DOMENIC A. SICA, MD*
Section of Clinical Pharmacology and Hypertension
Division of Nephrology
Virginia Commonwealth University Health System
Richmond, VA

Sodium and water retention in heart failure and diuretic therapy: Basic mechanisms

ABSTRACT

The pathophysiology of sodium and water retention in heart failure is characterized by a complex interplay of hemodynamic and neurohumoral factors. Relative arterial underfilling is an important signal that triggers heart failure-related sodium and water retention. The response to perceived arterial underfilling is modulated by the level of neurohormonal activation, the degree of renal vasoconstriction, and the extent to which renal perfusion pressure is reduced. Sodium retention can also be exceeded by water retention, with the result being dilutional hyponatremia. Sodium and water retention in heart failure also function to dampen the natriuretic response to diuretic therapy. The attenuated response to diuretics in heart failure is both disease-specific and separately influenced by the rate and extent of diuretic absorption, the rapidity of diuretic tubular delivery, and diuretic-related hypertrophic structural changes that surface in the distal tubule.

KEY POINTS

Neurohormonal systems activated in the course of heart failure promote renal sodium and water retention.

The sodium and water retention observed in heart failure is exaggerated by any reduction in glomerular filtration rate.

Diuretic dose-response relationships in heart failure are abnormal, resulting in a higher threshold for effect and a lesser peak effect.

Ineffective rates of urinary diuretic excretion result from poor and incomplete absorption of loop diuretics.

*Dr. Sica reported that he has no financial relationships that pose a potential conflict of interest with this article.

THE PATHOPHYSIOLOGY OF heart failure involves the activation and interplay of multiple neurohumoral and cellular systems (Figure 1).[1] Pathobiologically important alterations in the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), the vasopressin axis, and vasodilatory/natriuretic pathways have been described in heart failure. These disturbances are translated at the renal circulatory and tubular level in such a way that avid retention of sodium and water occurs.[1]

The blend of neurohumoral events that typically occurs in patients with heart failure produces uncertainty at the bedside because no one neurohumoral pathway is routinely the dominant factor in heart failure. As such, multiple mechanistic-based treatments can directly or indirectly influence sodium and water balance. These include beta-adrenergic receptor antagonism, angiotensin-converting enzyme (ACE) inhibition, and/or aldosterone receptor antagonism, as well as natriuretic peptides.

ARTERIAL UNDERFILLING

The state of the arterial circulation, as governed by cardiac output and peripheral vascular resistance, is the chief determinant of sodium and water retention in heart failure.[2] In particular, either a primary decrease in cardiac output or arterial vasodilatation brings about arterial underfilling, which activates neurohumoral reflexes that in turn incite sodium and water retention. These linked developments explain why plasma and blood volume increase in patients with heart failure, whether associated with low or high cardiac output, since otherwise normal kidneys persistently retain sodium and water.[3,4]

The question of what constitutes the afferent signal for continued retention of sodium and

Downloaded from www.ccjm.org on April 24, 2024. For personal use only. All other uses require permission.

water by the kidney in heart failure has been debated for years. An intrinsically normal kidney continues to retain sodium and water, despite expansion of extracellular fluid volume in heart failure, which implies that it must be responding to "inadequate" signals from the volume regulatory system. This suggests that some sensor in the vascular tree is "underfilled" or that some process for detecting body fluid appropriateness fails to perceive the elevated circulating volume. This arterial underfilling is picked up on by baroreceptors in the left ventricle, the aortic arch, the carotid sinus, and the renal afferent arterioles. Decreased activation of these receptors during the evolution of arterial underfilling leads to compensatory neurohumoral responses, which include stimulation of the sympathetic nervous system, activation of the RAAS, and nonosmotic release of vasopressin. These compensatory responses preserve circulatory integrity by increasing peripheral and renal vascular resistance and by fostering renal sodium and water retention.[4]

