–III	10
10	500–1000	10	IV–IIb	12
11	250–500	8	IV–III	14
12	500–2000	7	IV–IIb	12
13	250–500	5	IV–III	10
14	500–1000	5	IV–III	11
15	500–1000	9	IV–IIb	9
16	500–1000	5	IV–III	9
17	250–1000	11	IV–III	10
18	500–500	13	IV–III	12
19	250–1000	10	IV–III	10
20	250–1000	8	IV–IIb	10
21	500–1000	9	IV–III	14
22	500–1000	9	IV–IIb	14
23	500–1000	6	IV–III	12
24	500–1000	11	IV–IIb	11
25	500–1000	6	IV–IIa	10
26	250–500	10	IV–IIa	11
27	500–1000	7	IV–III	11
28	500–1000	11	IV–III	11
29	500–1000	6	IV–III	14
30	500–1000	10	IV–IIa	15

tone (RALES data were published recently). From October 1999 spironolactone was added to the treatment in both groups. All patients continued ACE-inhibitors as previously reported (captopril 75–150 mg/day).

4. 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 [19,25] and the rapid excretion of this volume by the action of ECF expansion itself and by the action of i.v. furosemide infusion. Furthermore, HSS by a demonstrated increase in renal blood flow [26] may facilitate the action of furosemide and help overcome an established furosemide resistance, frequently observed in these patients related to CHF itself [9–11] or to age-associated decrease in renal function [7,8]. Diuretics represent a cornerstone in the treatment of patients with symptoms of severe CHF and many reports have described their efficacy and limitations [1,4,6,11,27–30].

The overall response to loop diuretics depends on the time course and the amount of drug reaching urine, and the pharmacodynamic of response in the ascending limb of Henle's loop [8]. Renal blood flow in advanced CHF is often reduced and the response to diuretic is progressively attenuated. Intravenous administration is preferable in these patients to overcome the decreased absorption of the orally administered drug [1]. Furthermore, patients with CHF require higher concentrations of furosemide in the renal tubule to induce an adequate natriuretic response and a constant delivery rate of the drug provided by an intravenous infusion may optimized the diuretic treatment [12]. Interestingly, furosemide's action is achieved not only as a result of a potent diuretic activity but also because of a reduction in venous return that leads to a rapid relief of left ventricular heart failure symptoms [31]. In fact, a dose-dependent direct venodilator effect has been demonstrated in forearm blood flow studies, that appears to be mediated by local vascular prostaglandin synthesis [32].

Hemodynamic alterations operating during uncompensated heart failure comprising an expansion of venous circulating blood volume and a reduction of arterial circulating blood volume lead to the instauration of a 'low flow state' with substantial activation of the renin–angiotensin–aldosterone system (RAS) and consequent fluid and Na retention [15,16]. The reduced arterial blood flow may be worsened by the effect of endothelium edema, that further increases the hydraulic resistance [25].

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 [33]. Therefore, an increase in renal blood flow may be an important mechanism by which Na retention may be counteracted. Intravenous infusion of HSS determines a 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 [17,20]. Additionally, fluid shifted out of erythrocytes and endothelial cells to the extracellular space leads to a reduction in capillary hydraulic resistance [25]. The rapid expansion of ECF volume is responsible for the decreased plasma and peritubular oncotic pressure that along with and 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, since 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 furosemide with no need of higher doses (maximal dose, 2 g/day), and consequently limiting electrolyte disturbance, and other side effects (hypotension, tinnitus, etc).

The most important results of our study were the significant reduction of hospitalization time in patients receiving HHS vs. those without HHS, the maintenance of the achieved NYHA functional class at discharge, and a reduction of readmissions to hospital for CHF worsening. In addition we showed that mortality (cardiac causes) after 1 year of follow up was reduced in treated patients. This result must be interpreted with caution because of the small number of patients. Our data contrast with previously reported studies [35,36], in fact, no patients receiving HHS infusion were readmitted to the hospital during the follow-up period. 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. A further step is to study the changes in RAS, vasopresin, atrial natriuretic peptide, and cathecolamines in these subjects, considering that individual variable responses may con-

found the interpretation of circulating hormones measurements and that most of the subjects are already under ACE-inhibitors therapy, that actually counteracts negative hemodynamic effects induced by chronic therapy with diuretics on RAS [37].

It is noteworthy that the patients received at discharge a normosodic diet after achieving the goal in functional class, which in our opinion may have contributed to the maintenance of the clinical improvement by an additional counterbalance of RAS activation allowing adequate diuretic action. We are currently following the patients to evaluate the long-term effects of this therapy and including other patients to achieve a large sample of patients, to verify the effects on mortality (5 years). This is the first report of a new proposed therapeutical option for patients with refractory CHF.

We conclude that the combination of furosemide with HSS in an i.v. infusion is effective and well tolerated in patients with advanced and refractory CHF. The results were obtained in a short period of time and the clinical improvement was maintained over time. On the basis of our results, we infer that this treatment may consent to avoid or delay the utilization of non-pharmacology treatments such as ultrafiltration. In conclusion, the most striking results of the study were the safety and tolerability of the small-volume hypertonic saline solution and high-dosage furosemide. This pilot study demonstrates that treatment is effective in patients with advanced and refractory CHF. These are preliminary data which suggest further investigations are required.

4.1. Limits of the study

The major limitations of the study were the small number of patients and the single blind randomization. The reason for the single blind design of the present study is that for ethical reasons we needed to know the administered treatments because of the high-risk patients. However, the patients were strictly selected in order to test, for the first time, the effects of combination treatment with HSS plus high doses of furosemide, and for the same reason the patients were given single blind treatment.

