Intravenous High-Dose Furosemide and Hypertonic Saline Solutions for Refractory Heart Failure and Ascites

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Summary: Several studies have shown the efficacy of hypertonic saline solution infusion in conditions in which regional organ blood flow is impaired. Our group has shown that treatment of patients with diuretic-resistant heart failure with high-dose furosemide plus hypertonic saline is effective and well tolerated, improving symptoms of congestion, reducing plasma levels of markers of neurohormonal and inflammatory activation, decreasing hospital readmission rates, and reducing long-term mortality. The same regimen was shown to be better than repeated paracentesis in patients with cirrhosis and refractory ascites, yielding better control of ascites, pleural effusions, and/or leg edema without an increase of common adverse effects linked to high-dose furosemide such as hepatic encephalopathy.
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D espite near-universal use of diuretics in patients hospitalized with congestive heart failure and ascites, half of these patients are discharged at a weight that is greater than what it was on admission.[1] Failure to achieve negative fluid balance can be caused by inadequate diuretic dosing, excessive sodium intake, or diuretic resistance, often related to decreased renal function.

In cirrhosis and congestive heart failure, abnormalities of circulatory and volume homeostasis elicit neurohormonal responses influencing renal function and leading to retention of sodium and water.[2] In both disorders, an increase in efferent renal sympathetic nerve activity antagonizes the diuretic and natriuretic effects of atrial natriuretic peptides and contributes to renal sodium and water retention.

Diuretic therapy of heart failure and cirrhosis involves a delicate balance. The diuretic dose must be sufficient to effectively relieve fluid overload and its ensuing symptoms without stimulating adverse physiologic effects. Excessive diuresis produces hypovolemia and extracellular fluid contraction, leading to hypotension, reduced cardiac output, diminished glomerular filtration rate (GFR), and further impairment of renal function.[3,4] We have attempted to achieve an adequate duresis without compromising renal function using combined infusions of high-dose furosemide and hypertonic saline.

EFFECT OF HYPERTONIC SALINE SOLUTIONS ON THE HEART AND CIRCULATION

Several studies have shown the efficacy of hypertonic saline solution (HSS) infusion in conditions in which regional organ blood flow is impaired.[5-8] HSS was first applied in this way for the primary treatment of severe hemorrhagic and traumatic shock and this therapy promptly restored central hemodynamics and peripheral blood flow.[7] In experimental models of acute hemorrhage, within minutes after replacement of a small fraction of the blood volume lost with HSS, cardiac output reached or even exceeded prehemorrhage values and mean arterial pressure returned to near-baseline values. Intravenous infusion of hypertonic saline rapidly increases the plasma sodium concentration and plasma osmolality, which mobilizes fluid into the vascular compartment and increases renal blood flow.[5-7] As a result, renal blood flow was completely restored, whereas flow in myocardium, brain, skeletal muscle, adrenal glands, and small intestine and colon increased even above baseline values. The suggested mechanisms included a direct effect on myocardial performance and reduced sympathetic tone.[7,8]

Based on this experience, our group hypothesized that the combination of high-dose loop-active diuretic and small-volume HSS infusion could be effective in the treatment of patients with refractory CHF.

CARDIORENAL SYNDROME

A diseased heart has numerous negative effects on kidney function and, at the same time, renal insufficiency can significantly impair cardiac function.[9-15] Thus, direct and indirect effects of dysfunction of these two organs can initiate and perpetuate a combined disorder through a complex combination of neurohormonal feedback mechanisms that have been called the *cardiorenal syndrome*. Several subcategories of the syndrome have been de-

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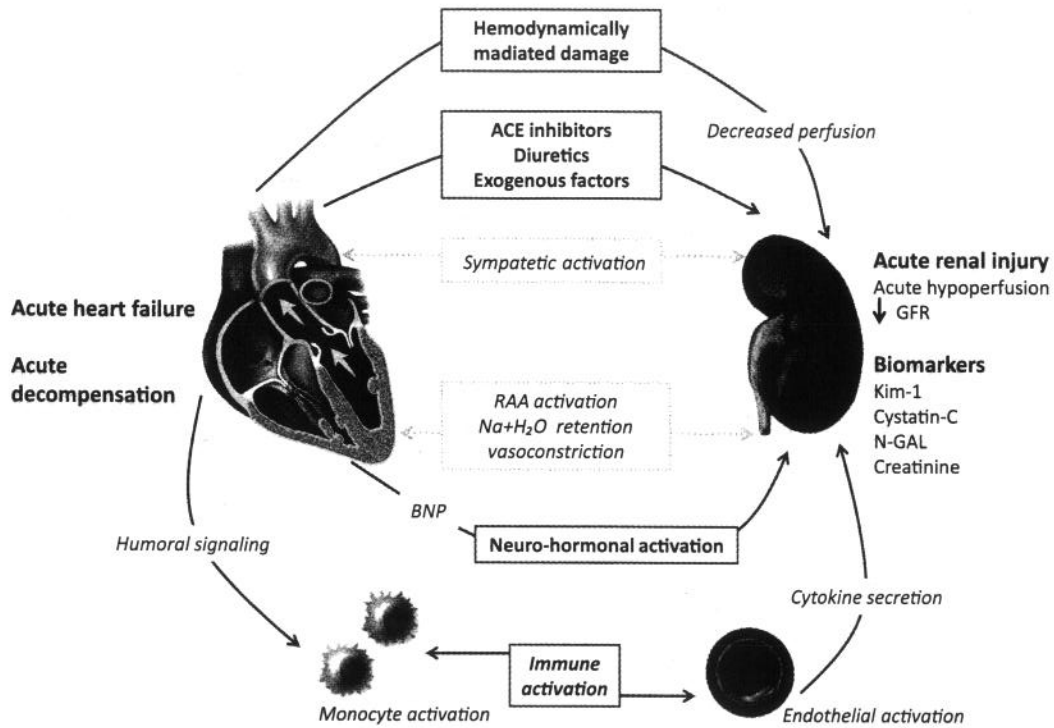
Figure 1. Acute cardiorenal syndrome (cardiorenal syndrome type 1).

