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UNRESOLVED PROBLEMS IN HEART FAILURE:

EDEMA, HYPONATREMIA, AND RENAL INSUFFICIENCY

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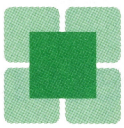

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Sodium and water retention in heart failure and diuretic therapy: Basic mechanisms

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

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.

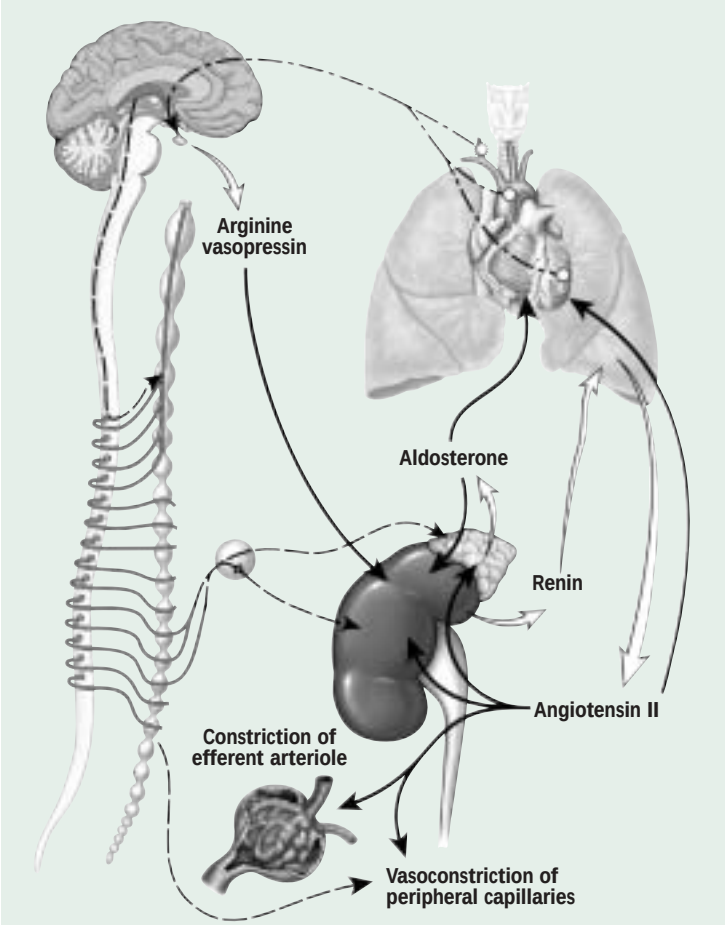

FIGURE 1. Efferent pathways in the sympathetic nervous system are activated in heart failure. Sympathetic nervous system activity contributes to peripheral and renal vasoconstriction and to sodium and water retention. Activation of renal sympathetic nerves leads to angiotensin II release, stimulating 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-

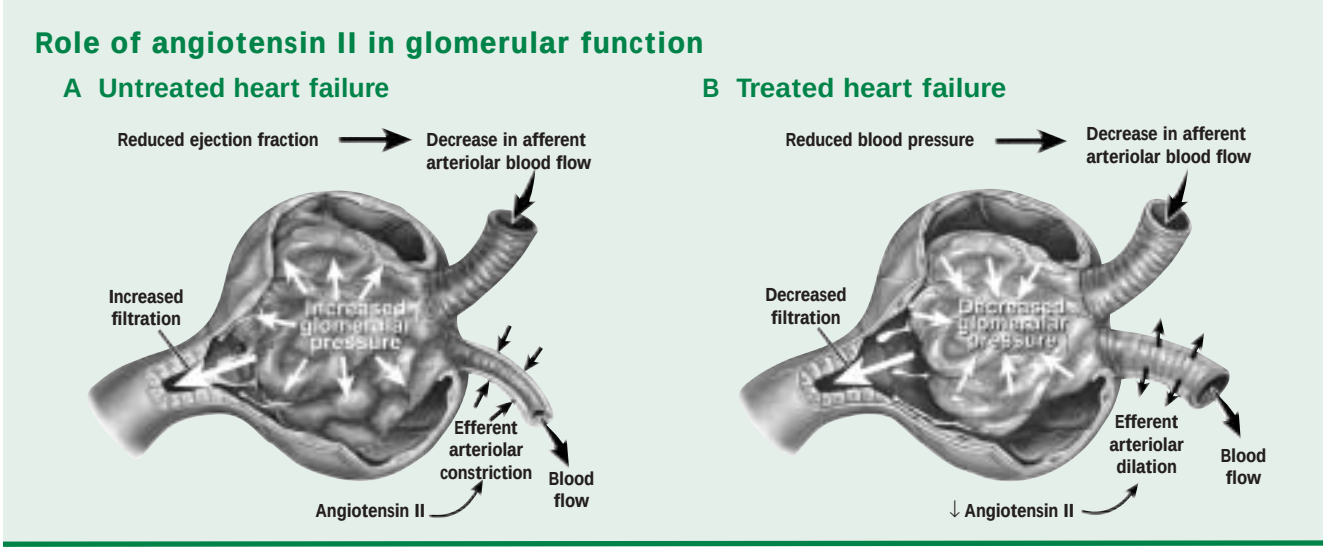

FIGURE 2. The glomerulus in untreated (A) and treated (B) heart failure. In untreated disease, release of angiotensin II causes efferent arteriolar constriction. Constriction of the draining arteriole increases glomerular pressure, allowing for a normal glomerular filtration rate. In heart failure treated 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

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

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

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.

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Acute decompensated heart failure: The cardiorenal syndrome

ABSTRACT

The cardiorenal syndrome is not well understood, and a uniform definition is lacking. Worsening renal function as determined by a decline in creatinine clearance in patients with decompensated heart failure is an identifier of patients with this syndrome. Treatment is a challenge. Diuretic therapy is valuable in treating congestion but may worsen renal function. Patients with decompensated heart failure are often refractory to diuretics, in which case higher doses must be used or alternate methods explored to reduce salt and water.

KEY POINTS

Worsening renal function is common in acute heart failure and increases mortality and hospital resource utilization.

A decrease in creatinine clearance or glomerular filtration rate can identify patients with cardiorenal syndrome.

Loop diuretics remain the mainstay of therapy but may worsen renal function, and patients may become refractory to them.

Fluid removal by ultrafiltration may be useful in the setting of chronic volume overload when renal function is declining with the use of loop diuretics.

*Dr. Francis reported that he is a consultant to and has done teaching and speaking for the Amgen, Merck, Novartis, and Otsuka corporations.

A CONSENSUS DEFINITION of the cardiorenal syndrome has not been established. Many believe that it is the final manifestation of deteriorating renal function in the presence of heart failure.

Not much is understood about the pathophysiology of the cardiorenal syndrome. An imbalance in interactions between the failing heart, neurohormonal systems, and host inflammatory responses has been implicated, leading to structural and functional damage to the heart and kidneys. Worsening renal function is common in decompensated heart failure and is associated with greater hospital resource utilization and mortality.

Because the process is complex, treatment can be a challenge. The worsening renal function in patients with this syndrome can also lead to resistance to many standard therapies and exacerbation of symptoms.

This article will explain the relationship between changes in creatinine clearance and prognosis in patients with acute heart failure exacerbations, the challenges in managing this syndrome (including diuretic resistance), and several alternate approaches to diuretic therapy to reduce salt and water retention.

CREATININE CLEARANCE PREDICTS PROGNOSIS

A rise in serum creatinine or diminishment in creatinine clearance in patients with acute decompensated heart failure is associated with a worsened prognosis.[1] The prognosis is even poorer if the increase in serum creatinine or the decrease in creatinine clearance is accompanied by oliguria (≤ 50 mL/hr), edema, hyponatremia, or refractoriness to diuretics.

Any detectable decrease in renal function in patients with heart failure is associated with increases in mortality and length of hospital

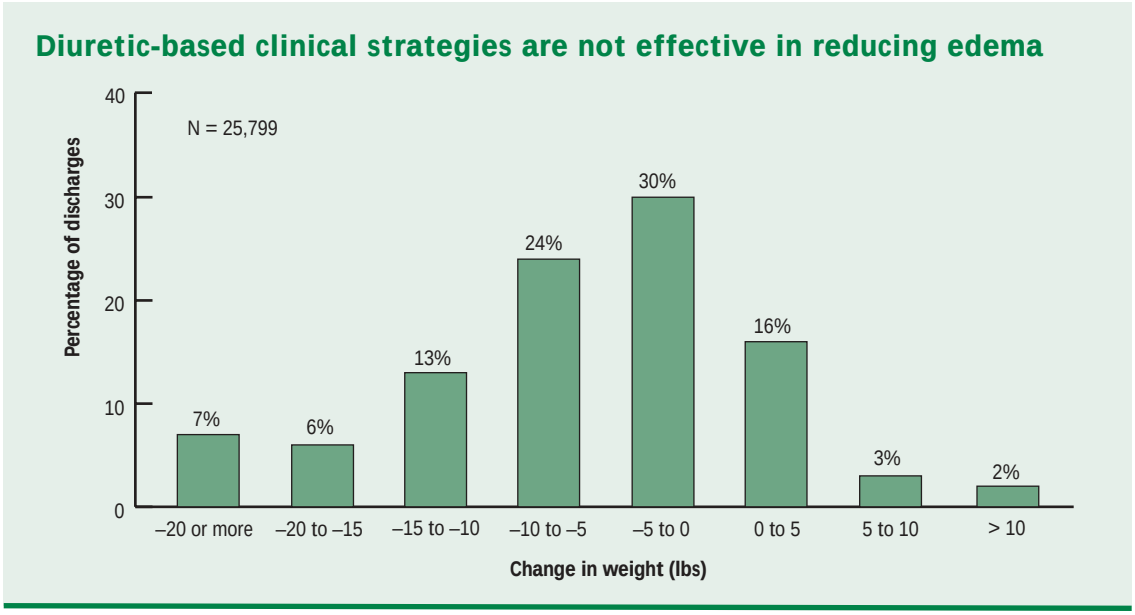

FIGURE 1. Nearly one fourth of patients with acute decompensated heart failure failed to lose weight from admission to discharge despite treatment with intravenous (IV) diuretics. Data are from the Acute Decompensated Heart Failure National Registry (ADHERE),[2] in which 90% of the patients received IV diuretic therapy.

stay, and although a rapidly rising creatinine level is more specific for these outcomes, smaller changes in creatinine are encountered more often in practice. Traditionally, loop diuretics or inadequate blood flow to the kidney have been blamed for these changes in renal function, but the actual cause is likely to be more complex.