Importance of GFR

The level of renal function is an important determinant of sodium and water excretion. The basis for sodium and water retention when heart failure first manifests relates to elements other than a reduced glomerular filtration rate (GFR). Over time, however, a gradually falling GFR, either in association with heart failure progression or relating to medication effects on the level of renal function, becomes more critical in sodium and water retention. Although serum creatinine values have often been offered as a good gauge of renal function, in most cases "true" renal function is appreciably lower than the "eyeball" estimate derived from a specific serum creatinine value.[5] In the heart failure patient with progressive renal disease, diuretics generally become less effective in that the filtered load of sodium drops in parallel with a falling GFR.[6]

In other instances, transient changes in GFR, provoked by hemodynamic change, can attenuate the natriuretic response to a loop diuretic.[7,8] For example, the reduction in blood pressure that occurs with ACE inhibitor therapy can reduce renal perfusion pressure (and GFR) to such a degree that diuretic action is significantly weakened.[7] Also, diuretic infusions may diminish the early, volume-independent activation of the RAAS triggered by the rapid increase in plasma loop diuretic concentration after bolus loop diuretic therapy.

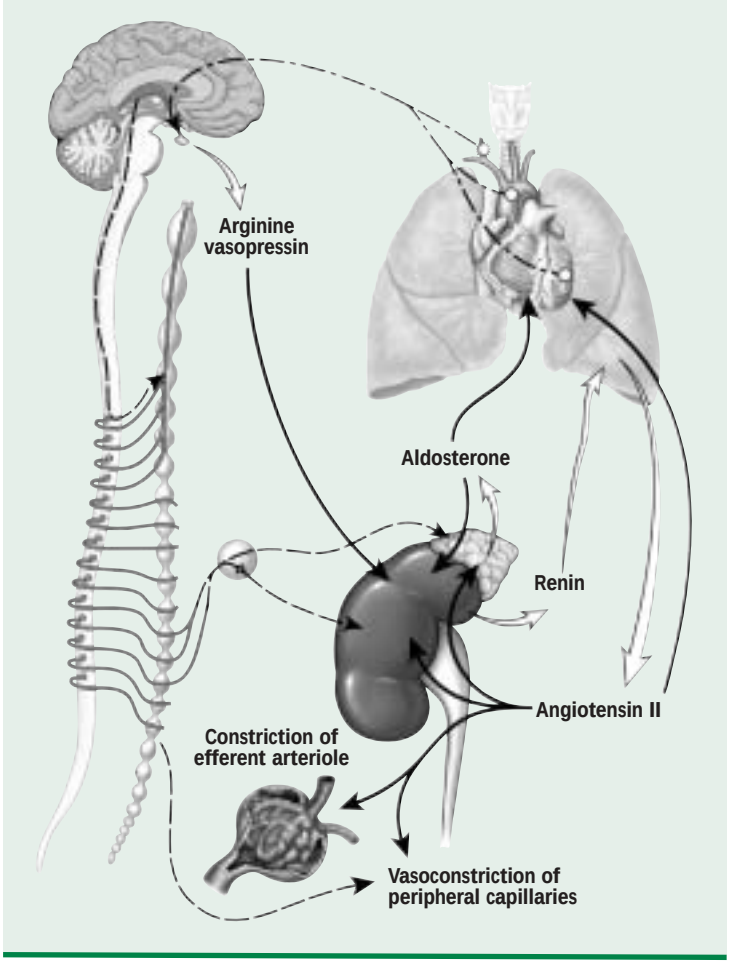

FIGURE 1. Efferent pathways in the sympathetic nervous system are activated in heart failure. Sympathetic nervous system activity contributes to peripheral and renal vasoconstriction and to sodium and water retention. Activation of renal sympathetic nerves leads to angiotensin II release, stimulating the renin-angiotensin-aldosterone system. Sympathetic stimulation also prompts release of arginine vasopressin, excess levels of which lead to water retention and hyponatremia. Angiotensin II acts as a potent vasoconstrictor, stimulates aldosterone release from the adrenal gland, and promotes renal tubule sodium reabsorption. Aldosterone increases reabsorption of sodium in the collecting duct.

