Hypertonic saline: A novel therapy for advanced heart failure?

Mark H. Drazner, MD, MSc,[a,b] and Biff F. Palmer, MD[c] *Dallas, Tex*

See related article on page 459.

The options available to treat patients with advanced heart failure, defined as persistent New York Heart Association class III or IV symptoms despite conventional medical therapy,[1] are limited. Cardiac transplantation is constrained by the scarcity of donor organs, whereas left ventricular assist devices are associated with a low 2-year survival rate.[2] Biventricular pacing has emerged as a novel therapy for improving symptoms of heart failure,[3] but it is presently recommended only for patients with a widened QRS interval, and predictors of response are not yet well defined. In patients who are hospitalized, the tailoring of medical therapy to specific hemodynamic goals may lead to clinical stability.[4,5] However, such data come from observational studies, and this approach is only now being tested in a randomized fashion.[6] Thus, there remains a need to develop novel therapies for patients with heart failure symptoms that are refractory to conventional medical therapy.

In this issue of the Journal, Licata et al[7] offer one such therapy. Their study population comprised patients aged between 65 and 90 years with decompensated and advanced heart failure, which was evidenced by profound limitations of exercise, obvious volume overload with marked peripheral edema, resistance to conventional doses of diuretics, and guarded survival. This study is an extension of an earlier report that described a subset of the present cohort.[8] In a single-blinded fashion, the investigators administered 150 mL infusions of hypertonic saline (range 1.4%-4.6% sodium infusions, depending on baseline serum sodium level) twice daily with high-dose intravenous furosemide (500-1000 mg twice daily) to 53 patients (group 1). The amount of sodium administered intravenously each day ranged from approximately 1.6 grams (300 mL/day of 1.4% hypertonic saline) to 5.4 grams (300 mL/day of 4.6% hypertonic saline). The remaining 54 patients in the study received comparable intravenous furosemide injections, but not hypertonic saline (group 2). Group 1 was also maintained on a 120 mmol dietary sodium restriction (approximately 2.8 grams sodium/24 hours), whereas group 2 was maintained on a more stringent 80 mmol dietary sodium restriction (approximately 1.8 grams sodium/24 hours). Patients in both groups were told to limit their total oral fluid intake to 1 L per day and received conventional medical therapy with angiotensin-converting enzyme inhibitors, diuretics, digoxin, appropriate potassium supplementation, and in the latter part of the study, spironolactone.

Both groups of patients had improvement in clinical status concordant with a comparable diuresis of approximately 20 pounds. However, patients randomized to receive hypertonic saline (group 1) had improved hospital outcomes compared with patients who did not receive hypertonic saline (group 2). Specifically, group 1, compared to group 2, had a shorter length of hospitalization, less renal dysfunction, higher discharge serum sodium levels, and fewer adverse effects (tinnitus) from furosemide. Even more striking, after a mean follow-up period of 31 ± 14 months, patients in group 1 were far less likely to have been hospitalized and more likely to be alive than patients in group 2.

Before considering potential mechanisms of the differences in outcomes between these 2 groups, it is important to recognize that the therapy described by Licata et al is unconventional and counterintuitive. During hospitalization, patients with decompensated heart failure are salt-restricted and usually do not receive intravenous sodium infusions. Furthermore, dietary sodium education[9] and restriction are considered essential in treating patients with heart failure, and a more, rather than less, stringent restriction would usually be recommended for patients with refractory symptoms.

How then should one interpret the results of this study? First, there remains the possibility that the conclusions of the study are not valid. The study population was small. An unintentional bias may have been introduced by the lack of double-blinding, although crude measures, such as angiotensin-converting enzyme inhibitor use, were similar between the 2 study groups. Bias may also have been introduced if randomization was thwarted in some way, although the similar baseline characteristics between the 2 study groups

From the [a]Heart Failure Research Unit, Donald W. Reynolds Cardiovascular Clinical Research Center, and the Divisions of [b]Cardiology and [c]Nephrology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Tex.
Reprint requests: Mark H. Drazner, MD, MSc, Division of Cardiology, University of Texas, Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9034.
E-mail: mark.drazner@utsouthwestern.edu
Am Heart J 2003;145:377-9.

0002-8703/2003/$30.00 + 0
doi:10.1067/mhj.2003.165

argue against that possibility. The investigators used supratherapeutic doses of intravenous furosemide (500-1000 mg twice daily) that may have resulted in adverse renal effects, perhaps caused by hypotension.[10] Supporting this contention is the significant increase in serum creatinine and blood urea nitrogen levels in patients who did not receive hypertonic saline. If the hypertonic saline infusions merely protected against adverse renal effects associated with high-dose furosemide, then the benefits associated with hypertonic saline may not occur in the setting of conventional diuretic doses.

An alternative hypothesis that warrants serious consideration is that the experimental therapy resulted in improved outcomes. The observable differences in the 2 groups in serum sodium and creatinine levels, both important prognostic factors in heart failure, at the time of hospital discharge suggests that events during the hospitalization resulted in the divergent outcomes during follow-up. If this is true, then it is likely that the hypertonic saline infusions played an important role, because the relative difference in the dietary sodium restriction was rather modest in comparison to the amount of sodium administered in the hypertonic saline infusions. Putative mechanisms of a benefit from hypertonic saline administration include restoration of effective arterial volume, decreased afterload, decreased renal vascular resistance, improved cardiac contractility, and enhanced diuretic responsiveness via renal effects.