Although the terms creatinine clearance and glomerular filtration rate (GFR) are often used interchangeably, creatinine clearance is a clinical laboratory test that requires 24-hour urine collection and a blood sample, whereas GFR is largely a research tool performed in general clinical research units. Calculation of GFR requires inulin or iothalamate infusion. Creatinine clearance tends to overestimate the GFR, which is the gold standard for measuring kidney function. GFR can be estimated by the Modification of Diet in Renal Disease (MDRD) equation, which can be found on many handheld computers.

Renal insufficiency is common

The Acute Decompensated Heart Failure National Registry (ADHERE) of 100,000 patients admitted with acute decompensated heart failure reveals that moderate and severe renal insufficiency, and even renal failure, are common in this population, and that normal renal function is rare. Most institutions use large doses of loop diuretics in an attempt to rescue these patients. Intravenous medications used less frequently are dobutamine, dopamine, milrinone, nitroglycerin, and nesiritide.

Diuretic therapy falls short

Unfortunately, diuretic-based strategies are not always effective in reducing edema. In ADHERE, 21% of patients admitted for decompensated heart failure were discharged without weight loss or with a gain in weight (Figure 1).[2] In my experience, patients who do not manifest weight loss in the hospital tend to have a poor prognosis.

Any detectable decrease in renal function is associated with increases in mortality and hospital stay

IDENTIFYING CARDIORENAL SYNDROME

Disconnect between serum creatinine and GFR

Commonly, a lower creatinine clearance or GFR, and not always an increase in serum creatinine, identifies patients with the cardiorenal syndrome. Relative to a decline in ejection fraction, a fall in GFR is more important to prognosis in patients with heart failure.[3] Measuring serum creatinine alone is probably misleading. Approximately two thirds of patients admitted to the Cleveland Clinic for acute heart failure have an inadequate GFR or

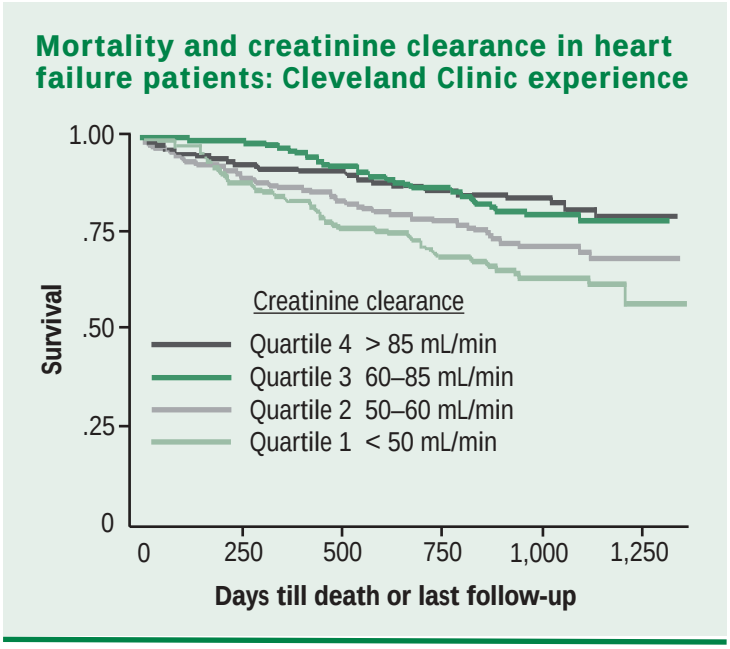

FIGURE 2. Among 585 ambulatory patients with chronic congestive heart failure, estimated creatinine clearance predicted all-cause mortality with follow-up of more than 3 years. Mortality increased with decreasing quartile of estimated creatinine clearance. Reprinted from reference 5, copyright 2002, with permission from the American College of Cardiology.

a reduced creatinine clearance, despite many of them having relatively preserved levels of serum creatinine.[4] Remarkably reduced rates of clearance are possible with levels of serum creatinine that are only slightly elevated. In a series of 585 patients with congestive heart failure at our institution, those with the lowest levels of creatinine clearance had the highest mortality when followed for more than 3 years (Figure 2).[5]

Cardiac output is not a reliable indicator

The presence of low filling pressures, a low cardiac index, or even reduced renal perfusion is not necessary to identify cardiorenal syndrome, as often believed. More often than not, in fact, cardiac output will be normal. Modest increases in serum creatinine and blood urea nitrogen rarely indicate reduced cardiac output or left ventricular filling pressure (ie, overdiuresis), but more often reflect a low creatinine clearance at baseline.

PROBLEMS WITH LOOP DIURETICS

Furosemide is the most commonly used loop diuretic for the treatment of patients hospitalized for an acute exacerbation of congestive heart failure. Although furosemide promotes diuresis, it does so at the cost of a further reduction in GFR (Figure 3).[6]

Hemodynamic response

In the 1980s it was recognized that transient hemodynamic abnormalities occurred with high-dose furosemide administration in patients with heart failure, and that these abnormalities subsided with adequate diuresis. A mechanism was proposed for this phenomenon, in which stimulation of the renin-angiotensin system and sympathetic nervous system by loop diuretic therapy was responsible for vasoconstriction, an increase in levels of arginine vasopressin (AVP), and an increase in afterload and preload, resulting in adverse hemodynamic effects.[7]

The hemodynamic response after administration of large doses of furosemide consists of an increase in heart rate, a slight increase in mean arterial pressure, a slight reduction in stroke volume, an increase in systemic vascular resistance, and a transient increase in filling pressure and right atrial pressure.[7] Levels of plasma norepinephrine and AVP increase, as does plasma renin activity, mimicking the changes in hemodynamics. Soon after administration, cardiac function is depressed, but as diuresis occurs, filling pressures fall and stroke volume increases. So although loop diuretics remain the mainstay of treatment for patients in a volume-overloaded state and achieve effective diuresis, they may be contributing to the worsening hemodynamics and progressive renal dysfunction in patients with heart failure.

Chronic diuretic therapy may also worsen renal function

This same deleterious effect on neurohormones occurs with chronic diuretic treatment. Bayliss and colleagues found that 4 weeks of furosemide and amiloride treatment resulted in an increase in plasma renin and aldosterone activity.[8]

Inadequate renal perfusion is not the entire explanation behind worsening renal function in acute heart failure. Deterioration in renal function occurs in patients with decompensated heart failure, increased right atrial pressure, and peripheral tissue congestion, even

though cardiac systolic function is preserved.[9] This decline in renal function despite presumed preserved blood flow to the kidney suggests that some mechanism in heart failure that is associated with a rise in atrial pressure and peripheral congestion is a major contributor to the cardiorenal syndrome.

MANAGING CARDIORENAL SYNDROME

Body weight is probably the single most important measurement in managing the cardiorenal syndrome. Hemodynamic monitoring is often required, especially if there is low blood pressure and uncertain filling pressure.

Free water restriction, although difficult, is advised if the patient is hyponatremic. In my practice, I restrict free water to less than 1,000 mL per 24 hours. In a few cases, volume expansion is required, especially if the patient has documented low filling pressure and hypotension.

In patients with oliguria and rising creatinine levels, a nephrology consultation is desirable.

Before starting loop diuretics, patients are often primed with 250 or 500 mg of intravenous chlorothiazide. It is difficult to obtain, however; hospital pharmacies may not carry it because it is used so infrequently. Furosemide drips, 5 to 10 mg per hour, may be useful. If the patient can take medications orally, 5 to 10 mg of metolazone may enhance the response to the loop diuretic.

Treating diuretic resistance

Overcoming diuretic refractoriness is part of the management of the cardiorenal syndrome. The braking phenomenon (short-term tolerance) is said to occur when the response to a diuretic is reduced after the first dose has been administered.[10] In this instance, we use a continuous infusion of furosemide, starting at 5 to 10 mg per hour, following an intravenous thiazide diuretic.

Other methods to reduce salt and water

Nesiritide. Although some choose to use nesiritide to treat patients with cardiorenal syndrome, the data are not supportive of this practice. Wang et al[11] found that urine flow, sodium excretion, GFR, and effective renal plasma flow were no different when comparing placebo and nesiritide infusions in patients with chronic heart failure and worsening serum creatinine. In a meta-analysis of five randomized studies, Sackner-Bernstein et al[12] reported that nesiritide significantly increased the risk of worsening renal function compared with controls not receiving inotrope-based therapy.

Furosemide monotherapy may cause significant decline in glomerular filtration rate

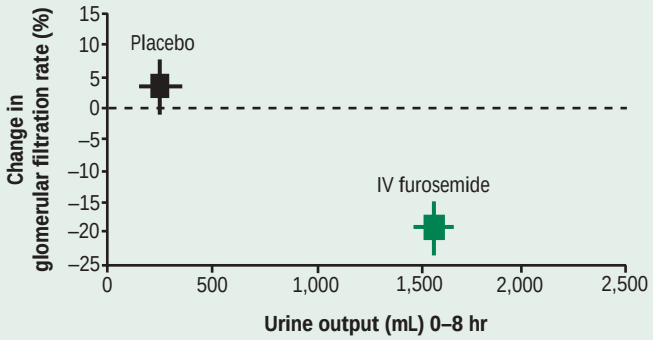

FIGURE 3. In a study of 63 patients with congestive heart failure, treatment with intravenous furosemide caused a decline in glomerular filtration rate compared with placebo. Adapted, with permission, from reference 6.

Ultrafiltration has been used in patients with therapy-resistant chronic volume overload.[13–26] Conventional ultrafiltration requiring central venous access is most often used, particularly if the patient is extremely edematous.

Generally, the hemodynamic changes produced by ultrafiltration are fairly modest.[19] The reduction in water with ultrafiltration is accompanied by decreases in right atrial pressure and wedge pressure. Cardiac output and stroke volume are unchanged or increase slightly. Importantly, the weight loss is sustained relative to furosemide treatment.[15]

The typical volume of water removed per ultrafiltration session is 3,000 to 4,000 mL. In a randomized study of 40 patients with decompensated heart failure, Bart et al[24] found that fluid removal after 24 hours was 4,650 mL in patients assigned to ultrafiltration and 2,838 mL in those assigned to usual care (P = .001)

A newer ultrafiltration method in which peripheral venous blood is removed was recently compared with standard intravenous diuretic therapy in 200 patients with acute decompensated heart failure.[27] Weight loss and net fluid loss at 48 hours were signifi-

Body weight may be the most important measure in managing the cardiorenal syndrome

cantly greater in the patients undergoing peripheral ultrafiltration. Moreover, the rehospitalization rate, the number of rehospitalization days, and the number of unscheduled office or emergency department visits at 90 days were also significantly lower in patients managed with ultrafiltration. There was no significant deterioration in renal function, but dyspnea was not improved.

