

# World Journal of *Cardiology*

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*World Journal of Cardiology*  
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Fax: +1-925-2238243  
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## Case Control Study

**Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure**

Gabrielle Lafrenière, Patrick Béliveau, Jean-Yves Bégin, David Simonyan, Sylvain Côté, Valérie Gaudreault, Zeev Israeli, Shahar Lavi, Rodrigo Bagur

Gabrielle Lafrenière, Patrick Béliveau, Valérie Gaudreault, Division of Cardiology, Department of Medicine, Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, QC G1R 2J6, Canada

Jean-Yves Bégin, Department of Psychoeducation, Université du Québec à Trois-Rivières, Trois-Rivières, QC G9A 5H7, Canada

David Simonyan, Clinical Research Platform, Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, QC G1R 2J6, Canada

Sylvain Côté, Department of Pharmacy, Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, QC G1R 2J6, Canada

Zeev Israeli, Shahar Lavi, Rodrigo Bagur, Division of Cardiology, Department of Medicine, London Health Sciences Centre, Western University, London, ON N6A5A5, Canada

**Author contributions:** Lafrenière G and Béliveau P contributed equally to this work; they participated with the conception and design, acquisition, analysis and interpretation of data and drafting of the manuscript; Bégin JY and Simonyan D created the database and performed analysis and interpretation of data and reviewed critically the manuscript for important intellectual content; Côté S participated with the elaboration of the drug therapy protocol, and reviewed critically the manuscript for important intellectual content; Israeli Z and Lavi S participated in the analysis and interpretation of data, and revising critically the manuscript for important intellectual content; Gaudreault V participated in patient recruitment of patients and revising critically the manuscript for important intellectual content; Bagur R participated in the acquisition, analysis and interpretation of data, and drafting of the manuscript; all authors have read and approved the final version of the manuscript.

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**Correspondence to:** Rodrigo Bagur, MD, PhD, FAHA, Assistant Clinical Academic Professor, Division of Cardiology, London Health Sciences Centre, Department of Medicine, Western University, 339 Windermere Rd, University Hospital, London, ON N6A5A5, Canada. [rodrigobagur@yahoo.com](mailto:rodrigobagur@yahoo.com)  
**Telephone:** +1-519-6633997  
**Fax:** +1-519-4343278

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**Abstract****AIM**

To test the safety and effectiveness of hypertonic saline solution (HSS + F) as a strategy for weight loss and

prevention of further deterioration of renal function.

## METHODS

Patients admitted with acute decompensated heart failure (ADHF) who received HSS + F were included in the study. After a period of a standard ADHF treatment, our patients received an intravenous infusion of furosemide (250 mg) combined with HSS (150 mL of 3% NaCl) twice a day for a mean duration of 2.3 d. Our primary outcomes were weight loss and a change in serum creatinine per day of treatment. The parameters of the period prior to treatment with HSS + F were compared with those of the period with HSS + F.

## RESULTS

A total of 47 patients were included. The mean creatinine on admission was  $155 \mu\text{mol/L} \pm 65 \mu\text{mol/L}$ , the ejection fraction was  $40\% \pm 17\%$ . The experimental treatment (HSS + F) resulted in greater weight loss per day of treatment than the standard treatment ( $-1.4 \text{ kg/d} \pm 1.4 \text{ kg/d}$  vs  $-0.4 \text{ kg/d} \pm 1.0 \text{ kg/d}$ ,  $P = 0.0168$ ). Importantly, the change in creatinine was not significantly different.

## CONCLUSION

This study supports the effectiveness of HSS + F on weight loss in patients with ADHF. The safety profile, particularly with regard to renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

**Key words:** Heart failure; Decompensated; Hypertonic saline; Renal failure; Fluid overload

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**Core tip:** Hypertonic saline solution (HSS) has been proposed in recent years as a potential therapy to facilitate diuresis in patients with decompensated heart failure and to overcome diuretic resistance. This study supports the effectiveness of HSS + F on weight loss in patients with acute decompensated heart failure and a high burden of comorbidities, despite a proportion of patients having preserved ejection fraction, right heart failure and advanced renal failure. The administration of small intravenous boluses of HSS in conjunction with intravenous furosemide can be a feasible and inexpensive therapeutic option which can prevent the use of costlier and more invasive treatments such as ultrafiltration, hemodialysis and inotropic infusion.