fined,[12] as follows: (1) acute heart failure of various causes, most notably cardiogenic shock, leading to acute kidney injury[16] (Fig. 1); (2) chronic congestive heart failure associated with progressive chronic kidney disease[17] (Fig. 2); (3) acute kidney disease leading to acute cardiac dysfunction (eg, heart failure, arrhythmia, ischemia); (4) primary chronic kidney disease (eg, chronic glomerulonephritis) contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events;
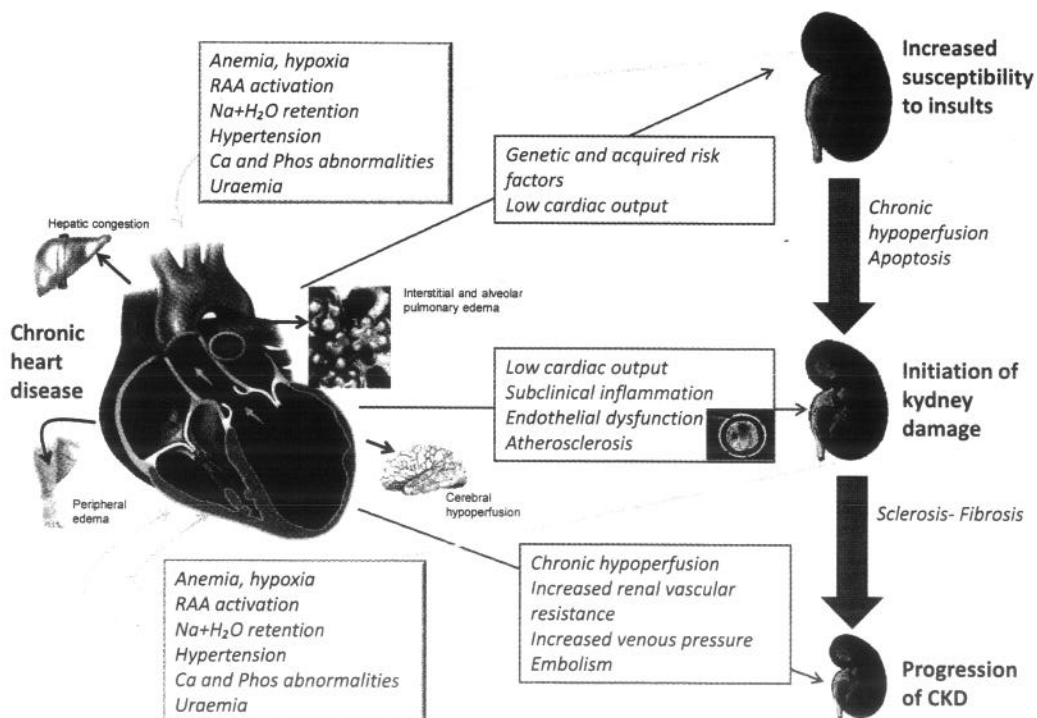

Figure 2. Chronic cardiorenal syndrome (cardiorenal syndrome type 2). CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system.

and (5) combined cardiac and renal dysfunction caused by acute or chronic systemic disorders (eg, sepsis, diabetes, amyloidosis, systemic lupus erythematosus, or sarcoidosis).

In patients with the cardiorenal syndrome, the overall goals of management should be to normalize volume status while avoiding overdiuresis and attendant renal dysfunction, and to implement evidence-based pharmacologic and device therapy to improve patient outcomes.