References

[1] Cody RJ. Management of refractory congestive heart failure. Am J Cardiol 1992;69:141G–149G.
[2] Rodeheffer RJ, Redfield MM. Congestive heart failure: diagnosis, evaluation, and surgical therapy. In: Murphy JG, editor. Mayo clinic cardiology review, 2000:55–74.
[3] Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J 1994;72:S3–S9.
[4] Cowie NM, Mosterd A, Wood DA et al. The epidemiology of heart failure. Eur Heart J 1997;18:208–225.
[5] American Heart Association Task Force on Practice Guidelines. Guidelines for the evaluation and management of heart failure. Circulation 1995;92:2764–2784.
[6] Smith ThW, Kelly RA, Stevenson LW, Braunwald E. Management of heart failure. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. Philadelphia: WB Saunders Co, 1997:492–514.
[7] The Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. Eur Heart J 1997;18:736–753.
[8] Cody RJ, Ljungman S, Covit AB et al. Regulation of glomerular filtration rate in chronic congestive heart failure patients. Kidney Int 1988;34:361–367.
[9] Brater C. Resistance to loop diuretics. Why it happens and what to do about it. Drugs 1985;30:427–443.
[10] Vasko NM, Brown-Cartwright D, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med 1985;102:314, 318.
[11] Brater DC. Diuretic resistance: mechanisms and therapeutic strategies. Cardiology 1994;84:57–67.
[12] Cody RJ. Diuretics in the management of congestive heart failure. Cardiologia 1998;43:25–34.
[13] Dormans TPJ, Van Meyel JJM, Gerlag PGG, Tan Y, Russel FGM, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996;28:376–382.
[14] Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intem Med 1991; 114:886–894.
[15] Dormans TPJ, Gerlag PGG. Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure. Eur Heart J 1996;17: 1867–1874.
[16] Packer M. Neurohumoral interactions and adaptations in congestive heart failure. Circulation 1988;77:721–730.
[17] Riegger AJG. Neuroendocrine excitation in heart failure. Br Heart J 1994;72(Suppl 2):28–30.
[18] De Felippe J, Timoner J, Velasco IT, Lopes OU. Treatment of refractory hypovolaemic shock by 7.5% sodium chloride injections. Lancet 1980;ii:1002–1004.
[19] Maningas PA, Mattox KL, Pepe PE, Jones RL, Feliciano DV, Burch JM. Hypertonic saline–dextran solutions for the prehospital management of traumatic hyptension. Am J Surg 1989;157:528–534.
[20] Kreimeir U, Bruckner UB, Schmidt J, Messmer K. Instantaneous restoration of regional organ blood flow after severe hemorrhage: effect of small volume resuscitation with hypertonic–hyperoncotic solutions. J Surg Res 1990;49:493–503.
[21] Monteiro-Pacheco A, Martins Coimbra RS, Kreimer U, Frey L, Messmer K. Hypertonic volume therapy: feasibility in the prevention and treatment of multiple organ failure and sepsis. Rev Paul Med 1995;113:1053–1060.
[22] Weiss ML, Claassen DE, Hirai T, Kenney MJ. Nonuniform sympathetic nerve responses to intravenous hypertonic saline infusion. J Autonomic Nerv Syst 1995;57:109–115.
[23] Mullins RJ, Judgens RW. Hypertonic saline resuscitates dogs in endotoxin shock. J Surg Res 1987;43:37–44.
[24] Armistead CW, Vincent JL, Preiser JC, Debacker D, Minh TL. Hypertonic saline solution-herestarch for fluid resuscitation in experimental septic shock. Anesth Analg 1989; 69:714–720.
[25] Paterna S, Parrinello G, Amato P et al. Tolerability and efficacy of high dose furosemide and small-volume hypertonic saline solution in refractory congestive heart failure. Adv Ther 1999, in press.
[26] Mazzoni MC, Borgstroem P, Arfors KE, Intaglietta M. Dy-

namic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage. Am J Physiol 1988;255:H629–H637.
[27] Kreimeier U, Brtickner UB, Niemczyk S. Hyperosmotic saline dextran for resuscitation from traumatic–hemorrhagic hypotension: effect on regional blood flow. Circ Shock 1990; 32:83–99.
[28] Taylor SH. Congestive heart failure. Towards a comprehensive treatment. Eur Heart J 1996;17(Suppl B):43–56.
[29] Taylor SH. Diuretics in heart failure: some known and unknowns. J Cardiovasc Pharmacol 1993;22(Suppl 3):S40–50.
[30] Taylor SH. Efficacy of diuretics in chronic heart failure. Prog Pharmacol Clin Pharmacol 1995;9:91–103.
[31] Taylor SH. Refocus on diuretics in the treatment of heart failure. Eur Heart J 1995;16(Suppl F):7–15.
[32] Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 1973;288:1087–1090.
[33] Pickkers P, Dormans TPJ, Russel FGM et al. Direct vascular effects of furosemide in humans. Circulation 1997;96: 1847–1852.
[34] Hollenberg NK, Schulman G. Renal perfusion and function in sodium retaining states. In: Seldin DW, Giebisch G, editors. The kidney: physiology and pathophysiology. New York: Raven Press, 1985:1119–1136.
[35] Reineck HJ, Stein JH, Seldin DW. Integrated responses of the kidney to alterations in extracellular fluid volume. In: Seldin DW, Giebisch G, editors. The kidney: physiology and pathophysiology. New York: Raven Press, 1985:1137–1161.
[36] Narang R, Cleland JGF, Erhardt L et al. Mode of death in chronic heart failure. A request and proposition for more accurate classification. Eur Heart J 1996;17:1390–1403.
[37] Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 1993;22(4 Suppl A):6A–13A.