Lafrenière G, Béliveau P, Bégin JY, Simonyan D, Côté S, Gaudreault V, Israeli Z, Lavi S, Bagur R. Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure. *World J Cardiol* 2017; 9(8): 685-692 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/685.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.685>

## INTRODUCTION

Heart failure (HF) is a well-recognized major public health problem affecting about 26 million people worldwide<sup>[1]</sup>. Its impact in terms of mortality, morbidity, quality of life and cost is considerable. Acute decompensated heart failure (ADHF) is a leading cause of hospitalization and a common issue in emergency departments. Loop diuretics have long been recognized as the key for the treatment of ADHF<sup>[2]</sup>, however, high doses can cause adverse effects, including electrolyte abnormalities and deterioration of renal function. In addition, patients can develop resistance to diuretics and congestive symptoms can persist despite treatment with high doses<sup>[3]</sup>. Currently available treatment options include higher doses or a continuous infusion of intravenous diuretics<sup>[4,5]</sup>, a combination of different classes of diuretics for their synergistic effects<sup>[6,7]</sup>, and in severe/advanced cases, parenteral inotropes<sup>[8-10]</sup> and ultrafiltration<sup>[11,12]</sup>. The last two options are not associated with a better prognosis, and in fact, can cause deleterious effects and their use is limited by the cost and availability<sup>[11-14]</sup>.

The hypertonic saline solution (HSS) has been proposed in recent years as an adjunctive therapy for intravenous loop diuretics to improve or restore their initial pharmacological efficacy<sup>[3]</sup>. Among the proposed mechanisms to explain the benefits of HSS, it has been reported that it would prevent intravascular depletion due to diuretics<sup>[15,16]</sup> and thus would maintain renal flow and the glomerular filtration rate (GFR) during intensive treatment of intravenous furosemide<sup>[17]</sup>.

Compared to the administration of high doses of intravenous furosemide alone, concomitant use of HSS (HSS + F) has shown, in patients with ADHF, a more rapid and complete resolution of the signs and symptoms of congestion by increasing urine volume and by potentiating weight loss<sup>[16,18,19]</sup>, the potential to protect against deterioration of renal function during intensive diuretic therapy<sup>[15,20]</sup>, an improvement of cardiac biomarkers and echocardiographic parameters<sup>[19,21,22]</sup>, a reduced length of hospital stay and frequency of re-hospitalizations<sup>[23]</sup> and a good safety profile<sup>[24]</sup>.

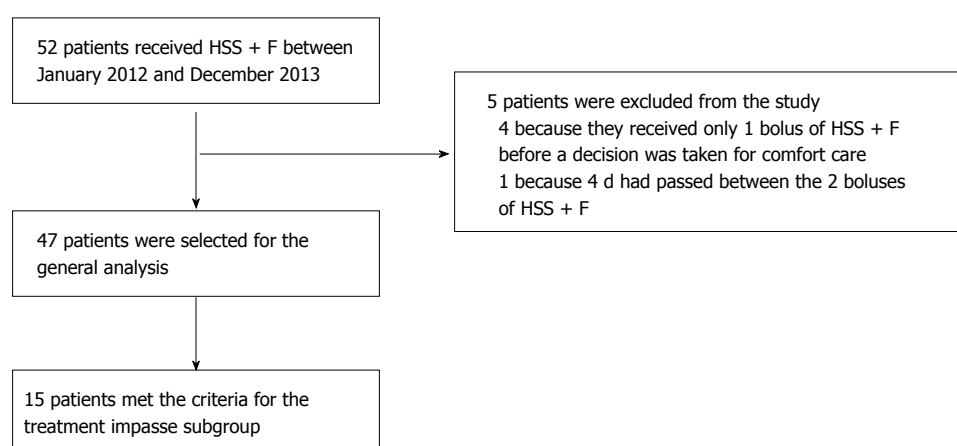
Therefore, the aim of the present report was to test the safety and effectiveness of HSS + F as a strategy for weight loss and prevention of further deterioration of renal function compared to the usual intensive treatment with intravenous furosemide alone.