Interestingly, activation of the RAAS by loop diuretic therapy is accompanied by deleterious hemodynamic effects.[8] Under these conditions, cardiac output, renal blood flow, and GFR can decrease, diminishing tubular delivery of the diuretic in the process.

RENIN-ANGIOTENSIN-ALDOSTERONE AXIS

The kidney contains all elements of the RAAS and is functionally independent in its genera-

Downloaded from www.ccjm.org on April 24, 2024. For personal use only. All other uses require permission.

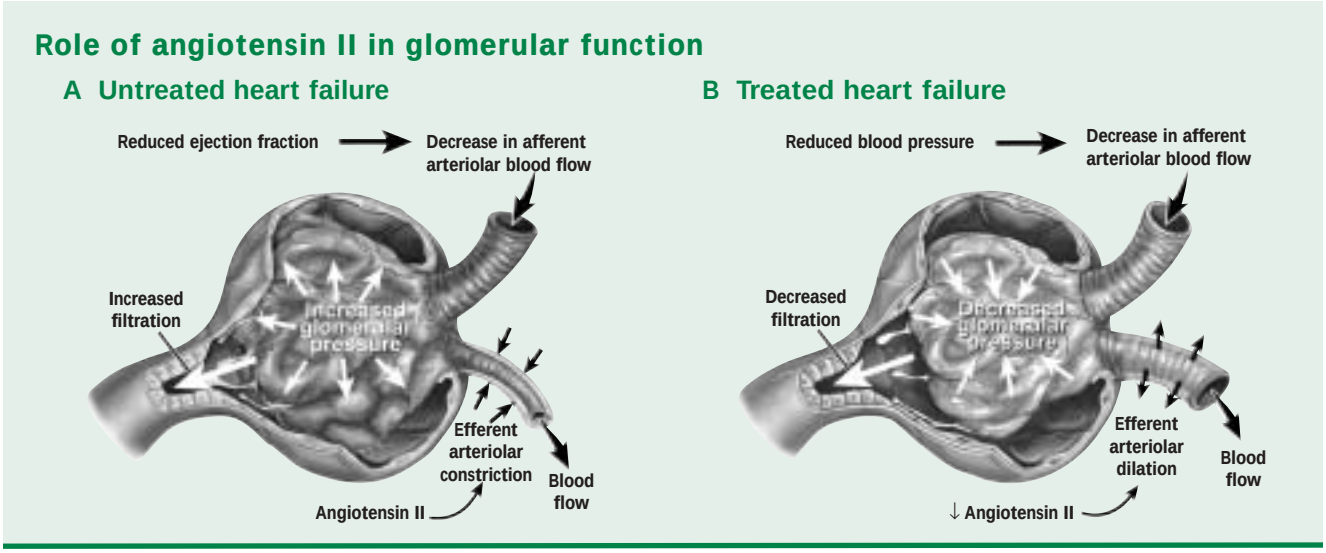

FIGURE 2. The glomerulus in untreated (A) and treated (B) heart failure. In untreated disease, release of angiotensin II causes efferent arteriolar constriction. Constriction of the draining arteriole increases glomerular pressure, allowing for a normal glomerular filtration rate. In heart failure treated with ACE inhibitor or angiotensin receptor blocker therapy, decreased afferent arteriolar blood flow, together with efferent arteriolar dilation, can decrease glomerular pressure.