USE OF DIURETICS IN CONGESTIVE HEART FAILURE

Diuretics are used routinely as first-line agents to rapidly alleviate symptoms related to fluid overload in congestive heart failure. Loop diuretics improve clinical symptoms of dyspnea and signs of pulmonary edema by acutely decreasing left ventricular preload, reducing wedge pressure, and increasing venous capacitance. When used in combination with vasodilators, loop diuretics reduce ventricular cavity size and mitral regurgitation, resulting in increased forward cardiac output.[18]

Appropriate diuretic therapy induces adequate fluid control in most patients with mild to moderate disease, leading to the resolution of pulmonary and peripheral edema. The diuretic's efficacy may be enhanced by concurrent therapy with an angiotensin-converting enzyme (ACE) inhibitor. Loop diuretics are the foundation of current acute decompensated heart failure therapy. Accordingly, the most recent practice guidelines from the Heart Failure Society of America recommend loop diuretics at "doses needed to produce a rate of diuresis sufficient to achieve an optimal volume status."[19] Nevertheless, in some patients, fluid overload persists despite higher diuretic doses. Diuretic resistance has been associated with worsened outcomes in patients with heart failure.

Diuretics have an S-shaped dose-response curve[20,21] (see the article by Brater, in this issue, p. 483). Heart failure and renal impairment influence the curve: heart failure shifts the curve to the right, such that a higher dose is required to achieve a maximal natriuretic response; renal impairment shifts the curve downward, such that the maximal natriuretic response that can be achieved is diminished, no matter how high the diuretic dose. Therefore, the combined effects of heart failure and renal impairment create a state of relative diuretic resistance. The increasing dose requirement and diminished responsiveness to diuretics increases as heart failure progresses. In addition to these alterations of the dose-response curve, physiologic adaptations within the nephron contribute to diuretic resistance. Immediately after the first dose of a loop diuretic there is a diminished response to subsequent doses, known as the *braking phenomenon*. Loop diuretics directly stimulate renin secretion from the macula densa and diuretic-induced volume loss increases the filtration fraction and stimulates efferent sympathetic nerves, which leads to enhanced NaCl reabsorption through a variety of mechanisms.[22]

With long-term diuretic therapy, there is increased delivery of solute distal to the loop of Henle, resulting in hyperplasia and hypertrophy of the thiazide-sensitive cells in the distal convoluted tubule and subsequent increase in distal sodium reabsorption.[22]

The term *diuretic resistance* remains inadequately defined. In general, failure to decrease the extracellular fluid volume despite liberal use of diuretics often is termed *diuretic resistance*. In clinical settings, diuretic resistance in edematous patients has been defined as a clinical state in which sodium intake and excretion are equalized before adequate elimination of fluid occurs.[23] Epstein et al[24] defined diuretic resistance as a failure to excrete at least 90 mmol of sodium within 72 hours of a 160-mg oral furosemide dose given twice daily. This definition encompasses both refractory ascites and congestive heart failure. These are very different syndromes that have in common an increase in efferent renal sympathetic nerve activity that antagonizes the diuretic and natriuretic effects of atrial natriuretic peptides.

Fluid accumulation producing edematous states is a common problem encountered in patients with refractory ascites and congestive heart failure. Management of the edematous state associated with these clinical conditions usually includes diuresis in combination with fluid and sodium restriction. However, this standard approach often fails as the edematous state progresses and diuretic resistance occurs.

Diuretics are an integral part of heart failure therapy. However, their overaggressive use or their use in combination with other factors, such as an intercurrent illness, frequently leads to hypovolemia, reducing cardiac output and GFR.[16,25] If there is adequate time for vascular refilling, fluid removal can be achieved with diuretics without compromising renal perfusion. However, vascular refilling time and the hemodynamic response to fluid removal can vary from patient to patient. If overaggressive diuresis leads to a decline in renal function, it should be reversed with appropriate fluid management before further and possibly irreversible renal damage ensues.

HIGH-DOSE FUROSEMIDE PLUS HSS IN REFRACTORY CONGESTIVE HEART FAILURE: PERSONAL EXPERIENCES

Refractory congestive heart failure is defined[26] as uncompensated heart failure (dyspnea, weakness, lower-limb edema, or anasarca) of New York Heart Association (NYHA) functional class IV that is unresponsive to treatment with high oral doses of furosemide (as much as 250-500 mg/d) and/or combinations of diuretics (thiazide, loop diuretic, and spironolactone), ACE inhibitors (equivalent to 75-150 mg/d of captopril), digitalis, and nitrates for at least 2 weeks before hospitalization. When diuretic resistance occurs, proposed therapeutic options include higher doses or constant furosemide infusion[27]; concomitant dopamine infusion to increase renal blood flow, potentiating diuretic activity[28]; and combinations of different classes of diuretics providing synergistic effects.[29]

We hypothesized that the maintenance of adequate vascular refilling and renal perfusion during treatment with high doses of furosemide may be useful in reducing the frequency of side effects associated with high-dose diuretics while enhancing their effectiveness; both of these goals can be achieved by combining high-dose furosemide with the administration of hypertonic saline.

