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Scientific Update™

Optimizing Patient Outcomes in Acute Heart Failure Syndrome: Strategies to Preserve Cardiorenal Function

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Acute heart failure (HF) is one of the leading causes of hospitalization in the western world. Concomitant and significant renal dysfunction is common in patients with HF. Increasingly, the syndrome of acute HF is one of cardiorenal failure, in which cardiac and renal dysfunction coexist, each accelerating the progression of the other. The term "cardiorenal syndrome" has been associated with cardiorenal failure and worsening renal function. One-quarter of patients hospitalized for the treatment of acute HF syndrome (AHFS) will experience significant worsening of renal function and poor clinical outcome. This issue of *Cardiology Scientific Update* reviews the presentation and pathophysiology of AHFS, the impact of renal dysfunction, the challenges in management, as well as the emerging perspectives in the management of AHFS and cardiorenal syndrome.

Variable presentations and pathophysiology of acute heart failure syndromes

AHFS can be defined as a new onset, or gradual or rapidly worsening of HF signs and symptoms requiring urgent therapy.[1] Irrespective of the underlying etiologies (eg, ischemic event) or precipitant (eg, severe hypertension), pulmonary and systemic congestion due to elevated ventricular filling pressures with or without a decrease in cardiac output is a nearly universal finding in patients with AHFS.[1] Patients may be classified into HF presenting for the first time (*de novo*) or worsening chronic HF.[1] In both groups of patients, the presence and extent of coronary artery disease (CAD) may determine initial, in-hospital, and post-discharge management.[2] The majority of AHFS patients have worsening chronic HF resulting in hospitalization, with the remaining 20% diagnosed *de novo*. The mean age is 75 years and more than half are women. Dyspnea and signs of congestion manifested by jugular venous distention and edema are common.[3,4] At presentation, ~25% of patients are hypertensive (systolic blood pressure [BP] >160 mm Hg), while <10% are hypotensive. Most are taking diuretics, 40% use angiotensin-converting enzyme (ACE) inhibitors, 50% take beta-blockers, and 20%-30% take digoxin.[3,5,6] A history of CAD is present in 60%, hypertension in 70%, diabetes in 40%, atrial fibrillation in 30%, and moderate to severe renal impairment in 20%-30%.[7] Approximately 50% of AHFS patients have relatively preserved systolic function;[3,8,9] these patients are older, and are more likely to be female, have a history of hypertension and atrial arrhythmias, and present with severe hypertension.[8,9] Patient characteristics may also differ depending on whether they are considered for clinical trials or not. For example, the sites that participated in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) enrolled 439 patients who had pulmonary artery catheterization (PAC) but without randomization, into a prospective registry. When compared with the trial patients, the registry patients had lower BP, worse renal function, less neurohormonal antagonist therapy, and higher use of intravenous inotropes compared with ESCAPE trial patients.[10] Although clinical assessment anticipated fewer cases of volume overload and more hypoperfusion among the registry population, measured filling pressures were similarly elevated in the registry and trial patients, whereas measured perfusion was slightly higher among registry patients. Registry patients had longer hospitalization and higher 6-month mortality (34% versus 20%; $P<0.001$) than

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trial patients. Thus, in clinical trial settings, the decision to use PAC without randomization identified a population with more severe disease and higher risk of mortality.

Although circulatory congestion is the main reason for hospitalization, many patients do not have a decrease in body weight during hospitalization and are often discharged with HF signs and/or symptoms.[6,8,10,11] A comprehensive assessment is often not performed (eg, cardiac catheterization, assessment for viable myocardium), and may result in underutilization of evidence-based therapies.[12] In patients admitted with worsening chronic HF, except for diuretic dose escalation, introduction of new or uptitration of evidence-based therapies (eg, ACE inhibitors, beta-blockers) is <5%-10%. In fact, they are often discharged on the same preadmission medications.[13,14]

Both the inhospital and postdischarge clinical event rates are high in patients hospitalized for AHFS.[1,15] Recent clinical trials and observational studies have identified prognostic factors in patients admitted with AHFS. These factors include low systolic BP, severe CAD, renal impairment, hyponatremia, signs of congestion and poor exercise capacity at the time of discharge, the presence of reactive airway disease, liver disease, and depression, and high natriuretic peptide levels.[4,15-17] Clinical models have recently been developed to predict short-term clinical outcomes in a broad patient population discharged after hospitalization for HF. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry is a comprehensive hospital-based registry and performance-improvement program for patients hospitalized with HF. From 4402 patients included in an analysis using this registry, 19 prespecified potential predictor variables were used in a stepwise Cox proportional hazards model for all-cause mortality. Logistic regression, including 45 potential variables, was used to model mortality or rehospitalization.[15] The most important predictors for the combined endpoint of death or rehospitalization were admission levels of serum creatinine and hemoglobin, systolic BP, discharge use of ACE inhibitors, and pulmonary disease.