Glomerular filtration rate is an important arbiter of sodium and water excretion

tion of angiotensin II. Angiotensin II, whether autocrine or paracrine in origin, has stimulatory effects on sodium transport in multiple nephron segments. This occurs by way of binding to plasma membrane angiotensin type 1 (AT1) receptors in the proximal tubule and cortical collecting duct.[9,10] In contrast to the stimulatory effects of AT1 receptors on sodium transport, angiotensin type 2 receptor stimulation is linked to increased urinary sodium excretion.[11]

The excess of angiotensin II in heart failure also has hemodynamic/cellular effects that influence renal handling of sodium and water. These include systemic vasoconstriction with an increase in afterload, efferent (postglomerular) arteriolar vasoconstriction, mesangial cell contraction, an increase in aldosterone and endothelin concentrations, and a strong stimulus to thirst (despite the typically low serum osmolality in heart failure).[9,10] Of note, local within-organ RAAS activation can explain the sodium retention, which can be seen occasionally in the absence of alterations in the circulating hormone.

Administration of an ACE inhibitor or an angiotensin receptor blocker in patients with low-output heart failure can either improve renal function (and facilitate sodium excretion)[12] or, in the case of patients with precarious renal hemodynamics, lead to deterioration in renal function (and have little effect, if not an adverse effect, on sodium balance).[13] For example, in untreated low-output forms of heart failure, the reduced ejection fraction and the ensuing decrease in afferent arteriolar blood flow are stimuli for localized release of angiotensin II (Figure 2A), which then preferentially constricts the efferent (postglomerular) arteriole. With efferent arteriolar constriction, hydrostatic pressures within the glomerulus are maintained—hence the concept of a preserved GFR despite a low-flow state.

When an ACE inhibitor or an angiotensin receptor blocker is administered in such a setting, the ensuing abrupt decrease in angiotensin II production (or activity) gives rise to abrupt dilation of the efferent arteriole (Figure 2B). In combination with a reduction in systemic blood pressure, this hemodynamic adjustment reduces hydrostatic pressures and glomerular filtration plunges.[13]

SYMPATHETIC NERVOUS SYSTEM ACTIVITY

Heart failure is characterized by heightened sympathetic nervous system activity, particularly directed to the heart and kidneys.[14] Although such neurohormonal activation initially helps to maintain systemic blood pressure and perfusion to vital organs, it is maladaptive in the long term.[15]

Increases in renal sympathetic nerve activity decrease urinary sodium and water excretion by increasing renal tubular sodium and water reabsorption throughout the nephron, decreasing renal blood flow and GFR by renal vasoconstriction, and increasing activity of the RAAS by stimulating renin release from juxtaglomerular granular cells. Thus, sympathetic

Downloaded from www.ccjm.org on April 24, 2024. For personal use only. All other uses require permission.

activation can be viewed as one of several contributors to the avid renal sodium and water retention in patients with heart failure.[15] In this regard, renal denervation has been shown to decrease sodium retention in experimental heart failure. Of note, this process may not be altered by alpha- and/or beta-blockade, although this remains controversial.[16,17]

If improvements in sodium and water handling occur with alpha- and/or beta-blockade, improvements in both renal hemodynamics (cardiac-related) and renal sodium excretory capacity (decrease in renal sympathetic nerve activity, RAAS activity, or both) are likely factors.[17]

WATER HANDLING IN HEART FAILURE

Water excretion occurs through a series of coordinated actions involving the glomerulus, the proximal tubule, the nephron diluting segment, and the distal tubule and collecting duct.

The glomerulus and proximal tubule operate in tandem to provide sufficient amounts of iso-osmotic ultrafiltrate to be processed by the diluting regions of the kidney. The ability to produce maximal free water clearance (urine osmolality of ≈ 50 mOsm/kg) once ultrafiltrate has proceeded past the proximal tubule is then a function of two axially distinctive processes. First, the distal diluting segments must be functional so that sodium and chloride can be extracted. Second, antidiuretic hormone (also known as arginine vasopressin [AVP]) must be suppressed so that free water generated at the distal diluting sites is not reabsorbed in the collecting system.[18]

A failure of one or more of these factors can impede the production of dilute urine, leading to progressive extracellular fluid volume expansion, hypo-osmolality, and dilutional hyponatremia. In heart failure, some or all of the requirements for excretion of maximally dilute urine may be compromised, opening the way to hyponatremia. This imbalance is much less common in mild to moderate heart failure but becomes more likely as cardiac output falls with more severe disease. Patients with severe heart failure may develop dilutional hyponatremia with as little as 1 to 2 L of water intake a day.