Preliminary studies to test the safety and tolerability of the combination of HSS and furosemide were undertaken in 1999.[30] Thirty patients aged 65 to 85 years, with refractory NYHA class IV congestive heart failure (CHF), were treated with an intravenous infusion of furosemide (250-2,000 mg/d) and small-volume hypertonic saline solution (150 mL of 1.4%-4.6% NaCl) twice a day for 6 to 12 days. A daily fluid oral intake of 1,000 mL and previous cardiac therapy were maintained. Clinical signs and symptoms of CHF, such as dyspnea, edema and weakness, improved, as did severity of illness as defined by NYHA class. After a 12-month follow-up period, 24 patients (80%) were alive and still in the NYHA class assigned to them on discharge from the hospital. In this study we showed that this therapeutic combination is effective and well tolerated and that it could represent an innovative approach to the management of refractory CHF.

To confirm these findings we subsequently performed a randomized single-blind study[31] comparing combined therapy with HSS and high-dose intravenous furosemide with furosemide alone in 60 hospitalized patients with NYHA class IV refractory heart failure. All patients met the Framingham criteria for refractory heart failure, showing unresolved dyspnea, weakness, and edema despite treatment with high oral doses of furosemide up to 250 to 500 mg/d and/or combinations of diuretics (thiazide, loop diuretic, spironolactone, ACE inhibitors in doses equivalent to captopril 75-150 mg/d, digitalis, and nitrates) for at least 2 weeks before the study and before hospitalization.

The experimental group received a 30-minute intravenous infusion of furosemide (500-1,000 mg) plus HSS (150 mL of 1.4%-4.6% NaCl) twice daily, and controls received an intravenous bolus infusion of furosemide (500-1,000 mg) without HSS twice daily, for a period of 6 to 12 days. In both groups, the daily dose of furosemide was determined for each patient, based on urine volume, blood pressure values, and severity of signs and symptoms of congestion. In the experimental group, the dose of HSS was determined in each patient by modifying the concentration of the HSS infusion according to the serum sodium (sNa) values: 4.6% NaCl for sNa of 125 mEq/L or less, 3.5% NaCl for sNa of 126 to 135 mEq/L; 1.4% to 2.1% NaCl for sNa of 135 mEq/L or greater. To prevent hypokalemia, 20 to 40 mEq of KCl was administered daily.

An improvement in clinical parameters such as dyspnea, lower-limb edema, anasarca, and weakness was obtained in all 60 enrolled patients. Urine output and sodium excretion increased in both groups, but to a significantly greater degree in the experimental group treated with HSS and furosemide than in controls receiving furosemide alone ($P < .05$). Urine output increased from 390 ± 55 mL/24 hours to $2,100 \pm 626$ mL/24 hours in the experimental group, and from 433 ± 141 to $1,650 \pm 537$ mL/24 hours in controls, whereas sodium excretion increased from 49 ± 15 to 198 ± 28 mEq/24 hours in the experimental group and from 53.83 ± 12 to 129 ± 39 mEq/24 hours in controls. The serum sodium concentration increased in the experimental group (from 135.9 ± 6.8 to 142.2 ± 3.8 mEq/L, $P < .05$) and decreased in controls (from 134.7 ± 7.9 to 130.1 ± 4.3 mEq/L). Body weight decreased by 5 to 20 kg in both groups (from 73.8 ± 9.1 to 63.8 ± 8.8 kg in the experimental group, and from 72.9 ± 10.2 to 64.5 ± 7.5 kg in the control group), and weight loss was proportional to increased urinary volume. We found greater improvement in NYHA class in patients receiving HSS. Serum creatinine level decreased in patients receiving HSS, possibly induced by the expansion of the extracellular fluid volume, whereas serum creatinine level increased in controls.

More recently, our group conducted another single-blind randomized study[32] to determine the long-term effects of our HSS plus high-dose furosemde regimen on morbidity and mortality. The experimental group received the previously described intravenous HSS/furosemide regimen given with a normal sodium (120 mmol/d) diet for 6 to 12 days in the hospital followed by high doses of oral furosemide and a normal sodium diet after discharge; controls received high doses of furosemide without HSS plus a low-sodium diet (80 mmol/d) for 6 to 12 days in the hospital and high doses of oral furosemide plus a low-sodium diet after discharge. We recruited 107 patients (39 women and 68 men; age range, 65-90 y) with refractory CHF of different etiologies. A prominent improvement in clinical parameters, such as dyspnea, lower-limb edema, anasarca, or weakness, was obtained in all patients studied and those with ascites and pleural and/or pericardial effusion experienced complete resolution of these findings (evaluated clinically and by radiography and echocardiography).

Similar to the previous study, urine output, urinary sodium losses, and weight loss in the hospital were greater in the experimental group than in controls. After discharge, during the follow-up period, patients who had been treated with intravenous HSS as inpatients and a higher dietary salt intake as outpatients had a lower rehospitalization rate than controls; if they did require re-admission to the hospital, they had a higher functional class at re-entry than they had at the time of the first hospital discharge (NYHA class III). The patients who did not require re-admission to the hospital maintained the same NYHA functional class achieved at the time of hospital discharge. The mortality rate was 45.3% in the HSS group versus 87% in the conventional treatment group.