AVP receptor inhibitors, which will be discussed in detail later in this supplement, tend to be aquaretic and may have a possible therapeutic role in volume-overloaded patients who are hyponatremic.

Targeted renal delivery of drugs has been proposed to increase local drug concentration in the hopes of enhancing renal effects or providing a previously unattainable effect. Direct intrarenal delivery will lead to renal first-pass elimination, resulting in less systemic exposure and reduction or elimination of serious adverse effects. Intrarenal delivery of fenoldopam was associated with a lower incidence of hypotension than intravenous fenoldopam,[28,29] which is also true of intrarenal vs intravenous administration of nesiritide (unpublished data). Given its potential advantages, intrarenal drug delivery is worthy of further study.

The typical volume of water removed per ultrafiltration session is 3,000 to 4,000 mL

SUMMARY

Management of the patient with cardiorenal syndrome is fraught with difficulty given the absence of a consensus definition. The pathophysiology is not well understood but seems only loosely coupled to central hemodynamics, ejection fraction, and GFR. Creatinine clearance is more valuable than serum creatinine level in identifying patients with this syndrome, and creatinine clearance is tied to prognosis.

Treatment is challenging, as the syndrome can be aggravated by diuretics and is not predictably responsive to inotropic agents or nesiritide. Ultrafiltration and selective renal artery infusion of drugs require further study.

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New approaches to detect and manage edema and renal insufficiency in heart failure

ABSTRACT

Earlier detection of edema and renal insufficiency, before overt decompensation, is fundamental to further advances in altering the natural history of heart failure. Progress is being made in the earlier detection of these complications through the use of new devices that monitor for hemodynamic compromise and through monitoring of select cardiac and renal biomarkers. In addition, diuretic-sparing approaches to heart failure management, novel drug classes, new devices, and nonpharmacologic therapies are emerging to reduce reliance on diuretic therapy and manage edema with less renal compromise.

KEY POINTS

Implantable devices are being developed to enable remote monitoring of intracardiac filling pressures and impedance in an effort to better guide outpatient heart failure therapy and avoid edema.

B-type natriuretic peptide, cardiac troponin T, and cystatin C show promise in clinical trials for identifying cardiac and renal distress in heart failure patients prior to organ damage.

As more heart failure patients are managed with neurohormonal antagonists, including the investigational adenosine type 1 receptor antagonists and vasopressin receptor antagonists, discontinuation of chronic diuretic therapy may be increasingly possible.

*Dr. Tang reported that he has served as a consultant to the FlowMedica, Medtronic, Neurocrine Biosciences, and Otsuka corporations.

ALTHOUGH CLINICIANS are increasingly able to reduce mortality and delay disease progression in patients with heart failure, too often these attempts come too late to have an effect. We do not yet fully understand the mechanisms that promote edema and renal insufficiency in heart failure, and we have not had satisfactory methods to proactively detect these complications in heart failure patients. As a result, we often identify patients at risk for edema and renal insufficiency only after these complications have already wreaked havoc on patients' clinical status.

Although diuretic therapy can manage edema and congestion effectively in patients with heart failure, it is commonly associated with renal insufficiency and other adverse effects, as discussed in the previous articles in this supplement.

A key challenge before us is how to identify sooner those heart failure patients who are at risk for edema and renal insufficiency. New devices and the use of biomarkers are showing promise for this purpose. Moreover, new strategies are emerging to more safely manage edema and congestion in heart failure, in the form of new, more kidney-friendly medications as well as devices and even invasive procedures. This article briefly reviews these emerging approaches and the rationale behind their development.

'ACUTE' HEART FAILURE IS NOT ALWAYS SO ACUTE

The broad objectives of heart failure therapy are to:

- Alter the natural history of the disease, in terms of reducing mortality and delaying disease progression
- Lessen the disease burden and costs, in terms of improving quality of life, reducing

symptoms and complications, and reducing hospitalizations.

In terms of clinical presentation, acute heart failure is defined as either the new onset (within hours to days) of symptoms of congestion and heart failure, or worsening of the signs and symptoms of previously stable heart failure.

In real-world practice, heart failure often is characterized according to where the patient is seen and treated, with the disease being deemed acute heart failure if we encounter the patient in the hospital. This tendency is unfortunate, since the evolution of fluid retention is not necessarily "acute" and could be detected sooner and managed better if we routinely monitored patients for it in the outpatient setting.

In a questionnaire-based study of 87 consecutive patients hospitalized for heart failure, Schiff and colleagues found that the median duration of symptom worsening (edema, weight gain, dyspnea) was 7 to 12 days prior to hospitalization.[1] They concluded that "there is a time window between symptom exacerbation and admission during which earlier access and intervention might prevent hospitalization." This is the premise of the many emerging strategies for early detection of edema and renal insufficiency.

Figure 1 illustrates the working hypothesis of how heart failure worsens during this time window. The worsening is believed to contribute to alteration in hemodynamics, as discussed in the previous articles in this supplement, as well as both pulmonary and peripheral congestion. The ultimate result is edema and renal insufficiency, although the mechanisms of their development are not well understood. At the same time, the physiologic variables involved in their development can be detected in a proactive manner, and emerging devices and techniques are making the detection of these variables increasingly efficient.

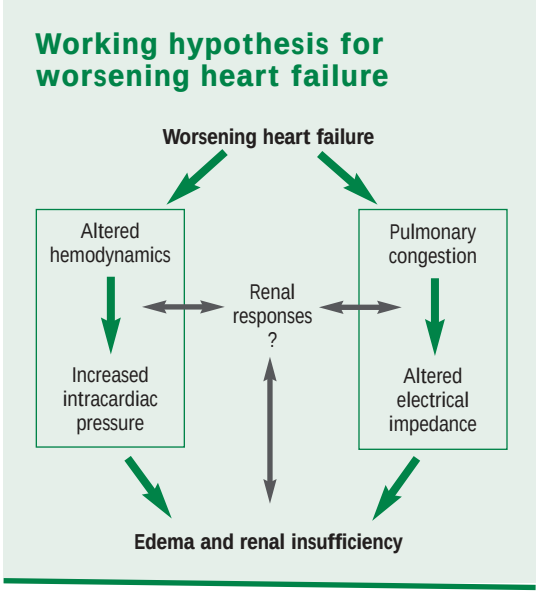

FIGURE 1. Progression of heart failure is believed to involve alterations in hemodynamics and pulmonary and peripheral congestion. Edema and renal insufficiency are among the consequences, but their development is not fully understood.

STRATEGIES FOR EARLIER DETECTION OF DECOMPENSATION

Earlier detection of decompensation, before overt presentation, is fundamental to further advances in altering the natural history of heart failure. Progress in earlier detection has focused on monitoring for hemodynamic compromise and on monitoring for select biomarkers.

The evolution of fluid retention is not necessarily 'acute'

Hemodynamic monitoring to guide therapy

There are two main targets in monitoring for hemodynamic compromise: rising intracardiac filling pressures and elevations in intrathoracic fluid volumes (or impedance). The past decade has seen a number of important advances in this area, which are outlined below.

Measuring intracardiac filling pressures. The randomized, single-blind COMPASS-HF trial assessed the clinical utility of an implantable hemodynamic device (Chronicle, Medtronic, Inc., Minneapolis, MN) in the management of heart failure. This investigational device allows remote monitoring of right ventricular systolic and diastolic pressure, estimated pulmonary artery pressures, and many other hemodynamic variables.

The study included 274 patients with New York Heart Association (NYHA) class III or IV heart failure. All patients had the device implanted, but data collected by the device were shared with the treating physician to guide therapy for only half of the patients ("full-access" group); the other half (control group) received usual care. The primary end-

point was the need for treatment for heart failure decompensation.

Results of the COMPASS-HF trial were presented at the 2005 scientific session of the American College of Cardiology.[2] There was no statistically significant difference in the primary endpoint between the groups at 6 months, but post hoc analysis revealed a significant reduction in heart failure–related hospitalizations in the full-access group compared with the control group (relative risk = 0.79; 95% confidence interval [CI], 0.64 to 0.98; $P = .029$). The benefit in avoiding hospitalization was limited to patients with class III heart failure. Although these pot hoc findings must be considered only hypothesis-generating, they suggest considerable promise for the utility of an implantable hemodynamic monitor.

Additional investigational devices for remote hemodynamic monitoring have not yet been assessed in large clinical trials, although studies are planned or under way.

Impedance and hemodynamic monitors may allow proactive monitoring of fluid status

Impedance cardiography. Another area of hemodynamic monitoring involves measurement of impedance, or the resistance of tissue to an electrical current. Impedance cardiography is a noninvasive means of obtaining continuous measurements of hemodynamic data based on the notion that variation in the impedance to flow of a high-frequency, low-magnitude alternating current across the thorax generates a measured waveform from which hemodynamic measures can be calculated. Interest has arisen in the use of impedance cardiography to estimate thoracic body fluid status or total fluid volumes.

Several impedance cardiographic monitors are now commercially available, each with its own algorithm. However, a lack of standardized definitions and the many potential confounders have posed challenges to broad application of impedance cardiographic monitoring in the clinical setting.

Promising results for the predictive utility of impedance cardiography in patients with heart failure were reported from the prospective PREDICT study of 212 patients who had had an episode of decompensated heart failure in the preceding 3 months.[3] Every 2 weeks for 6 months, blinded impedance cardiographic and clinical variables were collected from all patients; the BioZ ICG Monitor (CardioDynamics, San Diego, CA) was used for assessment of impedance. In multivariate regression analysis that included numerous baseline and clinical variables, a composite impedance score emerged as the strongest predictor of a heart failure event (all-cause death or a heart-failure–related hospitalization or emergency room visit) in the 14 days after any given study visit ($P < .0002$). Visits at which patients had a high-risk impedance score were 7.7 times more likely to be followed by a heart failure event within 14 days than were visits at which patients had a low-risk impedance score (95% CI, 5.5 to 10.4). This significant predictive ability of impedance cardiography extended to 90 days after a study visit. These preliminary results are the basis of a larger pivotal trial (PREVENT-HF) that is commencing in 2006.

New device-based impedance measurements have provided a more consistent assessment of intrathoracic impedance (InSync Sentry CRT-D, Medtronic, Inc.). In the MID-HeFT study of 33 patients with NYHA class III or IV heart failure, intrathoracic impedance was inversely correlated with pulmonary capillary wedge pressure and fluid balance and decreased up to 1 to 2 weeks prior to hospital admission for fluid overload.[4] Figure 2 illustrates the algorithm used by the device employed in this study.