The profound reduction in cardiac output in severe heart failure is an important mechanistic prompt for the development of hyponatremia. As cardiac output drops, renal blood flow and GFR follow suit. This reduces the rate of solute and water delivery to the distal diluting segment of the nephron, impairing the kidney's ability to excrete dilute urine. At the same time, enhanced fractional reabsorption in the proximal tubule diverts even more sodium and water from the diluting sites, further impairing the production of dilute urine.[18]

Hormonal abnormalities are also important contributors to abnormal water balance in heart failure. The RAAS is activated early in the course of heart failure, particularly when diuretics are used. Angiotensin II facilitates the retention of sodium and water by multiple renal mechanisms. These mechanisms include an increase in efferent arteriolar tone (which indirectly promotes sodium and water absorption via the accompanying rise in the filtration fraction) and a direct proximal tubular effect. Angiotensin II also stimulates the thirst center of the brain and provokes the release of arginine vasopressin.

The decrease in effective arterial filling in heart failure contributes to the breakdown of baroreceptor-mediated suppression of AVP release. Since defective baroreceptor stimulation of AVP release overrides its inhibition by a hypo-osmolar state, patients with severe heart failure may have elevated levels of circulating AVP.[19–22]

In heart failure, the relationship between the urinary sodium excretion rate and the urinary diuretic excretion rate is blunted

Although the concentration of AVP is not uniformly elevated in heart failure, even in the presence of hyponatremia, of equal importance is that concentrations of this water-retaining hormone are not totally suppressed as they should be in the setting of plasma hypo-osmolality. AVP levels typically are not suppressed appropriately with a water load in heart failure; however, there exists a subset of patients with heart failure in whom water loading results in appropriate reduction in AVP.[22] The elevated or "normal" levels of AVP in the presence of hyponatremia suggest that nonosmotic mechanisms for vasopressin release are essential factors in the hyponatremia that is characteristic of the complex heart failure syndrome.

REFRACTORINESS TO DIURETICS IN HEART FAILURE

The relationship between urinary sodium excretion and the urinary diuretic excretion

Downloaded from www.ccjm.org on April 24, 2024. For personal use only. All other uses require permission.

rate is blunted in patients with heart failure compared with normal subjects. Typically, heart failure patients with mild to moderate disease have a response that is one fourth to one third of that normally observed with maximally effective doses of loop diuretics. The response in patients with more severe disease is smaller yet.[6,23]

The reason for this attenuated response to loop diuretics in heart failure is threefold:

• Heart failure is characterized by an excess reabsorption of filtrate in the proximal tubule. This phenomenon substantially reduces delivery of filtrate to the thick ascending limb and distal tubule, which is where a loop or thiazide-type diuretic would be expected to work.[6] Therapies that decrease proximal tubular filtrate reabsorption can occasionally restore some level of diuretic responsiveness.[24]

• There is a disease-state–specific effect such that diuretic activity is attenuated in the thick ascending limb of the loop of Henle. One possible explanation for this is altered expression or activity of the Na^+-K^+-$2Cl^-$ transporter at the loop of Henle.[25]

• Mechanisms are activated distal to the thick ascending limb of Henle (ie, aldosterone) that check elimination of the filtered load that would otherwise escape absorption in the thick ascending limb.[26]

The result of these processes is refractoriness to all diuretics, whether given orally or intravenously. Diuretics with unpredictable absorption, such as furosemide and metolazone, are associated with a different form of diuretic resistance—ie, failure to rapidly achieve the plasma level needed for efficient diuretic delivery.[27,28] The loop diuretic torsemide, which is well and rapidly absorbed, is not associated with this form of resistance.[29]