Impact of renal dysfunction on AHFS

The majority of patients with AHFS have baseline renal dysfunction.[18,19] Moreover, HF treatment is limited by worsening renal function despite treatment and volume overload.[20] This connection between HF and renal dysfunction is termed the cardiorenal syndrome[21] and the treatment of patients with stable and unstable HF is challenging. A proposed definition of the cardiorenal syndrome is shown in Table 1.[22] In the Acute Decompensated HEart Failure National REgistry (ADHERE) database, at least 65% of patients with AHFS had moderate or severe chronic kidney disease, as defined by an estimated glomerular filtration rate (GFR) <60 mL/min/ 1.73 m^2 at the time of admission.[7] The presence of renal dysfunction is especially important given its association with increased morbidity and mortality in both AHFS[23] and stable HF.[24] Along with baseline renal dysfunction, HF patients are at risk for worsening renal function (WRF) during treatment. When patients are hospitalized with AHFS, an increasing serum creatinine level is commonly observed.[18-20,25] WRF risk factors include older age, hypertension, diabetes, and baseline renal dysfunction. Most studies have shown that WRF during management of AHFS is an independent predictor of increased hospital costs, morbidity, and mortality.[18-20,26] Indeed, even an increase in serum creatinine of 0.1 mg/dL carries prognostic significance.[27]

Table 1: Proposed definition of cardiorenal syndrome

- Coexistent cardiac and renal failure
- Worsening renal function during treatment of acute decompensated heart failure
- Refractory to diuretics despite persistent hypervolemia
- Inability to handle a sodium load
- Inability to use adequate doses of heart failure medications

When serum creatinine rises in patients with AFHS, clinicians often attribute WRF to prerenal azotemia in the setting of overdiuresis or hypovolemia. Although excessive diuresis may lead to WRF in a minority of patients, more often this occurs while patients remain with volume overload.[27] Potential alternative contributors include renal venous congestion,[28] increased intra-abdominal pressure,[29] persistent renal vasoconstriction,[30] drugs that modulate the renin-angiotensin-aldosterone system (RAAS) including ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists as well as high-dose diuretic therapy. Unfortunately, it may take some time for WRF to be recognized if one simply monitors serum creatinine alone.[27] Alternative markers of renal function and prognosis in these patients may be useful.

Recently, cystatin C, a novel marker of renal function, has been investigated for its prognostic value in AHFS as compared with N-terminal proB type natriuretic peptide (NT-proBNP) and other markers of renal function. In 480 patients with AHFS, cystatin C turned out to be a strong and independent predictor of an adverse clinical outcome at 12 months. Furthermore, cystatin C identified patients with poor prognosis despite normal plasma creatinine.[31] Urinary neutrophil gelatinase associated lipocalin (NGAL) is a novel cytokine that can serve as a marker for renal tubular damage. Preliminary data have demonstrated that urinary NGAL is increased in patients with HF, in parallel with severity of symptoms, and predicted mortality in these patients.[32,33]

Venous congestion is now recognized to be a very important factor in the worsening of renal function in patients with decompensated HF. In 145 consecutive patients admitted for AHFS treated with intensive therapy guided by PAC, patients who developed WRF (increase of serum creatinine >0.3 mg/dL during hospitalization) had a greater central venous pressure

(CVP) on admission and after intensive medical therapy. The development of WRF occurred less frequently in patients who achieved a CVP <8 mm Hg (P<0.01). Furthermore, the ability of CVP to stratify risk for developing WRF was apparent across the spectrum of systolic BP, pulmonary capillary wedge pressure, cardiac index, and estimated GFR.[34] A similar mechanism of increased central and renal venous pressures likely accounts for the recent observations of a relationship between tricuspid regurgitation and increased intra-abdominal pressure with renal dysfunction and adverse clinical outcomes.[29,34-37]

Diuretics are the mainstay of treatment for HF associated with volume overload. In patients with coexistent cardiac and renal failure, diuretic therapy is limited by the development of drug resistance.[38] Patients with advanced cardiac and renal dysfunction often require progressively higher doses of diuretics.[38] A prospective observational analysis of 183 patients in an advanced HF clinic stratified at baseline by diuretic dose demonstrated that patients taking high-dose diuretics had more markers of increased cardiovascular risk and were more likely to have a history of recent instability. High doses of diuretics were a strong univariate predictor of subsequent HF events; however, after adjustment for clinical stability, diuretic dose no longer remained significant. High-dose diuretics may be more of a marker than a cause of clinical instability.[39] In the management of patients with severe congestion, many physicians advocate using a continuous infusion of loop diuretics. In a recent Cochrane review that involved 8 trials and 254 patients, urine output was found to be significantly greater with infusion than bolus administration, although the difference (271 mL/24 hours, P<0.01) was modest.[40] The ongoing Diuretic Optimization Strategies in Acute Heart Failure (DOSE-AHF) trial, a randomized, controlled trial (RCT) sponsored by the National Institutes of Health (NIH), is comparing the safety and efficacy of high- versus low-intensification diuretic therapy as well as continuous infusion versus intermittent intravenous bolus.