In the future, it is conceivable that physicians and patients will be able to monitor fluid status in a manner analogous to self-monitoring of glucose or blood pressure levels. How well impedance data may guide therapy is currently unknown but will be assessed in upcoming trials.

Use of biomarkers

The other major front in hastening the detection of impending decompensation involves the use of novel biomarkers to assess cardiac and renal distress prior to organ damage. These biomarkers include those that signify cardiac distress, such as B-type natriuretic peptide (BNP) and troponin, and those that signify renal distress, such as cystatin C.

BNP is a polypeptide secreted by the heart's ventricles in response to myocyte

stress. It is a useful cardiac marker in a number of heart failure settings, as it has demonstrated diagnostic utility in acute dyspnea,[5,6] prognostic value in patients with chronic congestive heart failure and systolic dysfunction in the outpatient setting,[7–9] and prognostic value following discharge after hospitalization for severe decompensation.[10]

Interest also has arisen in a potential role for BNP-guided therapy in patients with chronic heart failure. Data from a small preliminary randomized trial showed that BNP-guided treatment of heart failure reduced the incidence of total cardiovascular events and delayed the time to a first event compared with intensive therapy guided by standard clinical assessment.[11] Several large, prospective outcomes trials are now under way or are being planned to further define the potential role of BNP-guided therapy in chronic heart failure.

Although BNP-guided therapy holds promise, it presents several challenges. First, the several BNP assays that are now commercially available show variation in their measurement of absolute BNP levels, with variances of as much as 30 pg/mL between different assays despite similar diagnostic performance.[12] Such variation means that any BNP-guided approach to therapy would have to ensure consistent use of the same assay in all treatment and laboratory settings or the harmonization of values from different assays. Second, there is the potential for confusion, particularly among clinicians, between BNP and the inactive compound N-terminal pro-BNP, levels of which may be much higher than BNP levels without causing concern. Finally, findings from recent small studies indicate that the potential utility of BNP levels in guiding therapy requires further investigation. In a retrospective study of 39 patients with severe heart failure, O'Neill and colleagues found that BNP levels did not accurately or consistently predict serial hemodynamic changes.[13] In a pilot study of 10 men hospitalized for pulmonary catheter–guided treatment of congestive heart failure, James and colleagues found that changes in blood volume do not correlate well with changes in BNP.[14]

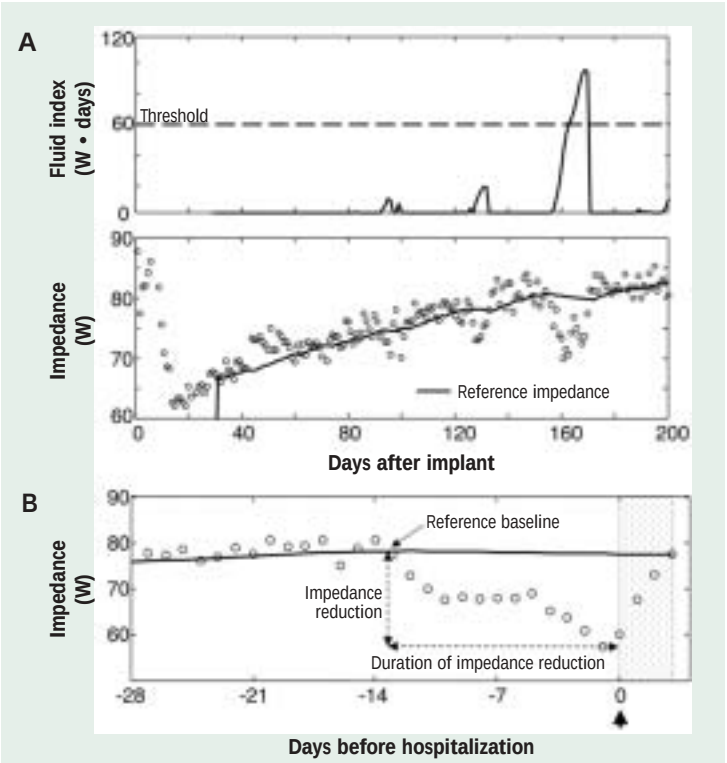

FIGURE 2. (A) Operation of an algorithm for detecting decreases in impedance over time. A fluid index (top panel) is calculated from differences between measured impedance (circles) and reference impedance (solid line) accumulated over time (second panel). Threshold is then applied to fluid index to detect sustained decreases in impedance. (B) Example of impedance reduction before heart failure hospitalization (day 0; arrow) for fluid overload and impedance increase during intensive diuresis during hospitalization (shaded portion). Reprinted, with permission, from reference 4.

Troponin T is a protein component of thin myofilaments that is released with myocyte damage. In addition to utility for the diagnosis of coronary artery disease and myocardial infarction, cardiac troponin T levels have been shown to predict prognosis in patients with decompensated heart failure. In a study of 84 patients with acute cardiogenic pulmonary edema, Perna and colleagues found that a troponin T level of 0.1 ng/mL or greater was associated with a significant reduction in 3-year survival (29% vs 76% in patients with levels < 0.1 ng/mL; $P <$ .001) and was a powerful independent predictor of mortality.[15] The mechanism of troponin T elevation in this setting is not well understood, and further studies are needed to better define both its specific clinical utility in this context and the variations among different commercially available assays observed specifically in the setting of heart failure.

Cystatin C is a novel marker of glomerular filtration rate whose emergence in the heart failure literature underscores the interrelationship between the kidney and the heart in heart failure progression. Cystatin C is a cysteine protease inhibitor that is produced by all nucleated cells. Its production is stable and serum levels are independent of body mass. Unlike creatinine, cystatin C is not cleared; it is freely filtered by the glomerular membrane and then metabolized by the kidneys.

An elevation in serum cystatin C has been shown to be an independent predictor of cardiac events in patients with heart failure.[16] In fact, the Cardiovascular Heart Study has demonstrated that cystatin C is superior to creatinine both in predicting incident heart failure in the elderly and in predicting mortality in elderly patients with heart failure.[17,18] Although the mechanism by which cystatin C predicts risk for heart failure or progression of heart failure is unclear, this biomarker holds considerable promise for improving risk stratification and guiding therapy.

Cystatin C is superior to creatinine in predicting mortality in heart failure

IMPROVING STRATEGIES TO LIMIT CARDIORENAL COMPROMISE

In addition to earlier detection of decompensation, other approaches and therapies are emerging to help us avert or better manage edema and renal insufficiency in heart failure.

Diuretic-sparing strategy

The previous articles in this supplement have detailed the rationale for diuretic therapy in heart failure as well as the adverse effects, both electrolytic and metabolic, of diuretic therapy in this setting. Most concerning is the finding that chronic therapy with a non–potassium-sparing diuretic raises the risk of arrhythmic death and all-cause death in patients with heart failure, as demonstrated in the SOLVD database[19] and other heart failure data sets.[20]

Although these analyses did not show such an increase with the use of potassium-sparing diuretics,[19,20] they underscore whether it might make sense to forgo diuretic therapy in some patients to reduce their risk of developing renal dysfunction. More than a decade ago, Grinstead and colleagues demonstrated that diuretic therapy can be safely discontinued in approximately 30% of patients with stable heart failure.[21] As more and more patients are managed with neurohormonal antagonists, this "peeling off" of chronic diuretic therapy may be increasingly worthy of consideration.

New drug classes

A diuretic-sparing approach is likely to be more feasible as additional drug classes emerge. Two novel classes have shown recent progress in development for heart failure management.

Adenosine type 1 (A_1) receptor antagonists promote excretion of excess fluid and sodium in animals and humans without major changes in glomerular filtration. These effects have been confirmed in patients with congestive heart failure.[22] Several A_1 receptor antagonists are in development for various indications (including KW-3902, from NovaCardia, Inc.; and BG-9928, from Biogen Idec), with several clinical trials under way for their use in heart failure.

Vasopressin receptor antagonists. Development of vasopressin receptor antagonists was prompted by the realization that levels of arginine vasopressin are elevated in heart failure and are believed to result in myocardial hypertrophy and vasoconstriction as well as water retention and hyponatremia. These agents offer the promise of preventing left ventricular dysfunction while also yielding an acute improvement in congestion and hyponatremia. As detailed by Gheorghiade later in this supplement,[23] a number of trials of vasopressin receptor antagonists in heart failure have been reported or are under way.

New devices and nondrug interventions

The most important nonpharmacologic advances in managing edema and renal insufficiency include ultrafiltration and targeted renal therapy, which were detailed by Francis earlier in this supplement.[24] In addition, highly invasive modalities such as continuous aortic flow augmentation[25] are being investigated for use in the intensive care unit for patients with severely acute decompensation and other complications.

SUMMARY

Current strategies that aim to "salvage" deteriorating clinical status in patients with heart failure are inadequate, largely because

we do not understand the optimal targets of therapy and we have not had effective ways to proactively detect edema and renal insufficiency. New devices and the use of biomarkers show promise, however, for improving our ability to monitor for and avert edema and renal insufficiency. Simultaneously, novel drug classes and emerging nonpharmacologic therapies offer the potential to reduce the use of diuretic therapy and manage heart failure with less renal compromise.

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'Peeling off' chronic diuretic therapy may be increasingly worth considering

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Vasopressin receptor antagonists: Mechanisms of action and potential effects in heart failure

ABSTRACT

Increased arginine vasopressin (AVP) secretion in heart failure may lead to vasoconstriction, left ventricular remodeling, and water retention—actions that promote afterload, preload, and hyponatremia and thereby cause disease progression. Interfering with AVP-mediated signaling pharmacologically may be beneficial in heart failure. Selective antagonism of the vasopressin 2 (V_2) receptor may facilitate a safe diuresis and normalize low serum sodium levels, as demonstrated in preliminary clinical trials. Pure V_2 antagonism, however, may stimulate AVP secretion and enhance V_{1a} signaling, while pure V_{1a} receptor antagonism may lead to unwanted V_2 stimulation and secondary water retention and volume expansion. Combined V_{1a} and V_2 receptor antagonism could potentially prove advantageous as a therapy for heart failure by acting synergistically to facilitate diuresis and improve hemodynamics.

KEY POINTS

AVP has multiple actions, mediated through the V_{1a} and V_2 receptors, which could contribute to heart failure progression.

Interfering with AVP signaling may have clinical benefits in acute and chronic heart failure.

Facilitation of diuresis, a safe diuresis, and normalization of serum sodium are potential mechanisms of benefit of V_2 antagonism in heart failure.

Combined V_{1a} and V_2 antagonism has theoretic advantages as a therapeutic strategy, including synergy in improving hemodynamics, but this strategy needs to be tested clinically.