Rotation of loop diuretics is a proposed but untested method of overcoming diuretic resistance

CONSIDERATIONS IN DIURETIC DOSING

There exists a unique and clinically relevant time course of urinary drug delivery at which the natriuretic response to a loop diuretic is optimized. This rate of drug delivery resides on the steep portion of the sigmoid diuretic dose-response curve, between the threshold concentration (or minimally effective dose) and the plateau concentration (or dose beyond which no additional efficacy is gained by an increase in the rate of tubular diuretic delivery).

Find the threshold rate

Typically, the dose-response curve for patients with heart failure is shifted downward and rightward. The clinical implication of this disease-based restructuring of the dose-response relationship is that the threshold for effect is noticeably increased. Failure to titrate the dose of a diuretic to this threshold is a common error in heart failure therapy. If this circumstance goes unrecognized, this inadequate dose is repeated unwittingly throughout the day, and with each succeeding dose there is a continued minimal response. A more prudent approach is to titrate the loop diuretic dose upward until a diuretic response is clearly established. Thereafter, the dosing frequency can be safely determined by clinical need.[6]

Diuretic rotation

In diuretic-resistant patients, rotation of loop diuretics within a class has been suggested as another means of reestablishing response. Anecdotal observations suggest that patients who are refractory to furosemide may experience spontaneous diuresis when given torsemide, bumetanide, or ethacrynic acid. This phenomenon has not been critically examined, however. When diuretics are rotated this way, the rate and extent of diuretic absorption potentially varies among class members, and a different and more efficient time course of urinary drug delivery ensues. Alternatively, when intravenous loop diuretics are rotated, "improved" hemodynamic conditions often allow a diuresis to be established when a patient had otherwise been resistant to diuretic effect.[6]

STRUCTURAL EFFECT OF CHRONIC LOOP DIURETIC USE

Recently, attention has centered on a series of compensatory processes that take place in the distal tubule following long-term diuretic therapy. As loop diuretics repetitively expose distal tubular cells to sodium, these cells undergo morphologic adaptation fueled by the need for increased cellular sodium reabsorption. As distal tubular sodium absorption increases, the number of membrane Na^+-K^+-ATPase pumps on the basolateral membrane surface dramatically increases. For example, when animals are infused with furosemide, both the size of the

Downloaded from www.ccjm.org on April 24, 2024. For personal use only. All other uses require permission.

distal tubular cells and their ability to transport sodium chloride increases substantially. As a result of this increased sodium reabsorptive capacity, any previously established dose-response relationship for a loop diuretic deteriorates in favor of considerably less sodium chloride reaching the final urine, despite continued adequate drug delivery.[26]

Diuretics that are active at the distal tubule, such as thiazide diuretics, not only block the increase in sodium chloride transport but may also prevent cellular hypertrophy or cause its regression. Reversing this sequence of events is but one of several explanations for the diuretic synergy that occurs with coadministration of a distal tubular diuretic, such as metolazone, with a loop diuretic.[27]

SUMMARY

Sodium and water handling becomes abnormal early in the development of heart failure. This tendency to retain sodium and water is a byproduct of a complex interplay between hemodynamic forces and the often generous increase in neurohumoral factors, cytokines, and growth factors that marks this disease. The abnormal sodium and water handling in untreated heart failure carries over to the response to diuretics as well. Diuretic resistance in heart failure is a byproduct of multiple factors, and its management can prove quite challenging.