## MATERIALS AND METHODS

Patients admitted with ADHF and who received HSS + F between January 2012 and December 2013 at the Quebec University Hospital Centre were included for the analysis. The decision to prescribe HSS + F following the standard treatment for a given patient was left to the discretion of the treating cardiologist,

Eligible patients
Men or women older than 18 years
ADHF with congestive symptoms and signs
Refractory to standard treatment of ADHF
Worsening renal function due to increased diuretics doses
Poor responsiveness to treatment with furosemide
Constant increase of body weight
Persistence of peripheral or pulmonary edema
Reduction of urine volume
Orthostatic hypotension with increased diuretic doses
Patients who should not receive protocol
Hypertensive crisis
Baseline hyponatremia
No congestive symptoms and signs
Prescription protocol
Infusion of HSS + F: 150 mL of 3% NaCl + 250 mg of furosemide
Administered over one hour
Twice a day for a suggested period of 48 h
Other prescriptions
Fluid restriction of 1.5 L/d
Vital signs and weight must be recorded daily
Serum Na, serum K and creatinine must be recorded daily

**Figure 1 Study protocol.** ADHF: Acute decompensated heart failure; HSS: Hypertonic saline solution.



**Figure 2 Data collection protocol and observation periods.**

who had received at the beginning of the study a list of the suggested inclusion and exclusion criteria (Figure 1). All clinical, echocardiographic and laboratory data were prospectively collected in a dedicated database. Institutional review board approval and patient consent were not required because of the nature of this study.

### Intervention

On admission for ADHF, most patients were on fluid restriction of 1.5 L/d, received an intravenous furosemide dose that was adjusted according to the clinical response and the conventional HF treatment that was considered appropriate by the treating physician based on current recommendations<sup>[25,26]</sup>. When patients were considered to be refractory to this treatment, based on a poor response to standard therapy (weight, creatinine, clinical judgment), intravenous furosemide was replaced by an intravenous infusion of HSS + F (150 mL of 3% NaCl + 250 mg of furosemide) administered

over one hour twice a day for a suggested period of 48 h that could be extended or shortened depending on the clinical response. Patients underwent the usual daily medical examination for the evaluation of the signs and symptoms of HF. Vital signs and weight were recorded daily; serum creatinine, sodium (Na) and potassium (K) levels were closely monitored during treatment. Moreover, the clinician's impression concerning the treatment effectiveness was recorded in the medical notes. Patients were all compared to themselves with a before and after study design. The effects of treatment with intravenous furosemide alone (standard treatment) were compared to the treatment with intravenous furosemide plus HSS (HSS + F) (experimental treatment) administered following the standard treatment. The results available from days one to four prior to the initiation of saline treatment were analyzed and compared to the experimental treatment d (Figure 2).

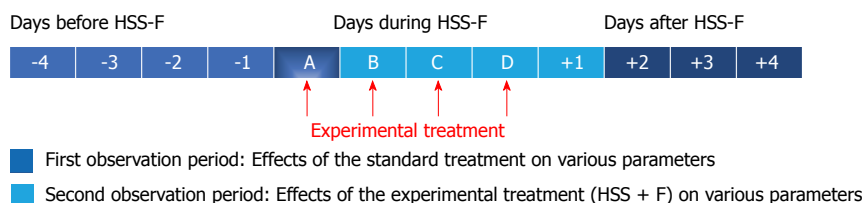


Figure 3 Flow diagram of participants in the study. HSS: Hypertonic saline solution.

## Outcomes

Our primary outcomes were the decrease in weight and the change of creatinine per day of treatment. Secondary outcomes were the effect of the experimental treatment on the serum Na and K levels and its safety profile regarding neurological events.

## Subgroup analysis

The effects of HSS + F on weight and creatinine were studied in the “treatment impasse” subgroup defined as all patients with increased weight and creatinine per day of treatment despite standard therapy.

## Statistical analysis

Continuous data are presented as mean  $\pm$  SD or median [interquartile range (IQR)] depending on variable distribution, and categorical data are presented as frequencies (percentage). Differences between the weight reduction in the experimental treatment and the standard treatment periods were assessed by Wilcoxon Signed Rank test for paired samples. The same approach was used for all other analyses as the change of creatinine per day of treatment between these two periods and analyses in the “treatment impasse” subgroup. The level of statistical significance was set as  $P < 0.05$ . Data were analyzed using the SAS statistical software, version 9.3.

## RESULTS

A total of 52 patients received HSS + F for ADHF. Five patients were excluded from the study; four because they received one bolus of HSS + F before the decision of giving end-of-life comfort care only, and one patient was not selected because four d had elapsed between the two boluses of HSS + F, making interpretation difficult.