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AN UNDERSTANDING OF the imbalances in the neurohormonal axis has prompted the greatest insights into the pathophysiology and treatment of heart failure to date. From a cardiorenal perspective, neurohormonal imbalances drive much of the sodium and water retention in this disease. These imbalances also contribute to abnormal loading conditions that predispose to a deterioration in hemodynamics and circulatory abnormalities. Even when volume is controlled, neurohormonal imbalances drive cellular and molecular processes that cause progression of this syndrome.

Therapy for heart failure today is built around interfering with two neurohormonal systems—the renin-angiotensin system and the sympathetic nervous system—with the addition of diuretics as needed for reducing volume expansion. Efforts to further exploit this neurohormonal approach may be warranted. Specifically, the possible contribution of the nonapeptide arginine vasopressin (AVP) to heart failure progression has recently been appreciated. This article reviews the actions of AVP and the evidence for AVP signaling in heart failure, and explores the therapeutic potential of interference with AVP signaling.

MECHANISMS FOR DISEASE PROGRESSION

Distinct load-dependent and load-independent mechanisms are responsible for disease progression in heart failure. The load-dependent mechanisms involve diastolic wall stress (eccentric hypertrophy) and systolic wall stress (concentric hypertrophy). The load-independent mechanisms come into play because of direct stimulation of processes at the cellular and intracellular level. The various neurohormones implicated in heart failure can contribute to disease progression by all of these mechanisms.

Actions of AVP in heart failure

AVP may contribute to heart failure through several mechanisms because AVP has a complicated set of receptor systems (Table 1). The major actions of AVP in heart failure are mediated through the vasopressin 1a (V_{1a}) and vasopressin 2 (V_2) receptors.

Consequences of V_{1a} activation. The V_{1a} receptor is located on blood vessels and in the myocardium. It is a classic G-protein–coupled receptor, increasing intracellular calcium through the IP3 pathway. Its intracellular signaling pathway is similar to that of angiotensin II and the alpha-adrenergic portion of the sympathetic nervous system. The predictable consequences of V_{1a} activation are vasoconstriction (other than endothelin, it is the most potent vasoconstrictor in the body) and inotropic and mitogenic effects.

Consequences of V_2 activation. The V_2 receptor, located primarily on the renal tubule, is the receptor that governs water retention. When V_2 receptors are activated, they change the expression of aquaporin channels in the renal collecting duct. The aquaporin channels translocate and then render the tubule more permeable to water so that water is retained. V_2 receptors are also present on the endothelium and are linked in a complicated way to secretion of von Willebrand factor, so V_2 receptors may contribute to hemostasis. Evidence is unequivocal that the V_2 receptor also has an endothelium-dependent vasodilatory function. This function is not observed in normal humans until plasma AVP reaches fairly high levels; the plasma levels of AVP at which V_2 receptors exert this action in patients with heart failure or in the presence of neuorhormonal blockade is unknown.

AVP signaling

In linking what is known about AVP signaling to potential progression of heart failure, AVP through the V_{1a} receptor could cause vasoconstriction, increase afterload, and thereby contribute to left ventricular (LV) remodeling and disease progression. AVP could also contribute to LV remodeling and disease progression directly through V_{1a} receptor activation. By triggering water retention, AVP stimulation of the V_2 receptor could exacerbate preload, which could also lead to adverse LV remodeling and disease progression. Another mechanism by which AVP could lead to disease progression is its possible contribution to hyponatremia.

TABLE 1

Actions of vasopressin

RECEPTOR	SIGNALING	LOCATION	ACTIONS
V_{1a}	G-protein-coupled; IP3 activation; raises intracellular Ca^{++}	Blood vessels	Vasoconstriction
		Myocardium	Inotrope/mitogen
V_2	Adenyl cyclase	Renal tubule	H_2O retention
		Endothelium	Hemostasis
			Vasodilation (high levels)

The evidence for V_{1a} signaling in heart failure is the hemodynamic benefit achieved with acute and short-term V_{1a} antagonism in numerous animal models of congestive heart failure. The human data are extremely limited, however, and V_{1a} signaling may not be adequate for an effect to be observed in all settings.

Infusions of AVP in patients with chronic congestive heart failure produce hemodynamic deterioration (decrease in cardiac output and increase in systemic vascular resistance) with small changes in plasma AVP.[1] This effect is presumably mediated by the V_{1a} receptor, which causes vasoconstriction and deterioration of LV function. Early work by Creager et al with an intravenous (IV) AVP antagonist showed a drop in systemic vascular resistance in patients with heart failure following V_1 antagonism.[2] Because these studies were performed in the 1980s, neither was conducted over a background of current standard therapy for heart failure, although other experimental evidence points to V_{1a} signaling being *more* potent in the presence of other neurohormonal blockade.

AVP has a mitogenic effect that could potentially contribute to remodeling. Stimulation of the V_{1a} receptor directly induces hypertrophic growth of neonatal myocytes in rat heart cells.[3]

By triggering water retention, V_2 receptor stimulation could exacerbate preload

THERAPEUTIC POTENTIAL

No pure V_{1a} receptor antagonists are under development because competitive antagonism of the V_{1a} receptor alone may lead to unwanted V_2 stimulation and secondary

TABLE 2

Predictive value of hyponatremia in patients hospitalized with heart failure*

	HYPONATREMIC PATIENTS (n = 256)	NORMONATREMIC PATIENTS (n = 687)	P
60-day mortality (%)	16	7	.0001†
Readmission or death within 60 days (%)	42	33	.017

From the OPTIME-CHF trial.[7]

* Hyponatremia defined as serum sodium ≤ 136 mEq/L at study baseline.

† Log-rank statistic.

water retention and volume expansion.

As noted, the V_2 receptor is linked to water retention, expansion of preload, diastolic wall stress, and ventricular remodeling. Unlike with the V_{1a} receptor, evidence is plentiful for the potential of V_2 receptor antagonism in heart failure. All antagonists of the V_2 receptor—tolvaptan, lixivaptan, and conivaptan—produce effective aquaresis and weight loss. Gheorghiade and colleagues demonstrated a significant net loss in volume with tolvaptan compared with placebo during hospitalization in patients admitted with worsening heart failure.[4] Regardless of AVP levels in heart failure, interfering with V_2 signaling produces an aquaresis, making it theoretically possible that V_2 receptor antagonists would be useful to relieve congestion.

AVP has a mitogenic effect that potentially contributes to remodeling

SHORTCOMINGS OF LOOP DIURETICS IN HEART FAILURE

Inefficient congestion relief. As reviewed in previous articles in this supplement, loop diuretics, the current standard of therapy to relieve congestion, are ineffective and inefficient, especially in patients with severe heart failure or renal dysfunction.

Neurohormonal stimulation. Loop diuretics also activate the same neurohormonal forces that chronic heart failure treatment is designed to inhibit.

Administration of loop diuretics has clearly been shown to activate neurohormones, both acutely and chronically, in patients with congestive heart failure. In animal studies, these drugs have the same effect; by comparison, administration of tolvaptan was not associated with this degree of neurohormonal activation, and attenuated that seen with furosemide when given together with this agent.[5] In heart failure, this "neurohormonal-sparing effect" could be important, if it can be demonstrated in patients.

Heart failure exacerbation. Data from an animal model indicate that excessive reliance on loop diuretics can exacerbate experimental heart failure.[6] In this study, animals with pacing-induced heart failure that were given furosemide had worse ventricular function and an acceleration of death compared with animals not given furosemide, despite relief of congestion and reduction of body weight with furosemide. The cause of death was not sudden death due to electrolyte depletion but a worsening of heart failure, as evidenced by the shortened time to left ventricular dysfunction in the furosemide group.

V_2 receptor antagonism in patients with heart failure may therefore have the benefit of a facilitated diuresis, leading to enhanced preload reduction, reduced wall stress, and diminished remodeling stimuli, assuming these effects can be demonstrated with long-term treatment.

HYPONATREMIA AND OUTCOMES

Hyponatremia is a marker for poor outcome in heart failure. Among heart failure patients treated with angiotensin-converting enzyme (ACE) inhibitors, diuretics, and beta-blockers, even a small decline in serum sodium levels, to 136 mEq/L or less, was associated with more than twice the risk of 60-day mortality and a significant increase in risk of readmission or death within 60 days compared with serum sodium levels greater than 136 mEq/L (Table 2).[7]

In a study of patients with end-stage heart failure, Italian investigators attempted to isolate the effect of an increase in serum sodium on clinical outcome.[8] They randomized 107 patients with refractory heart failure to receive an IV infusion of furosemide plus hypertonic saline solution 3% or an IV bolus of furosemide twice a day without hypertonic saline. Survival over a mean follow-up of 31 months was 55% in the group that received hypertonic saline compared with 13% in those that did

not receive hypertonic saline ($P < .001$). This suggests that normalization of a low serum sodium may be another potential mechanism of benefit of V_2 antagonism in heart failure.

The benefits of pure V_2 antagonism, however, may come at a cost of stimulation of AVP secretion in response to rising plasma osmolality and an unwanted enhancement of V_{1a} signaling.

COMBINED V_{1a}/V_2 ANTAGONISM

Combined antagonism of the V_{1a} and V_2 receptors may be a way to overcome some of the disadvantages with pure antagonism of either the V_{1a} or V_2 receptor. The data are encouraging in the preclinical setting and in the acute clinical setting, but are lacking with chronic therapy.

Conivaptan is a combined V_{1a}/V_2 receptor antagonist. Although it is orally and intravenously active, only the IV form is being developed and released. Conivaptan has been approved by the US Food and Drug Administration for treatment of euvolemic hyponatremia, making it the first AVP receptor antagonist to gain US marketing approval. A Phase 2 pilot study of conivaptan for treatment of acute congestive heart failure has been completed; data release is scheduled for late 2006.

Hemodynamics of combined antagonists. In an experimental model of heart failure, combining a V_{1a} antagonist with a V_2 antagonist produced a synergistic effect in terms of increasing cardiac output and reducing systemic vascular resistance.[9] This study offered early evidence that combined V_{1a} and V_2 antagonism could result in more beneficial hemodynamic responses than a V_{1a} antagonist alone.

Potential synergy with ACE inhibition. In rats with experimental myocardial infarction, V_{1a}/V_2 receptor antagonism with conivaptan given concomitantly with the ACE inhibitor captopril had a synergistic effect on reducing systolic blood pressure at 1 week.[10] This effect may represent an interruption of V_{1a} signaling if blood pressure is considered a surrogate for V_{1a} signaling. Combined therapy also led to a significant reduction in right ventricular weight as an index of remodeling, which probably represents a blocking of V_2 signaling. These data suggest a potentially clinically meaningful effect on right ventricular compensation with the combination of ACE inhibition and dual V_{1a}/V_2 receptor antagonism.