Useful in epidemiologic studies and clinical trials in advanced heart disease,[33,34] natriuretic peptides also have been shown to be very powerful prognostic markers. Therefore, we next performed[35] a randomized double-blind study to determine the effect of the furosemide/HSS regimen on brain natriuretic peptide (BNP) plasma levels in patients with advanced CHF (NYHA functional class IV). As in the previous study, the HSS group was maintained on a 120-mEq NaCl diet whereas controls were fed an 80-mEq NaCl diet. Most study patients in both groups experienced functional improvement. In addition, we observed that plasma levels of BNP were significantly lower in the HSS group in comparison with the non-HSS group at 6 days and at 30 days after treatment.

Reduced BNP in patients treated with HSS is probably owing to a rapid and clinically important reduction in plasma volume and a subsequent decrease in cardiac wall stress. It is possible that, in addition to the direct effects on renal hemodynamics, the therapeutic effects of this treatment also are mediated by modulation of neurohormones.

Heart failure is characterized by neurohormonal activation and inflammation. These responses relate to outcome, and they are a therapeutic target. To evaluate the effects of our furosemide/HSS regimen on natriuretic peptides and immunoinflammatory marker levels, 120 patients with heart failure treated with our regimen were matched with 30 subjects with heart failure treated with high-dose furosemide wihthout HSS, 30 controls with asymptomatic left-ventricular dysfunction, and 30 controls without heart failure or left-ventricular dysfunction.[36] We evaluated plasma levels of natriuretic peptides and cytokine levels at baseline, after treatment, and after an acute saline load. Compared with treatment with furosemide alone, treatment with furosemide/HSS resulted in a significant lowering of plasma levels of atrial natriuretic peptide (ANP), BNP, tumor necrosis factor-α, interleukin (IL)-1β, and IL-6. An acute saline load (15 mL/kg of 0.9% NaCl) administered after an 8-day course of the furosemide/HSS regimen resulted in a lower percentage change of ANP, BNP, tumor necrosis factor-α, and IL-1β compared with control groups. The reasons for the response to saline are somewhat difficult to explain, but it could be that the combined effects of reduced extracellular volume owing to furosemide and the rapid increase in serum sodium concentration owing to HSS led to a stretching relief that could influence natriuretic and immunoinflammatory markers. However, these proposed mechanisms are only hypothetical.

USE OF DIURETICS IN ASCITES

Ascites, the most common complication of advanced liver disease, result from hemodynamic changes in the splanchnic vasculature and neurohumoral changes that result in systemic vasodilatation. These changes cause avid sodium retention related to decreased glomerular sodium filtration and increased tubular sodium reabsorption. According to a recent hypothesis, the initiating factor would be vasodilatation of the splanchnic bed, which leads to a decrease in the effective blood volume. This results in activation of vasoconstrictor systems (catecholamine, renin-angiotensin, arginine-vasopressin), which produces renal vasoconstriction, particularly in the cortex, with subsequent decrease in the glomerular sodium filtration rate; a concomitant increase in aldosterone secretion results in enhanced sodium reabsorption by the renal tubule (a discussion of the pathogenesis of sodium retention in liver disease can be found in the article by Dr. Schrier, p. 503).

Therapeutic algorithms for ascites include a low-sodium diet, diuretics, paracentesis, transjugular intrahepatic portasystemic shunt, surgery, and extracorporal elimination.[37] Some randomized controlled studies[38,39] of paracentesis showed an increase in effective arterial blood volume, cardiac output, and concentration of the plasma ANP, and a decrease in plasma renin activity, plasma aldosterone concentration, and plasma norepinephrine. However, this early phase was rapidly followed by a post-paracentesis circulatory dysfunction syndrome, characterized by an irreversible reduction in effective arterial blood volume, with a negative impact on the evolution of the disease.

Although paracentesis is the first-choice treatment of massive ascites, moderate ascites should be treated with salt restriction and diuretics to create a negative sodium balance.[40,41] Diuretics also are required to prevent or delay further paracentesis in patients with massive ascites.[42]

Because renal perfusion and GFR are preserved in the early stages of ascitic decompensation, secondary hyperaldosteronism is the principal pathogenetic factor, and sodium retention mainly occurs at the distal nephron.[43] In more advanced stages, once GFR has declined, proximal sodium reabsorption progressively increases and may become prevalent. A rational choice[44] of diuretics should rely on this pathogenetic background: antimineralocorticoids, whose efficacy has long been shown by clinical trials,[45] should always be used, and loop diuretics become necessary when proximal sodium reabsorption is prominent because the ideal drug acting at the proximal renal tubule is not available.

Having found that aldosterone antagonists represent the first-line diuretics in the treatment of ascites in cirrhosis,[46] two different schedules are being used in clinical practice. The first consists of the administration of increasing doses of spironolactone, adding furosemide only to those patients who did not respond to the high recommended doses of aldosterone antagonist (sequential diuretic treatment). The second schedule provides the simultaneous administration of an aldosterone antagonist and loop diuretic from the beginning of the treatment, increasing the dose of both diuretics if no response is achieved (combined diuretic treatment).[47]

One study,[47] performed on a relatively small number of nonazotaemic patients, has been published. Patients were randomized to be treated with either furosemide or spironolactone, followed by furosemide if necessary, or a combination of furosemide and spironolactone. All regimens achieved comparable success rates, but furosemide monotherapy required repeated upward dose adjustments and massive KCl supplementation. The cumulative incidence of diuretic-induced complications also was similar, even though severe hyperkalaemia was more frequent on combination therapy. The investigators concluded that treatment with furosemide alone should be avoided, and they advised either sequential or combination therapy.