Hence, a total of 47 patients (32 men, 68%), mean age of  $77.6 \pm 9.5$  years, were included in the study (Figure 3). Thirty-two (68%) patients had chronic kidney disease based on an estimated GFR (eGFR)  $\leq 60$  mL/min per  $1.73 \text{ m}^2$ . Moreover, the mean creatinine was  $155 \pm 65 \mu\text{mol/L}$ , leading to an eGFR of  $42 \pm 22$  mL/min per  $1.73 \text{ m}^2$  on admission. Of note, 12 (25.5%) presented with a serum Na  $< 135$  mmol/L. The left ventricle ejection fraction (LVEF) was  $40\% \pm 17\%$  and half of the patients had  $\leq 40\%$  (Table 1). In addition, 31 patients had pleural effusion, 11 had ascites, 11 presented with arterial hypotension and/or orthostatic

hypotension and 13 had acute kidney injury defined as a 1.5-fold increase in serum creatinine or absolute increase in serum creatinine of  $\geq 26.4 \mu\text{mol/L}$  from their baseline value<sup>[27,28]</sup>.

Before receiving HSS + F, six (12.8%) patients required non-invasive ventilation and three (6.4%) patients were intubated for respiratory failure, but no form of mechanical ventilation was initiated during treatment with HSS + F. In addition, eight (17%) patients had a thoracentesis during hospitalization (two during the HSS + F treatment period and six outside of the observation period) and four (8.5%) patients had a paracentesis (two during the standard treatment and none during the HSS + F treatment). Moreover, eight (17%) patients received an infusion of inotropes, but only three during the observation period (one during the experimental treatment, one throughout the two treatments studied and the remaining during the standard treatment only). Six (12.8%) patients underwent coronary angiography during hospitalization, but only two patients had it during the observation period (one during the standard treatment and the other had two coronary angiograms: One before and another during treatment with HSS + F).

## Intervention

Patients received a mean of  $5.1 \pm 2.0$  doses of HSS + F for a mean duration of  $2.3 \pm 1.0$  d. During the treatment period with HSS + F, patients lost  $3.9 \pm 3.8$  kg. Interestingly, the treating physician reported a significant improvement in signs and symptoms of congestion with this experimental treatment on 38 (81%) patients. In addition, weight loss per day of treatment was significantly greater with HSS + F treatment than with the standard treatment ( $-1.4 \pm 1.4$  kg/d vs  $-0.4 \pm 1.0$  kg/d, mean difference of  $0.8 \pm 1.8$  kg/d,  $P = 0.0168$ ) (Table 2). The change in creatinine per day of treatment was not statistically different between treatments (Table 2). The mean serum Na increased by 2.4 mmol/L (95%CI: 1.6-3.1,  $P < 0.0001$ ) and the mean serum K decreased by 0.2 mmol/L (95%CI: -0.4 to -0.1,  $P = 0.0001$ ) with the experimental treatment compared to the standard treatment. The mean daily dose of intravenous furosemide given during the standard treatment period was  $106 \pm 67$  mg. Four patients received an additional continuous infusion of furosemide for a mean duration of 2.3 d. Nine patients received mainly oral furosemide, with a correspondingly larger mean daily

**Table 1** Baseline characteristics of the study population *n* (%)

Variables	<i>n</i> = 47
Age (yr)	77.6 ± 9.5
Males	32 (68.1)
Body mass index (kg/m <sup>2</sup> )	28.2 ± 7.2
Hypertension	46 (97.9)
Diabetes	28 (59.6)
NYHA functional class (admission)	
III	16 (38.1)
IV	23 (54.8)
Coronary artery disease	33 (70.2)
Ischemic heart failure	29 (61.7)
Stroke or transient ischemic attack	11 (23.4)
Vascular disease	22 (46.8)
Atrial fibrillation	27 (57.4)
Oxygen-dependent COPD	4 (8.5)
Active cancer	11 (23.4)
Baseline creatinine (μmol/L) <sup>1</sup>	140.1 ± 65.5
Chronic kidney disease (eGFR ≤ 60 mL/min per 1.73 m <sup>2</sup> )	32 (68.1)
Admission creatinine (μmol/L)	154.8 ± 65.4
Admission eGFR using MDRD (mL/min per 1.73 m <sup>2</sup> )	42.2 ± 22.3
Admission serum Na concentration < 135 mmol/L	12 (25.5)
Echocardiographic data	
Left ventricle ejection fraction	39.9 ± 17.4
LVEF > 40%	23 (48.9)
LVEF ≤ 40%	24 (51.0)
Severe aortic stenosis	1 (2.2)
Moderate and/or severe mitral regurgitation	16 (34.8)
Severe tricuspid regurgitation	6 (13.0)
Pulmonary hypertension ≥ 50 mmHg	19 (41.3)
Severe diastolic dysfunction	11 (23.9)
Right ventricular dysfunction/dilatation	28 (60.9)
Medications	
ACEI/ARBs	28 (59.6)
Hydralazine	3 (6.4)
Beta-blocker	39 (83.0)
Diuretics	
Oral furosemide	39 (83.0)
Thiazide	9 (19.1)
Spironolactone	8 (17.0)
Zaroxolyn	1 (2.1)
Furosemide dose per day (mg)	128.2 ± 106.7