CONCLUSIONS

AVP clearly has multiple actions that could contribute to the progression of heart failure. Interfering with the V_{1a} and/or the V_2 receptor-mediated actions of AVP could therefore be expected to be beneficial in the treatment of acute and chronic heart failure. Selective interference with only one set of receptors, however, could in theory trigger counterproductive increased signaling at the other sites. Combined V_{1a} and V_2 antagonism might therefore be preferable as a therapeutic strategy, especially in the chronic setting, but this hypothesis has yet to be tested clinically.

Evidence is plentiful for the potential of V_2 receptor antagonism in heart failure

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The clinical effects of vasopressin receptor antagonists in heart failure

ABSTRACT

The neurohormone arginine vasopressin (AVP) is a promising target in the treatment of heart failure because AVP promotes congestion and hyponatremia, each of which is associated with poor outcomes. Diuretics are standard therapy for heart failure, but they have several limitations, including worsening renal function and hyponatremia. Blocking AVP leads to effective aquaresis, improvements in hemodynamics and renal function parameters, weight loss, and normalization of serum sodium, without changes in blood pressure or heart rate. In placebo-controlled trials in the inpatient and outpatient setting, the AVP receptor antagonist tolvaptan reduced body weight and edema and normalized serum sodium in patients with heart failure.

KEY POINTS

Arginine vasopressin (AVP) is activated in heart failure. Among its many deleterious effects, elevated levels of AVP lead to congestion and hyponatremia.

Hyponatremia, even when mild, is associated with an increase in mortality in patients with heart failure.

Congestion is responsible for most hospital admissions and readmissions in patients with heart failure.

Antagonists of AVP produce an acute improvement in congestion and hyponatremia. Weight loss and increases in serum sodium with AVP receptor antagonists are sustained.

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OF THE MANY neurohormonal modulators that are activated in heart failure, arginine vasopressin (AVP) is unique in that it promotes water retention, sodium retention, and congestion.[1] An antagonist of AVP may therefore address important problems in heart failure.

The rationale for the use of AVP receptor antagonists in heart failure is threefold. First, congestion is an important target for therapy in patients with heart failure because it represents the leading cause of hospitalization and rehospitalization in this population. Second, diuretic therapy has important limitations. Finally, mild hyponatremia is common and is a major predictor of outcome in patients hospitalized with heart failure.

This article examines in detail this rationale for the role of AVP receptor antagonism in heart failure therapy and reviews available clinical studies of the utility of AVP antagonists in patients with chronic or acute heart failure.

ADMISSIONS AND READMISSIONS ARE FREQUENT

In the United States, a primary diagnosis of heart failure is responsible for 1 million hospital admissions per year, and a primary or secondary diagnosis of heart failure is implicated in 3 million admissions.[2] Even more striking is the postdischarge event rate associated with a heart failure hospitalization: 35% of patients die or are readmitted within 60 days of a hospitalization for heart failure.[2] No other common medical syndrome is associated with such a high mortality and rehospitalization rate.

Approximately 80% of patients hospitalized with heart failure are admitted for worsening chronic heart failure.[2] The main reason for their hospitalization is systemic congestion, as

evidenced by a high rate of dyspnea, rales, and peripheral edema at presentation. Less than 5% have low cardiac output on admission.[2]

Congestion contributes to heart failure progression

Although the primary cause of hospital admissions and readmissions in heart failure patients is congestion, more than 50% of patients have little or no weight loss during hospitalization.[3] What is often not recognized is that hemodynamic congestion, defined as a high left ventricular (LV) filling pressure, may contribute to the progression of heart failure. Among the potential deleterious effects of congestion in heart failure are the following[4]:

- LV remodeling, resulting in increased afterload (wall stress) and worsening mitral regurgitation
- Increased pulmonary artery/renal artery pressure
- Neurohormonal activation
- Subendocardial ischemia and cell death by necrosis and/or apoptosis
- Changes in extracellular matrix structure and function
- Progression of LV dysfunction
- Impaired cardiac drainage from coronary veins (diastolic dysfunction)
- A lower threshold for arrhythmias.

DIURETICS HAVE SEVERAL SHORTCOMINGS

Currently, diuretics are the only therapy in chronic heart failure to reduce fluid overload that results in congestion. Although rapid symptomatic improvement and a decrease in volume overload are observed with diuretic therapy for the acute heart failure syndrome, an alternative to diuretics would be welcome given that diuretic therapy also has several disadvantages. Among these are increased neurohormonal activation, worsening renal function, and electrolyte disturbances.

Hyponatremia as a prognostic predictor

Decreased serum sodium osmolality is one of the electrolyte disturbances caused by diuretic therapy. Even a minor decrease in serum sodium predicts prognosis: in hospitalized patients, each 3-mEq decrease in serum sodium is associated with a 20% increase in mortality within 60 days.[5] These findings were confirmed by the large Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) database (Figure 1), which also revealed that hyponatremia retains its predictive value regardless of whether patients have systolic or diastolic heart failure.[6]

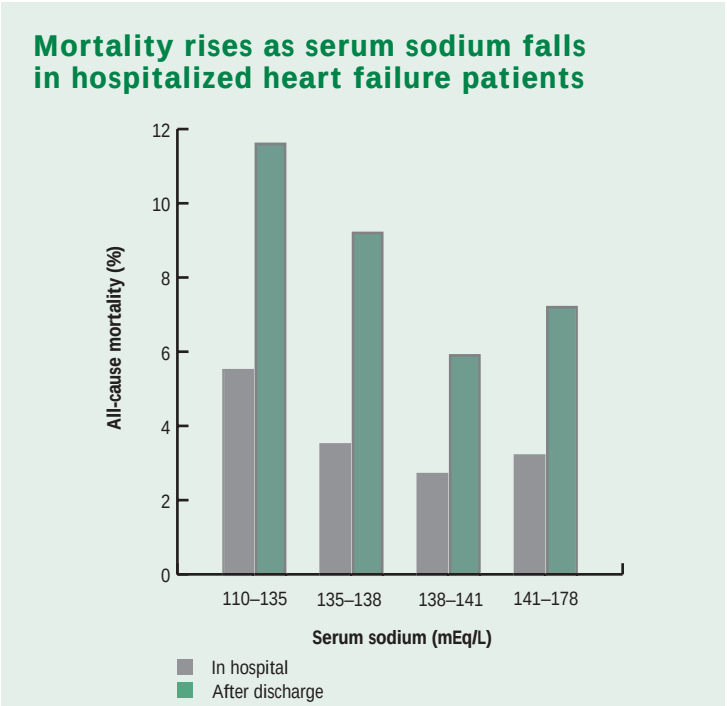

FIGURE 1. The OPTIMIZE-HF database of 48,612 patients hospitalized for heart failure reveals that all-cause mortality, both during the hospitalization and after discharge, increases as serum sodium levels decline. Data from reference 6.

These data are noteworthy because 25% of patients admitted with chronic heart failure have a mild degree of hyponatremia (< 135 mEq/L).[5]

Increasing serum sodium during the hospitalization improves outcomes; an increase in serum sodium of 2 mEq/L or greater is associated with a 14% relative reduction in the risk of mortality at 60 days compared with no change in serum sodium.[7]

BLOCKING AVP

AVP is a nonapeptide hormone synthesized in the hypothalamus. The two distinctive types of AVP receptors are the vasopressin 1 (V_1) and vasopressin 2 (V_2) receptors. The V_1 receptor mediates vasoconstriction and

AVP antagonism exerts favorable hemodynamic effects

This figure reprinted from reference 8. Permission not granted to reprint this figure online.

Please see original source figure (figure 2A) in: *Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 2001; 104:2417–2423.*

FIGURE 2. A single intravenous dose of conivaptan 20 mg or 40 mg resulted in an improvement in pulmonary capillary wedge pressure (PCWP) in patients with advanced heart failure.

mitogenesis in the vascular smooth muscle cells; the V_2 receptor mediates the effect of AVP in water excretion. Administration of an AVP receptor antagonist results in aquaresis without activation of plasma neurohormones. The main site of action for the aquaretic effects of AVP receptor antagonists is the V_2 receptor.

Three orally active AVP receptor antagonists have been developed or are under development. Conivaptan is a dual V_1/V_2 receptor antagonist. Tolvaptan and lixivaptan are selective for the V_2 receptor in the principal cells of the renal collecting duct.

To date, two of the AVP receptor antagonists have been studied in human heart failure. Conivaptan has been evaluated in a short-term hemodynamic study, and tolvaptan has been evaluated for acute and longer-term treatment of heart failure in inpatient and outpatient settings.

Favorable hemodynamic changes

Favorable changes in hemodynamics have resulted from AVP receptor antagonism. Udelson et al[8] showed that blocking AVP with the dual V_1/V_2 receptor antagonist conivaptan in patients with advanced heart failure caused a significant decrease in pulmonary capillary wedge pressure (Figure 2) with no significant effect on cardiac index, blood pressure, pulmonary vascular resistance, systemic vascular resistance, or heart rate.

Positive effects on renal physiology

In a direct comparison with the diuretic furosemide in patients with congestive heart failure, the V_2 receptor antagonist tolvaptan increased effective renal plasma flow, renal blood flow, and glomerular filtration rate (GFR).[9] Significant sodium excretion occurs with furosemide but not with tolvaptan administration. These data suggest that furosemide produces negative effects on renal physiology, whereas tolvaptan, acting via a more physiologic mechanism, increases urine production without reductions in renal blood flow and GFR.

Weight loss promotion

In a comparison in patients with heart failure, tolvaptan and furosemide independently contributed to a decrease in body weight at 8 days.[10]

Normalization of serum sodium

In a small, randomized study of patients with hyponatremia (serum sodium < 135 mEq/L), a significant improvement or normalization of serum sodium was observed in the patients assigned to tolvaptan, whereas those randomized to fluid restriction had no significant change in serum sodium levels.[11]

CLINICAL TRIALS IN OUTPATIENTS WITH HEART FAILURE

Tolvaptan was studied in a double-blind, randomized trial of 254 patients with mild systolic or diastolic heart failure who were receiving standard heart failure therapy (ie, diuretic, angiotensin-converting enzyme inhibitor, digoxin, beta-blocker).[12]

After a run-in period, the patients were randomized to 25 days of placebo or one of three doses of tolvaptan (30, 45, or 60 mg/day).