More recently, two prospective randomized clinical trials compared the efficacy and safety of the stepwise sequential and combination treatments.[47,48] Santos et al[47] evaluated 100 nonazotemic cirrhotic patients with moderate ascites randomly assigned to be treated with spironolactone and furosemide or with spironolactone alone and they reported that the response rate, the rapidity of ascites mobilization, and the incidence of complications induced by diuretic therapy was similar in both groups. Angeli et al[48] compared sequential versus combined diuretic therapy in patients with cirrhosis, moderate ascites, and without renal failure. The investigators evaluated 100 patients randomly assigned to sequential treatment with potassium canrenoate (an aldosterone antagonist) at the initial dose of 200 mg/d, then increased to 400 mg/d or to combined treatment with potassium canrenoate in an initial dose of 200 mg/d, then increased to 400 mg/d and 50 mg/d of furosemide, and then increased to 150 mg/d. They showed that adverse effects, particularly hyperkalaemia, were more frequent in patients who received sequential therapy and that the number of patients who resolved ascites without changing the effective diuretic step was higher in those who received the combined treatment.

Patients with ascites can be divided into categories based on their response to treatment.[49] Less than 10% have natural sodium excretion (ie, without diuretics) more than 78 mEq/d. These patients have relatively preserved liver functions and will respond to dietary salt restriction (88 mEq or 2,000 mg/d) alone. As liver function deteriorates, patients excrete less sodium in the urine and sodium restriction alone is no longer enough to create a negative sodium balance and control ascites. Most patients will need diuretics combined with a sodium-restricted diet. This regimen is effective in about 90% of patients. Over time, up to 20% of patients who initially were diuretic-responsive will become diuretic-resistant,[50] and 5% to 10% of patients never respond to this regimen and have refractory ascites.

Ascites may be refractory to diuretics because these drugs induce complications (ie, hyponatremia or renal failure) or cannot mobilize ascites (or prevent its reaccumulation after paracentesis). Refractory ascites was defined according to the International Ascites Club criteria[43] as either: (1) diuretic-resistant refractory ascites: less than 1.5 kg/wk weight loss while being treated with furosemide (160 mg/d) and spironolactone (400 mg/d) or an equivalent dose of a loop-acting and distal-acting diuretic; or (2) diuretic-intractable refractory ascites: less than 1.5 kg/wk weight loss as a result of the inability to use an effective dose of diuretic because of the development of diuretic-induced hyponatremia (sodium level, <125 mEq/L), hyperkalemia (potassium level, >5.5 mEq/L), renal failure (doubling of serum creatinine level or serum creatinine values >2.5 g/dL) or encephalopathy; or (3) previous dietary restriction of sodium between 50 and 66 mEq/d.

Thus, there are two types of refractory ascites: diuretic-intractable ascites and diuretic-resistant ascites. Different treatments have been proposed in patients with refractory ascites: paracentesis and plasma volume expansion, peritoneovenous shunt, or transjugular intrahepatic portosystemic shunt. Unfortunately, these procedures have not been shown to improve survival.

An assessment of the response to a diuretic in subjects with cirrhosis and ascites also may be used for the diagnosis of refractory ascites. Spahr et al[51] studied the usefulness of an 8-hour, furosemide-induced natriuresis test to identify reliably such patients. On this basis an inadequate natriuretic response to diuretic at adequate doses can be used to define refractory ascites.

The mechanisms of diuretic resistance to furosemide in cirrhotic patients with ascites have been described in several stuides.[52,53] It is now well recognized that furosemide pharmacokinetics are not altered by cirrhosis.[54] The diminished response can be explained by several factors: (1) there is reduced delivery of furosemide to the renal tubule, which is proportional to the reduction in GFR; (2) vasoconstriction of the renal cortex observed in patients with resistant ascites leads to a decrease in the number of nephrons with the most important natriuretic potential; and (3) increased proximal reabsorption of sodium decreases the amount of sodium and water reaching the ascending limb of Henle's loop, the site of action of furosemide.

Few studies have compared paracentesis with diuretics in the treatment of tense or refractory ascites. Quintero et al[52] randomly assigned patients with tense ascites to treatment with either paracentesis plus intravenous albumin infusion or diuretics, and found similar outcomes. Paracentesis, however, poses a number of issues in patient management and alternative treatments to overcome the limitations of diuretic therapy and repeated paracenteses certainly are needed.