<sup>1</sup>Average of the five most recent creatinine values before hospitalization. Values are expressed as mean ± SD or *n* (%). NYHA: New York Heart Association; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease equation; LVEF: Left ventricle ejection fraction; ACEI: Angiotensin-converting-enzyme inhibitor; ARBs: Angiotensin II receptor blockers.

dose of 196 ± 165 mg. Seven doses of metolazone were given during the standard treatment and 7 doses during the experimental treatment.

The administration of HSS + F was well tolerated by all patients and no major adverse events were observed. It is noteworthy to be highlighted that there was no pulmonary congestion or neurological consequences due to HSS + F strategy. However, the HSS + F treatment was discontinued in 2 (4.3%) patients due to an excessive increase in serum Na (*i.e.*, from 120 mmol/L to 128 mmol/L) in 1 patient and a significant decrease in blood pressure for the other.

A total of 7 (15%) patients died during the hospital stay. The median time between death and the end

**Table 2** Weight loss and creatinine change per day of treatment (*n* = 47)

Variable	mean ± SD	95%CI	<i>P</i> value
Weight loss (kg/d)			
Standard treatment	-0.39 ± 1.02	(-0.77, -0.03)	
Experimental treatment	-1.43 ± 1.43	(-1.86, -1.02)	
Standard-experimental difference	0.80 ± 1.77	(0.15, 1.44)	0.0168
Change in creatinine (μmol/L per day)			
Standard treatment	3.48 ± 9.89	(0.51, 6.68)	
Experimental treatment	-0.69 ± 9.62	(-3.51, 2.00)	
Standard-experimental difference	4.20 ± 14.25	(-0.49, 8.88)	0.331

of treatment with HSS + F was 3 (IQR: 1-33) d. However, two of these deaths were attributed to a shift to end-of-life palliative care requested by the family (treatment with HSS + F originally scheduled for 48 h was discontinued). The average hospital stay was 20 ± 12 d with a median of 16 (IQR: 11-24) d.

Notably, in the impasse treatment subgroup (*n* = 15), consisting of patients selected because of their negative response to the standard treatment, in addition to a significant weight loss achieved with the experimental treatment (-1.2 kg/d ± 1.3 kg/d vs -0.3 kg/d ± 0.6 kg/d with the standard treatment, mean difference of 1.5 kg/d ± 1.7 kg/d, *P* = 0.0026), there was an increase in creatinine level with the standard therapy that was not seen with the experimental therapy; indeed, the mean creatinine difference was also statistically significant (11 ± 13 μmol/L per day, *P* = 0.008) (Table 3).

## DISCUSSION

In a population of patients admitted with ADHF, the administration of HSS + F led to a greater weight loss per day of treatment compared to the standard intravenous furosemide strategy; even if a considerable proportion of them presented HF with preserved LVEF and/or advanced renal failure.

The difference in weight loss achieved through treatment with HSS + F is comparable to that demonstrated in previous studies<sup>[16,18,19,21-23,29,30]</sup>. Among these studies, the difference between the average in weight loss in the group treated with HSS + F compared to the group treated with intravenous furosemide alone ranged from 0.3-5.6 kg<sup>[21,30]</sup>. Because patients generally had some weight loss with the treatment with intravenous furosemide alone before starting treatment with HSS + F, it is possible that we have underestimated the weight loss due to HSS + F that could have been achieved without the prior use of intravenous furosemide alone.