Early and sustained weight loss

At day 1, patients randomized to tolvaptan had decreases in body weight from 0.79 to 0.96 kg from baseline, compared with an increase of 0.32 kg in those assigned to placebo ($P < .001$ for all treatment groups vs place-

bo). The decrease in body weight in patients randomized to tolvaptan was maintained throughout the 25 days.[12]

No change in blood pressure

Unlike other neurohormonal modulators, tolvaptan had no effect on blood pressure.[12] This finding is advantageous because a decrease in blood pressure is one of the most important predictors of a poor outcome in patients hospitalized with acute heart failure [M. Gheorghiade, unpublished pooled data].

Serum sodium change dependent on baseline level

The most common adverse events with tolvaptan in this trial[12] were polyuria, urinary frequency, and thirst. Across the three dose groups, tolvaptan produced a small transient increase in serum sodium, with a differential response according to baseline serum sodium level. Patients with hyponatremia (mean serum sodium < 136 mEq/L) experienced a significant increase in serum sodium starting at day 1, and this increase was maintained throughout the 25-day study period (Figure 3). In contrast, in normonatremic patients (mean baseline serum sodium ≥ 136 mEq/L), serum sodium levels returned to their prerandomization levels following an increase on day 1.

No evidence of remodeling

Tolvaptan had no effect on LV remodeling in another recent double-blind, placebo-controlled outpatient study of 240 subjects with mild to moderate chronic heart failure.[13] No significant changes in ejection fraction or LV end diastolic or LV end systolic volume occurred in response to 30 mg/day of tolvaptan. A post hoc analysis showed that the addition of tolvaptan to standard heart failure therapy reduced mortality and the incidence of worsening heart failure compared with placebo (P = .027), although the effect of therapy on these clinical endpoints was not part of the study design.

CLINICAL TRIAL IN ACUTE HEART FAILURE SYNDROME

The effect of tolvaptan in addition to optimal medical therapy was examined in 319 hospitalized patients with exacerbation of known systolic heart failure and fluid overload despite standard therapy.[14] Within 72 hours, patients were randomized to standard therapy plus placebo or standard therapy plus one of three doses (30, 60, or 90 mg/day) of tolvaptan. Treatment was intended to continue in the outpatient setting, for up to 60 days total, but 77 of the patients discontinued outpatient study participation. The most robust data, therefore, come from the in-hospital course of therapy.

In hospitalized patients, each 3-mEq decrease in serum sodium is associated with a 20% increase in 60-day mortality

The primary endpoint was body weight change at 24 hours. The median body weight at 24 hours decreased by approximately 2 kg in the tolvaptan groups compared with 0.60 kg in the placebo group ($P \leq .008$ for all tolvaptan groups vs placebo). The change in body weight with tolvaptan was not dose-dependent and was sustained throughout the hospitalization (Figure 4).[14]

Decrease in signs of congestion

At the time of discharge, fewer patients treated with tolvaptan had dyspnea, jugular venous distention, and edema compared with placebo recipients, but only the difference in dyspnea reached statistical significance (P = .04).[14]

Favorable safety profile

As in the outpatient study discussed above,[12] there were no changes in blood pressure,

AVP antagonism rapidly raises serum sodium in hyponatremic patients

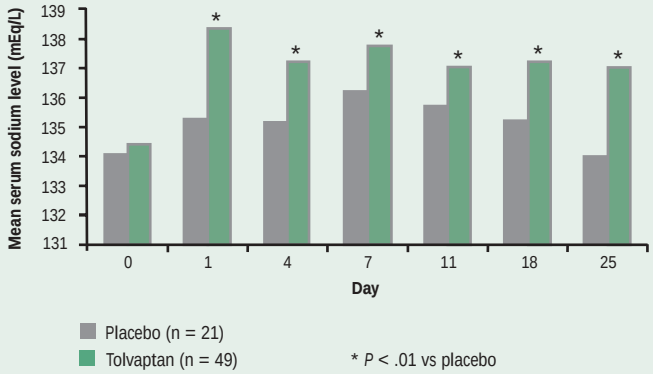

FIGURE 3. In chronic heart failure patients with hyponatremia (mean serum sodium levels < 136 mEq/L), tolvaptan improved serum sodium levels starting on day 1, an improvement that was sustained over the 25-day duration of the study. Tolvaptan results are pooled from the study's three dose groups (30, 45, and 60 mg/day). Data from reference 12.

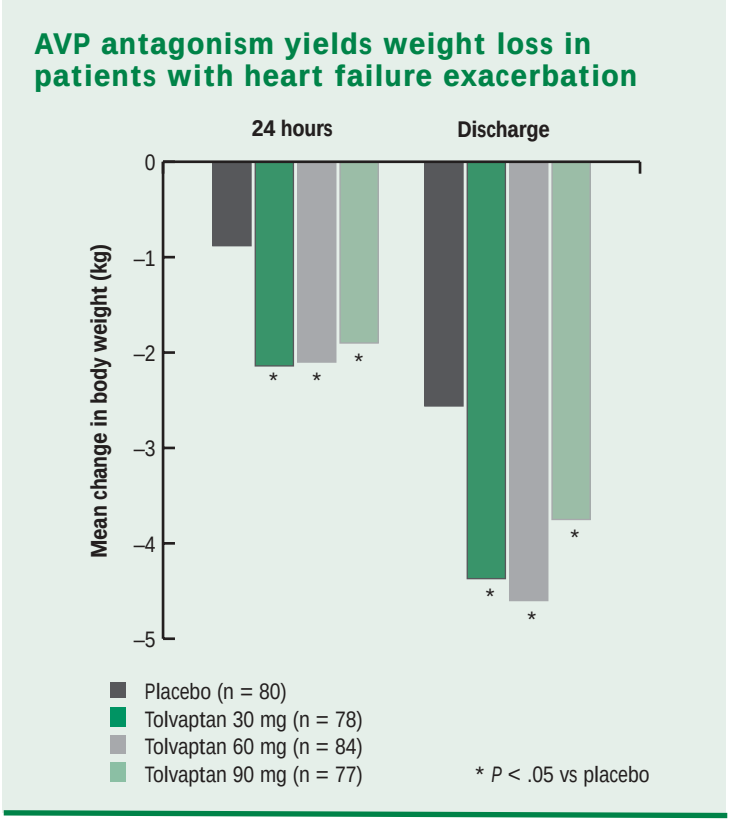

FIGURE 4. In patients hospitalized with a heart failure exacerbation, tolvaptan administration at any dose was associated with weight loss at 24 hours after administration, with further weight loss until discharge. Data from reference 14.

heart rate, serum creatinine levels, or blood urea nitrogen (BUN) levels in tolvaptan recipients in this inpatient trial, and serum potassium levels also remained unchanged despite the loss in body weight.[14]

Normalization of serum sodium is sustained

Also in accordance with the outpatient studies, serum sodium levels normalized within 1 day of initiating tolvaptan in the 30% of patients with hyponatremia (mean serum sodium ≤ 135 mEq/L) at randomization, and this normalization was sustained throughout the study.[14]

Decrease in mortality with elevated BUN, severe congestion

There were no differences between groups in in-hospital mortality or the incidence of worsening heart failure, defined as death, rehospitalization, or unscheduled visits for heart failure.[14]

A post hoc analysis uncovered a reduction in 60-day mortality in the combined tolvaptan groups compared with the placebo group among patients with elevated BUN levels (> 29 mg/dL) and among those with severe systemic congestion at randomization (defined as the presence of edema, dyspnea, and jugular venous distention). Although these differences reached statistical significance ($P < .05$), this post hoc analysis is useful only for generating hypotheses and requires confirmation in larger studies. Of note, all-cause mortality at 60 days was more than triple in patients with mild hyponatremia compared with normal serum sodium levels, was increased fivefold in patients with elevated vs normal levels of BUN, and was more than double in patients with severe congestion compared with patients without severe congestion.[14]

SUMMARY AND FUTURE RESEARCH

AVP receptor antagonists have many favorable properties compared with loop diuretics. Loop diuretics decrease serum sodium levels, serum potassium levels, plasma osmolality, renal blood flow, and GFR; may precipitate orthostatic hypotension; activate neurohormones such as norepinephrine and plasma renin; and may increase BUN/serum creatinine levels. In contrast, the V_2 receptor antagonist tolvaptan normalizes or improves serum sodium levels; has no effect on serum potassium levels, blood pressure, BUN/creatinine levels, and neurohormonal activity; increases plasma osmolality; and may increase renal blood flow and GFR. The increase in plasma osmolality may explain the enhanced diuresis with tolvaptan compared with loop diuretics.

The AVP receptor antagonist tolvaptan is the best-studied AVP receptor antagonist in heart failure to date. When added to standard therapy, it produces rapid and sustained decreases in body weight in hospitalized and ambulatory patients with congestive heart failure. Tolvaptan use is associated with normalization of serum sodium in patients with mild hyponatremia. The addition of tolvaptan did not cause acute or chronic changes in blood pressure, heart rate, serum potassium, BUN, or creatinine. There is no apparent dose effect among the three doses of tolvaptan tested (30, 60, and 90 mg/day).

Whether these encouraging changes in surrogate markers with AVP antagonist therapy will translate to improved clinical outcomes is being investigated in a multicenter, double-blind, placebo-controlled clinical trial involving more than 4,000 patients hospitalized with worsening congestive heart failure. Patients have been randomized to tolvaptan 30 mg/day or standard care for a minimum of 60 days, with the primary endpoints being time to all-cause mortality and time to cardiovascular mortality or hospitalization for heart failure.[15] Preliminary results are expected at the end of 2006.

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Serum sodium levels improved or normalized within 1 day of initiating tolvaptan, and these changes were sustained

Panel discussion

The symposium that formed the basis for this supplement included the following panel discussion in which the faculty fielded questions and comments from the audience.

Question from audience: What is the mechanism for progressive renal failure in patients who have persisting heart failure?

Dr. Domenic Sica: This is an interesting question and one with several possible answers.

First, heart failure and renal disease can have a common disease-state origin. For example, diabetes, diabetic nephropathy, and heart failure often coexist; if renal failure progresses in that setting, it can be on the basis of the diabetic nephropathy.

Second, urinary protein excretion tends to increase in the setting of advanced heart failure, and the degree of proteinuria accelerates the rate of renal functional decline.

Age-related GFR decline is accelerated in the presence of heart failure.
—Dr. Domenic Sica

A third consideration is that many heart failure patients have macrovascular disease, microvascular disease, or both. The impact of occlusive disease on renal perfusion, particularly at the low blood pressures seen in systolic forms of heart failure, can prove significant in patients prone to ischemic nephropathy.

Fourth, the cytokine and growth factor excess that marks heart failure also has the potential to act on the kidney; in so doing, it can promote glomerular and/or interstitial disease.