HIGH-DOSE FUROSEMIDE PLUS HSS IN REFRACTORY ASCITES: PERSONAL EXPERIENCES

By using our experience with the treatment of refractory heart failure[30-32] we evaluated the safety and efficacy of intravenous high-dose furosemide plus HSS compared

Table 1. Clinical and Laboratory Variables Before (at Admission) and After Treatment With High-Dose Furosemide + HSS or After Serial Paracentesis

	Furosemide Plus HSS (n = 60)			Serial Paracentesis (n = 24)		
	Before	After	P	Before	After	P
Number of subjects	60	60		24	24	
Weight, kg	78 ± 5.6	70 ± 7.4	<.001	77 ± 3.8	73.8 ± 3.8	<.001
Urine output, mL/24 h	550 ± 147	1,805 ± 131	<.05	580 ± 112	750 ± 124	.07
Serum creatinine level, mg/dL	1.7 ± 0.5	1.45 ± 0.3	.06	1.56 ± 0.6	1.76 ± 0.6	.08
Serum uric acid level, mg/dL	4.4 ± 0.7	5.7 ± 0.4	.05	4.2 ± 0.6	4.3 ± 02	.79
Serum sodium level, mEq/L	133 ± 1.4	137 ± 3.8	.88	134 ± 1.7	133 ± 4.6	.73
Serum potassium level, mEq/L	4.2 ± 0.8	4.4 ± 0.6	<.001	4.3 ± 0.3	4.2 ± 0.5	.04
Urine sodium level, mEq/24 h	49.5 ± 9.4	158 ± 25	<.05	47.8 ± 18	54.5 ± 12.4	.70
Urine potassium level, mEq/24 h	56.3 ± 7.6	83 ± 21	<.05	54.3 ± 11.1	59 ± 29	.63
Ascites, n (%)	60 (100)	14 (23.3)	<.001	24 (100)	11 (45.8)	<.001
Grade I	—	8 (13.3)	<.001	—	—	
Grade II	14 (23.3)	3 (5)	<.001	5 (20.8)	9 (37.5)	.032
Grade III	46 (76.6)	3 (5)	<.001	19 (79.1)	2 (8,3)	<.001
Ammonium level, μg/dL	37 ± 7	38 ± 9	.58	34 ± 7	34 ± 2	.28
Leg edema, n (%)	49 (81.6)	4 (6.6)	<.001	18 (75)	16 (66.6)	.04
Pleural effusion, n (%)	11 (18.3)	2 (3.3)	<.001	5 (20.8)	4 (16.6)	.07
Child–Pugh score, median	9.2	7.6	.037	9.8	8.9	.045
Hepatic encephalopathy, n (%)	9 (15)	8 (13.3%)	.82	4 (16.6)	3 (12.5)	.78
Bacterial peritonitis, n (%)	—	—	—	—	2 (8.3)	.05

NOTE. Laboratory variables are expressed as mean ± standard deviation. Ascites grade was evaluated by Ascites International Club criteria.

with repeated paracentesis and a standard oral diuretic schedule in patients with cirrhosis and refractory ascites.

In our study[55] 84 patients (59 men and 25 women), including 58 patients with diuretic-resistant refractory ascites and 26 patients with diuretic-intractable refractory ascites, were assigned randomly to treatment with intravenous furosemide plus HSS or to repeated paracentesis. The fursomeide/HSS group (n = 60; age 64 ± 13.6 y) received intravenous infusions of furosemide (doses, 250-1,000 mg twice a day) plus small volumes of HSS (150 mL 1.4%-4.6% NaCl), from the first day after admission until 3 days before discharge, along with water restriction and a normal sodium diet. The paracentesis group (n = 24; age 64.8 ± 8.1 y) received repeated paracentesis (4-6 L/d) from the first day after admission until 3 days before discharge with albumin re-infusion at a rate of 5 to 8 g/L of removed ascites. For the last paracentesis (at 3 days from admission) 8.7 ± 2.5 L of ascitic fluid was removed and 8 g of albumin was given intravenously per liter of ascitic fluid removed following a method previously described.[41] After the last mobilization of ascites, patients were assigned to receive diuretic therapy with oral furosemide (increasing doses up to a maximum of 160 mg/d) and oral spironolactone (400 mg/d). Throughout their hospital stay, patients were maintained on a normal sodium diet with fluid restriction.

At discharge (Table 1), patients treated with furosmide/HSS showed significantly higher diuresis and plasma sodium concentrations, significantly lower body weight, and leg edema and pleural effusion prevalence.

Fourteen subjects (23.3%) in the furosmide/HSS group had ascites (detected clinically or by ultrasound) at discharge versus 11 subjects (45.8%) in the paracentesis group. The median change in Child-Pugh score at discharge was significantly higher in the furosemide/HSS group compared with patients treated with paracentesis. Serum creatinine levels in patients were slightly lower in patients treated with furosemide/HSS (1.45 ± 0.3 mg/dL versus 1.7 ± 0.5 mg/dL), but this difference did not reach statistical significance. No other significant difference was observed in terms of other laboratory and clinical variables between the two groups (ammonium, potassium plasma levels, new-onset episodes of hepatic encephalopathy, gastrointestinal bleeding, acute renal failure or pre-existing renal failure progression, hepatorenal syndrome, or mortality).