REFERENCES

1. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999; 341:577–585.
2. Peters JP. The role of sodium in the production of edema. N Engl J Med 1948; 239:353–362.
3. Cadnapaphornchai MA, Gurevich AK, Weinberger HD, Schrier RW. Pathophysiology of sodium and water retention in heart failure. Cardiology 2001; 96:122–131.
4. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. N Engl J Med 1988; 319:1065–1072.
5. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006; 52:5–18.
6. Sica DA, Gehr TW. Diuretic combinations in refractory oedema states: pharmacokinetic–pharmacodynamic relationships. Clin Pharmacokinet 1996; 30:229–249.
7. McLay JS, McMurray JJ, Bridges AB, Fraser CG, Struthers AD. Acute effects of captopril on the renal actions of furosemide in patients with chronic heart failure. Am Heart J 1993; 126:879–886.
8. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med 1985; 103:1–6.
9. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. J Am Soc Nephrol 1999; 10(Suppl 12):S258–S265.
10. Burns KD, Li N. The role of angiotensin II–stimulated renal tubular transport in hypertension. Curr Hypertens Rep 2003; 5:165–171.
11. Padia SH, Howell NL, Siragy HM, et al. Renal angiotensin type 2 receptors mediate natriuresis via angiotensin III in the angiotensin II type 1 receptor–blocked rat. Hypertension 2006; 47:537–544.
12. Eiskjaer H, Bagger JP, Danielsen H, et al. Mechanisms of sodium retention in heart failure: relation to the renin-angiotensin-aldosterone system. Am J Physiol 1991; 260:F883–F889.
13. Schoolwerth A, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin-converting enzyme inhibitor therapy. A Statement for Healthcare Professionals From the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation 2001; 104:1985–1991.
14. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation 1986; 73:615–621.
15. DiBona GF, Herman PJ, Sawin LL. Neural control of renal function in edema-forming states. Am J Physiol 1988; 254:R1017–R1024.
16. Dupont AG. Effects of carvedilol on renal function. Eur J Clin Pharmacol 1990; 38(Suppl 2):S96–S100.
17. DiBona GF, Sawin LL. Effect of metoprolol administration on renal sodium handling in experimental congestive heart failure. Circulation 1999; 100:82–86.
18. Sica DA. Hyponatremia and heart failure—pathophysiology and implications. Congest Heart Fail 2005; 11:274–277.
19. Szatalowicz VL, Velazquez H, Chaimowitz C, et al. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. N Engl J Med 1981; 305:263–266.
20. Goldsmith SR, Francis GS, Cowley AW, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. J Am Coll Cardiol 1983; 1:1385–1390.
21. Funayama H, Nakamura T, Saito T, et al. Urinary excretion of aquaporin-2 water channel exaggerated dependent upon vasopressin in congestive heart failure. Kidney Int 2004; 66:1387–1392.
22. Goldsmith SR, Francis GS, Cowley AW Jr. Arginine vasopressin and the renal response to water loading in congestive heart failure. Am J Cardiol 1986; 58:295–299.
23. Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney Int 1984; 26:183–189.
24. Pretzlaff RK, Vardis RJ, Pollack MM. Aminophylline in the treatment of fluid overload. Crit Care Med 1999; 27:2782–2785.
25. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol 2003; 284:F11–F21.
26. Ellison DH, Velazquez H, Wright FS. Adaptation of the distal convoluted tubule of the rat. Structural and functional effects of dietary salt intake and chronic diuretic infusion. J Clin Invest 1989; 83:113–126.
27. Sica DA. Metolazone and its role in edema management. Congest Heart Fail 2003; 9:100–105.
28. Murray MD, Haag KM, Black PK, Hall SD, Brater DC. Variable furosemide absorption and poor predictability of response in elderly patients. Pharmacotherapy 1997; 17:98–106.
29. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther 1995; 57:601–609.

Address: *Domenic A. Sica, MD, Division of Nephrology, Medical College of Virginia Campus of Virginia Commonwealth University, Box 980160, MCV Station, Richmond, VA 23298-0160; dsica@mail2.vcu.edu.*

Downloaded from www.ccjm.org on April 24, 2024. For personal use only. All other uses require permission.