Advancing age is an additional determinant of a decline in kidney function. The rate of glomerular filtration rate (GFR) decline with aging in a patient with heart failure proves to be greater than the age-related decline in GFR in a person without heart failure. This is an important consideration in light of our ability to keep many heart failure patients alive for a longer period of time.

Question from audience: Although a reduction in cardiac output is proposed as the source for a reduced perfusion of the kidney, isn't elevation in central venous pressure and renal vein pressure at least as important?

Dr. Sica: I would agree that this is not simply a matter of reduced perfusion.

The role of an increase in renal vein pressure in determining the state of renal function and/or sodium retention is a complicated one in that it interplays with multiple other sodium-retaining stimuli. Renal venous pressure may prove to have its greatest applicability in preserved systolic forms of heart failure, in which the usual signals heralding salt and water retention (such as a reduction in cardiac output and a fall in blood pressure and renal perfusion) are not present. This is a fertile area for future investigation.

Dr. Mihai Gheorghiade: The model described by Dr. Sica implicates low cardiac output and/or systemic vasodilatation in reduced renal perfusion. However, the majority of patients admitted with heart failure do not have low cardiac output or vasodilatation. Nevertheless, their renal perfusion is diminished. Recently it has been demonstrated that high venous pressure may contribute independently to reduced renal perfusion. For this reason, I would emphasize the importance of treating a high venous pressure in itself, even in patients without low cardiac output.

Question from audience: What is the appropriate route of administration for diuretic therapy?

Dr. Steven Goldsmith: When patients are severely congested, you should give diuretics intravenously. We cannot tell from the Acute Decompensated Heart Failure National Registry (ADHERE) database whether there was a big difference in the response between intravenous (IV) or oral diuretic therapy, but the neurohormonal and electrolyte effects have been shown to occur with IV therapy.

Question from audience: What is your first choice of loop diuretic, and to which agent might you switch following a decline in renal function?

Dr. Goldsmith: My own bias is to use IV furosemide because it is inexpensive and it

usually works, but once the creatinine clearance declines to 30 or 40 mL/min, IV or oral torsemide may be preferable. I personally switch to torsemide when the renal function is down or for oral therapy if the patient is grossly congested because absorption is much better with torsemide.

Dr. Gary Francis: We do not have bumetanide on the formulary at the Cleveland Clinic, because it is too expensive. We do use a lot of torsemide, though.

Dr. Sica: Oral torsemide is an excellent choice in the treatment of volume overload in heart failure. First, not only is it almost completely absorbed but it is also quickly absorbed. This distinguishes it from furosemide, which is quite erratically absorbed on a day-to-day basis. Second, torsemide appears to have a modest anti-aldosterone effect. This is not seen with the other loop diuretics. The clinical significance of this property is unclear.

Question from audience: There is a concern that although vasopressin antagonism is beneficial because it will reduce volume, it does not reduce total body salt. Do you share this concern?

Dr. Goldsmith: Like anything else in heart failure, one size probably does not fit all. We give loop diuretics because they move salt out and water out with it. If the patient is hyponatremic, though, the sodium level drops further, so there is no question that the group at highest risk, based on everything we know, are volume-expanded hyponatremic patients. These are the patients in whom a vasopressin 2 receptor antagonist, with or without a vasopressin 1 receptor antagonist, would be likely to show the greatest benefit.

The other mechanisms come into play in patients with a normal level of serum sodium. We should have an answer to these questions once the results of the Efficacy of Vasopressin antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) are released. Whether or not the net balance in a normonatremic patient is positive or negative is going to be interesting to see. My guess is that if tolvaptan proves beneficial in EVEREST, even in the low- or normal-sodium patient, it will coincide with less loop diuretic use. If we could reduce the amount of loop diuretic by one half to three fourths and replace it with an effective aquaretic, we would remove some of the neurohormonal activation associated with loop diuretics.

Dr. Gheorghiade: In patients with a high wedge pressure, lowering the wedge pressure is important clinically. A drug, independent of its mechanism, that safely reduces the wedge pressure will be beneficial clinically. The discussion about the relative importance of reducing total body water and total body sodium is interesting, but from a clinical point of view the goal is to reduce the filling pressure and body weight.

Dr. Francis: I agree. It's about decongestion and not necessarily about improving forward flow.

Question from audience: A small segment of patients is receiving cardiac resynchronization therapy. What is the effect of that on deterioration or preservation of renal function in heart failure?

Dr. Francis: We have put in about 800 cardiac resynchronization devices, and about one third of patients improve, one third show no improvement, and one third get worse.

Improvement has been much more consistent now that we've been able to identify who is going to respond to biventricular pacing. So, if anything, I think that cardiac resynchronization tends to forestall the worsening of renal function, and there is now a demonstrated mortality benefit.

Question from audience: What role do hemodynamics play in the acute cardiorenal syndrome? Studies have shown that in advanced heart failure, renal blood flow correlated best with hemodynamics (ie, wedge pressure, pulmonary artery pressure, and right atrial pressure), not with cardiac output. Clinical observation indicates that acute deterioration of renal function in heart failure reflects hemodynamics. For example, the serum creatinine declines when acute mitral regurgitation or excessive bradycardia are corrected. Also, acute correction of severe anemia leads to a reduction in the creatinine level by 24 hours. Another probable factor is a diuretic response; for example, ultrafiltration, despite removal of

V_2 receptor antagonism is is likely to show the greatest benefit in volume-expanded patients with hyponatremia.
—Dr. Steven Goldsmith

the same amount of fluid, does not change kidney function unless the patient becomes hypovolemic. Third, hypotension that occurs during treatment, either from excessive diuresis or from some other mechanism, will lead to a decreased GFR. Correction of the hypotension, such as by removing a vasodilator, will lead to an improvement in serum creatinine, particularly if the patient has chronic kidney disease, because the autoregulation curve is shifted to the right.

Dr. Francis: You are correct in that low blood pressure has predicted a poor outcome in every study of this syndrome. If blood pressure is marginal, you can expect the worst. What's more curious is that some patients present with normal systolic function, normal ejection fraction, and normal cardiac output, and yet develop severe congestion and the cardiorenal syndrome, as best as we can define it. Therefore, it seems that it is not solely inadequate flow to the kidney that is the cause. Inadequate renal perfusion clearly can contribute when the cardiorenal syndrome develops, but not all patients have it. I don't think we understand this syndrome at all.

Low blood pressure has predicted a poor outcome in every study of the cardiorenal syndrome.
—Dr. Gary Francis

Dr. Gheorghiade: Our data in patients admitted with heart failure, soon to be published, found that blood urea nitrogen and not creatinine clearance is an important marker for postdischarge mortality and hospitalization. These data suggest that often we are dealing with a vasomotor nephropathy related to further activation of neurohormones and an increase in venous pressure. This vasomotor nephropathy is not an irreversible process and may improve with neurohumoral modulation and/or a decrease in venous pressure.

Question from audience: Do you believe that a low serum sodium is not the problem, but rather that total body water is massively elevated? Do patients who are hyponatremic in fact have an elevated total body sodium? If patients with heart failure, despite being hyponatremic, are massively overloaded with sodium in their body, it suggests that removal of both water and salt is needed if we are to achieve full decongestion.

Dr. Francis: I agree that, generally, the hyponatremia in the cardiorenal syndrome is a dilutional hyponatremia. The total amount of sodium in the body, which must be measured using pretty exotic techniques, can be either normal or increased. It is clear that there is too much water. It is also quite clear that congestion is playing a major role. It is not just the cardiac output or ejection fraction.

I agree with Dr. Gheorghiade that the cardiorenal syndrome is reversible. These patients can sometimes be rescued. The treatment is inconsistent from hospital to hospital, and there is clearly a lot to learn.

Dr. Gheorghiade: We have seen from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) that patients with hyponatremia have the best clinical and hemodynamic response during admission. Those were the patients who had a significant decrease in body weight and the greatest increase in cardiac index. In spite of the huge clinical and hemodynamic improvement, and a decrease in body weight, their serum sodium level did not change during hospitalization. More important, there was a threefold increase in mortality in those patients who had hyponatremia. These data show that outcome is not entirely related to fluid because the patients who were hyponatremic had the best response in terms of diuresis.

Question from audience: Conivaptan has some significant drug interactions, along the cytochrome P450 pathway. Is that a problem with all drugs in this class?

Dr. Wilson Tang: Both conivaptan and tolvaptan are metabolized via the CYP3A4 pathway. I think that the main reason that conivaptan has been developed as an intravenous drug is because the oral form had drug interactions, but clinical trials to date have shown good tolerability with oral tolvaptan.

Dr. Sica: Conivaptan proved to be both a substrate for and an inhibitor of CYP3A4. When given orally, the consistency of its pharmacokinetics was somewhat unpredictable, at least partly because of variable absorption. Its intravenous administration still carries a significant drug-drug interaction potential for compounds metabolized by CYP3A4.

Question from audience: Are there any effects of vasopressin antagonists on the QT interval?

Dr. Gheorghiade: I am not aware of any increase in the QT interval with either tolvaptan or conivaptan.

Question from audience: It seems that we have discovered several parallel mechanisms that promote the congested state and that we have been able to block activation of some of these mechanisms with angiotensin-converting enzyme inhibitors and beta-blockers. Does blocking one of these pathways activate other pathways so that we are destined to keep chasing the next pathway that comes into play pathologically in this state?

Dr. Francis: Yes, as a short answer. It's a very complicated question, but it is theoretically and practically the case.

Dr. Tang: We also have an inability to tell which pathways are more activated than others in certain patients. We do not know because our ability to accurately quantify congestion and renal insufficiency, and to measure renal hemodynamics, is not very good and hasn't evolved.

Question from audience: Does anyone on the panel buy into the concept of a diuretic holiday with procedures such as ultrafiltration, in which the diuretic is eliminated completely to try to restore diuretic sensitivity? In this way, once patients are ambulatory, we can restore sensitivity to the diuretics that kept them well compensated for the months prior to their admission.

Dr. Gheorghiade: It's a valid concept. Theoretically, diuretic therapy may be a contributor to the cardiorenal syndrome that contributes to postdischarge mortality and hospitalization. Breaking this vicious cycle (the use of high-dose diuretics) by ultrafiltration or other means may be beneficial.

Dr. Sica: Restoring diuretic sensitivity by providing a diuretic holiday is an interesting concept and one that has been anecdotally described from time to time. If it holds true, it could possibly relate to a downturn in neurohumoral activation and/or regression of distal tubular cell hypertrophy.

Blood urea nitrogen, but not creatinine clearance, is an important marker for postdischarge mortality and hospitalization.
—Dr. Mihai Gheorghiade