We concluded that treatment with high-dose furosemide plus a small volume of HSS is safe and more effective than repeated paracentesis plus diuretic treatment in subjects with refractory ascites. A potentially important finding of our study was that high-dose furosemide diuresis may not be as injurious to the kidney as high-volume paracentesis, a finding that contrasts with what has been a long-standing belief; serum creatinine levels after furosemide/HSS were lower than after paracentesis (albeit not statistically significantly lower). Furthermore, in contrast to previous studies[56-59] we did not observe a higher rate of hepatic encephalopathy in the group treated with high-dose furosemide. A combined derangement of cellular osmolarity coupled with cerebral

hyperemia can explain the development of brain edema in encephalopathy.[23] It is possible that HSS infusion may have avoided hepatic encephalopathy by osmotically reducing the severity of brain edema, but future studies should evaluate this issue.

WHY IS COMBINED THERAPY WITH HYPERTONIC SALINE AND FUROSEMIDE EFFECTIVE?

The mechanism 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[60] and the rapid excretion of this volume by the action of ECF expansion itself and by the action of intravenous furosemide infusion. Furthermore, HSS, by a demonstrated increase in renal blood flow,[61] may facilitate the action of furosemide and help overcome an established furosemide resistance frequently observed in these patients related to CHF itself[19,20,62] or to an age-associated decrease in renal function.[17,49]

The pathophysiology of heart failure has several similarities to the response to hemorrhage. Thus, given the well-documented influence of the renal blood supply on sodium 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 sodium retention in patients with advanced disease.[63] Therefore, an increase in renal blood flow may be an important mechanism by which sodium retention may be counteracted. Intravenous infusion of hypertonic saline rapidly increases the plasma sodium concentration and plasma osmolality, instantaneously mobilizing fluid mobilization into the vascular compartment, increasing plasma volume and renal blood flow.[6,7] In addition, fluid shifted out of erythrocytes and endothelial cells to the extracellular space leads to a reduction in capillary hydraulic resistance.[7] The rapid expansion of extraceulllular 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.[64]

The simultaneous administration of furosemide at high doses enhances renal sodium excretion because the increment in renal blood flow allows furosemide's concentration in the loop of Henle to be optimal.

Treatment with furosemide/HSS could be beneficial in patients with ascites because of both volume expansion and reduced sinusoidal portal pressure, resulting in a decrease in plasma renin activity and serum aldosterone levels, an increase in renal blood flow and GFR, and, therefore, improved natriuresis. This effect occurs despite a possible exacerbation of the hyperdynamic circulation, with a further decrease in systemic vascular resistance and a further increase in cardiac output. Nevertheless, it is possible that in our patients treated with furosemide/HSS, the HSS-related volume expansion served to compensate the underfilling mechanisms that characterize ascitic cirrhosis. Small-volume HSS clearly increases plasma sodium concentration and plasma osmolality, driving a rapid redistribution of fluid into the vascular compartment and, consequently, an increase in renal plasma flow.[7,65-67] The rapid expansion of the extracellular fluid volume also reduces peritubular oncotic pressure that, in combination with increased hydrostatic pressure, reduces reabsorption of sodium in the proximal tubule.[8,61] HSS thus can improve diuretic efficiency because HSS expands the arterial circulating volume and increases delivery of sodium to the ascending limb of the loop of Henle.

CONCLUSIONS

Diuretic drugs usually are effective treatment for edema when used judiciously. However, many patients become resistant to their effects. Adaptation to diuretic drugs and diuretic resistance may be caused by similar mechanisms, and heart failure and ascites represent two very frequent clinical settings of diuretic resistance.

Several treatment strategies have been proposed to overcome diuretic resistance in ascites and congestive heart failure. Studies of intravenous high-dose furosemide in association with small-volume HSS in refractory congestive heart failure and refractory ascites suggest that strategy may be a viable option to manage these clinical conditions. Our group showed the safety and tolerability of this treatment and its effectiveness in both these clinical conditions. In patients with refractory CHF, treatment with high-dose furosemide and HSS is effective and well tolerated,[30,31] improves the quality of life through the relief of signs and symptoms of congestion,[32] reduces the plasma levels of markers of neurohormonal and inflammatory activation,[36] may delay more aggressive treatments, and it has long-term benefits, reducing mortality and hospital readmission rates.[32] In patients with refractory ascites[55] the control of ascites, pleural effusions, and/or leg edema was deemed significantly better in patients treated with high-dose furosemide and HSS without an increase of common adverse effects linked to high furosemide dosages such as hepatic encephalopathy.

Nevertheless, further studies are needed to confirm our findings and to evaluate hemodynamic and neurohormonal changes after treatment with high-dose furosemide and small-volume HSS and to determine the possible relationship between these changes and the therapeutic effectiveness of this type of treatment. Future studies also should analyze the effects of this type of treatment on renal function, using a more direct marker of GFR and of early acute kidney injury such as cystatin C.[68]

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