We were unable to demonstrate a statistically significant difference in terms of creatinine, although it tended to decrease with the experimental treatment while the trend was reversed with the standard treatment. It has been previously shown an increase in

**Table 3** Weight loss and creatinine change per day of treatment in the impasse subgroup (*n* = 15)

Variable	mean ± SD	95%CI	P value
Weight loss (kg/d)			
Standard treatment	0.25 ± 0.64	(-0.04, 0.58)	
Experimental treatment	-1.20 ± 1.30	(-1.89, -0.57)	
Standard-experimental difference	1.45 ± 1.65	(0.54, 2.36)	0.0026
Change in creatinine (μmol/L per day)			
Standard treatment	7.33 ± 8.65	(3.01, 11.70)	
Experimental treatment	-3.79 ± 11.34	(-10.41, 1.63)	
Standard-experimental difference	11.13 ± 13.29	(3.77, 18.49)	0.008

creatinine among those treated with intravenous furosemide alone, while there is either a decrease in creatinine in patients treated with HSS + F<sup>[16,18,22,23]</sup> or a mild increase that is less than furosemide alone<sup>[19,21,30]</sup>. It is noteworthy to be outlined that the lack of statistical significant in creatinine levels may be explained in part by the inclusion of patients with advanced renal failure. Indeed, Engelmeier *et al.*<sup>[29]</sup> recruited patients with advanced renal failure (eGFR < 40 mL/min) and did not demonstrate a significant advantage of using HSS for the prevention of worsening renal function. Moreover, another study showed that HSS affords a protective role in the deterioration of renal function induced by loop diuretics, but does not exert a substantial protective effect in patients with ADHF who have pre-existing advanced renal failure and exhibiting a mean creatinine  $\geq 194$  μmol/L<sup>[15]</sup>. However, in our study, the renal function of many patients worsened during treatment with intravenous furosemide alone, so the change in creatinine during treatment with HSS + F could be a reflection of the previous treatment.

Treatment with HSS + F was well tolerated and its safety profile was reassuring as demonstrated in previous studies<sup>[18,24]</sup>. Of note, although we did not adjust the Na concentration in the HSS depending on the patient's serum Na as done in most studies, there were no severe electrolyte disturbances, except in one patient who had an increase in serum Na of 8 mmol/L within 24 h, but without any neurological symptoms or further consequences. Our results indicate that serum Na levels should be monitored, but adjusting the tonicity of the HSS based on the serum Na level may not be necessary. This facilitates the administration of HSS and reduces the risk of errors.

The result for the impasse subgroup, with few available treatment options, is of particular interest. Those patients, who increased their weight and creatinine while treated with intravenous furosemide alone, had benefited from the therapy in terms of weight loss and renal function.

The use of parenteral inotropes in a number of patients hospitalized for HF is potentially deleterious and requires tighter monitoring<sup>[31]</sup>. Moreover, the treatment of advanced ADHF by ultrafiltration or intravenous inotropes is not associated with a better prognosis and is limited

by the cost and availability<sup>[11-14]</sup>. Therefore, according to some studies<sup>[19,30]</sup>, simultaneous administration of appropriate doses of HSS during treatment with intravenous diuretics reduce diuretic resistance, which in fact, is the phenomenon of a decrease in the natriuretic response and thus, requires the use of further increasing doses of diuretics that often results in the deterioration of renal function<sup>[3]</sup>. Hence, the administration of small intravenous boluses of HSS associated with intravenous furosemide is a valid and inexpensive therapeutic option.

### Limitations

The main limitation of this study lies with the fact of a small sample size and even prospective, the non-randomized nature of the study. Therefore, the fact that certain clinical variables that appeared to account more frequently in some group but finally did not reach statistical significance were related to the small sample size. Patients were compared to themselves under the standard and experimental treatments, and the latter being influenced by the previous one. In addition, since the standard treatment was at the discretion of the clinician, the doses of furosemide, the doses of other drugs and the use of thoracentesis or paracentesis were not the same for both treatments. Thus, confirming these results in a larger series of randomized patients might have a high impact on patient selection and clinical decision-making in this high-risk group of patients.

In conclusion, the results of this study support the effectiveness of HSS + F on weight loss. The safety profile, particularly with regard to renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

## COMMENTS

### Background

Compared to the administration of high doses of furosemide monotherapy, the concomitant use of hypertonic saline solution (HSS + F) has shown, in some single-centre studies, clinical benefits and a good safety profile in patients with acute decompensated heart failure (ADHF).

### Research frontiers

Patients can develop resistance to diuretics and congestive symptoms may persist despite treatment with high doses of furosemide.

### Innovations and breakthroughs

This study supports the effectiveness of HSS + F on weight loss in patients with ADHF.

### Applications

The safety profile, particularly regarding renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

### Terminology

This study aims to test the safety and effectiveness of HSS + F as a strategy for

weight loss and prevention of further deterioration of renal function.

## Peer-review

This is a well-written manuscript about the treatment of severe acute heart failure.

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