Evidence suggesting that hypertonic saline led to a more effective repair of effective arterial blood volume included an increase in urine volume, preservation of renal perfusion as measured by blood urea nitrogen and creatinine levels, and a rise rather than a fall in serum sodium level. Additionally, the group that received hypertonic saline did not have significantly higher urinary potassium losses, despite the enhanced urinary sodium excretion. This would suggest that aldosterone levels were lower in the hypertonic saline group, again presumably because of the improved effective arterial blood volume. Such improvements in the neurhoromonal milieu may have directly contributed to improved outcomes, analogous to spironolactone administration.[11]

The benefits of hypertonic saline may also be mediated through its effect on cardiac function. Earlier studies have shown that hypertonic saline improved hemodynamics in patients with shock,[12] led to diuresis after cardiac surgery,[13] and improved preload and cardiac index after mitral valve repair.[14] Some,[15] but not all,[16,17] studies have shown an improvement in cardiac contractility.

Hypertonic saline may also result in an increase in diuretic efficiency. In patients with severe congestive heart failure, sodium is avidly reabsorbed in the proximal nephron. If hypertonic saline expands effective arterial blood volume and enhances sodium delivery past the proximal nephron to the thick ascending limb of Henle (site of action of furosemide), then natriuresis would be enhanced. Administration of hypertonic saline may also improve diuretic efficiency by limiting hypertrophy of distal renal tubular cells,[18] the latter of which is associated with diuretic resistance. Reductions in circulating angiotensin II or aldosterone from improved intravascular volume may have attenuated the distal renal tubular hypertrophy.[19] A recent study demonstrated that chronic furosemide administration decreased the tonicity in the renal medullary interstitium, resulting in a decreased production of pronatriuretic prostaglandin E_2.[20] If hypertonic saline or the more modest dietary sodium restriction attenuated the fall in tonicity of the medullary interstitium, then synthesis of natriuretic prostaglandins and diuretic effectiveness may have been preserved.

The study by Licata et al[7] challenges many of our preconceived notions about therapy for patients with advanced heart failure. Lest one dismiss it too abruptly, we need to recall the experience with β-adrenergic blocker therapy, which was previously contraindicated but is now recommended in patients with heart failure.[21] The study by Licata et al is a first step. It is not clear which component of the strategy (hypertonic saline or more modest dietary salt restriction) led to the benefits. Will this therapy be effective with more conventional doses of diuretics or more modest fluid restrictions? Would hypertonic saline be effective for patients with less-advanced heart failure or patients treated with β-blockers? Additional studies, including measurement of cardiac output and left-sided filling pressures, changes in neurohormonal levels, and quantification of furosemide and cumulative sodium excretion are needed to determine the mechanism of this therapy. Finally, larger, double-blinded, randomized trials are needed to rule out the play of chance or unintentional bias. We eagerly await such studies to know whether hypertonic saline will join the therapeutic armamentarium for patients with advanced and decompensated heart failure.

References

1. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. JAMA 2002;287:628-40.
2. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345:1435-43.
3. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
4. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or non-

ischemic dilated cardiomyopathy. Am J Cardiol 1990;66:1348-54.
5. Drazner MH, Solomon MA, Thompson B, et al. Tailored therapy using dobutamine and nitroglycerin in advanced heart failure. Am J Cardiol 1999;84:941-3.
6. Shah MR, O'Connor CM, Sopko G, et al. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. Am Heart J 2001; 141:528-35.
7. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart J 2003;145: 459-66.
8. Paterna S, Di Pasquale P, Parrinello G, et al. 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. Eur J Heart Fail 2000;2:305-13.
9. Neily JB, Toto KH, Gardner EB, et al. Potential contributing factors to noncompliance with dietary sodium restriction in patients with heart failure. Am Heart J 2002;143:29-33.
10. Cotter G, Weissgarten J, Metzkor E, et al. Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. Clin Pharmacol Ther 1997; 62:187-93.
11. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
12. de Felippe J Jr, Timoner J, Velasco IT, et al. Treatment of refractory hypovolaemic shock by 7.5% sodium chloride injections. Lancet 1980;2:1002-4.
13. Jarvela K, Kaukinen S. Hypertonic saline (7.5%) after coronary artery bypass grafting. Eur J Anaesthesiol 2001;18:100-7.
14. Sirieix D, Hongnat JM, Delayance S, et al. Comparison of the acute hemodynamic effects of hypertonic or colloid infusions immediately after mitral valve repair. Crit Care Med 1999;27:2159-65.
15. Kien ND, Reitan JA, White DA, et al. Cardiac contractility and blood flow distribution following resuscitation with 7.5% hypertonic saline in anesthetized dogs. Circ Shock 1991;35:109-16.
16. Constable PD, Muir WW III, Binkley PF. Hypertonic saline is a negative inotropic agent in normovolumic dogs. Am J Physiol 1994;267:H667-77.
17. Goertz AW, Mehl T, Lindner KH, et al. Effect of 7.2% hypertonic saline/6% hetastarch on left ventricular contractility in anesthetized humans. Anesthesiology 1995;82:1389-95.
18. Kaissling B, Bachmann S, Kriz W. Structural adaptation of the distal convoluted tubule to prolonged furosemide treatment. Am J Physiol 1985;248:F374-81.
19. Beck FX, Ohno A, Muller E, et al. Inhibition of angiotensin-converting enzyme modulates structural and functional adaptation to loop diuretic-induced diuresis. Kidney Int 1997;51:36-43.
20. Castrop H, Vitzthum H, Schumacher K, et al. Low tonicity mediates a downregulation of cyclooxygenase-1 expression by furosemide in the rat renal papilla. J Am Soc Nephrol 2002;13:1136-44.
21. Eichhorn EJ, Hjalmarson A. Beta-blocker treatment for chronic heart failure: the frog prince. Circulation 1994;90:2153-6.