Ultrafiltration (UF) uses a semipermeable membrane to remove fluid isotonic to plasma, promote euvolemia, and offers an effective means of restoring sodium balance. In addition, UF provides rapid and predictable fluid removal, has no effects on serum electrolytes, and may restore diuretic responsiveness.[41,42] Although promising results have been demonstrated with "up front" UF in AHFS,[43] its use in patients with refractory HF and renal dysfunction may occasionally be associated with progressive renal failure.[44] A recent RCT comparing UF and intravenous diuretics in patients hospitalized for AHFS demonstrated that UF did not cause any significant differences in renal hemodynamics compared with diuretics.[45] An NIH-sponsored RCT, the Cardiorenal Rescue Study in Acute Heart Failure (CARRESS), will address the question whether UF improves renal function and relieves congestion compared with stepped pharmacological care.

Improving patient outcomes in AHFS: changing the face of treatment of the cardiorenal syndrome

Many therapeutic strategies have been developed to target cardiorenal syndrome, although few, if any, have proven safe and effective.[21,38] Positive inotropic agents may be used as adjuncts to loop diuretics, but are associated with proarrhythmia and possibly excess mortality. Nesiritide, or recombinant human BNP, at low doses may improve diuretic responsiveness. However, there are concerns that moderate to higher doses of nesiritide may actually worsen renal function, possibly due to drug-induced hypotension.[46] Vasopressin-receptor antagonists act via V1 and V2 receptors to mediate systemic vasoconstriction and free water loss, respectively.[38] Some of these agents (eg, tolvaptan) have been shown to improve hemodynamics, relieve dyspnea, and correct hyponatremia in patients with AHFS,[47] but have not been shown to improve serum creatinine or clinical outcomes,[48] nor have they been approved by the United States (US) Food and Drug Administration for this indication.

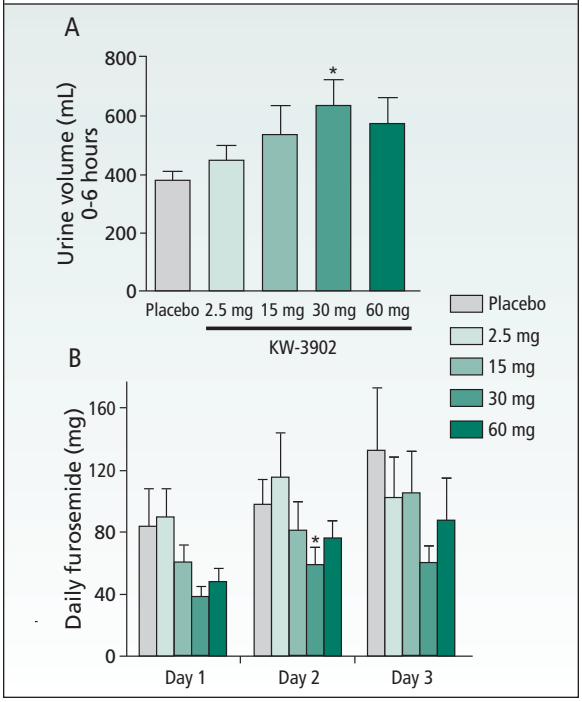
Throughout the body, adenosine acts primarily as a vasodilator. The effects on the kidney, however, are more complex. The initial response to adenosine infusion in healthy animals is overall renal vasoconstriction that is both rapid in onset and short in duration.[49] With continuous adenosine administration, renal vasoconstriction persists with subsequent decrease in GFR by up to 50%-80%. However, total renal blood flow is preserved due to areas of concomitant renal vasodilation.[50] In healthy humans, adenosine infusion produced a similar fall in GFR with preservation of renal blood flow while also causing vasodilation and tachycardia.[51] The renal effects of adenosine are mediated through the actions of 3 receptors: A1, A2, and A3. All receptors belong to the G-protein receptor superfamily. The A1 and A3 pathways inhibit adenylyl cyclase and stimulate phospholipase C; conversely, A2 receptors stimulate adenylyl cyclase.[49] A1 activation leads to afferent glomerular arteriolar vasoconstriction,[52] increased sodium reabsorption in proximal and possibly distal tubules,[53] and inhibition of renin secretion.[49] The role of A2 receptors appears to be more prominent in preserving renal medullary blood flow through vasodilation, although A2 activation also dilates postglomerular arterioles.[49] A3 receptor function has yet to be fully characterized, but its antagonism appears to have no effect on renal excretory functions.[54] Importantly, an adenosine-mediated decrease in GFR occurs via afferent arteriolar vasoconstriction and not efferent arteriolar vasodilation.[55] Thus, A1 activation mediates GFR reduction, while A2 stimulation preserves renal blood flow. Volume is regulated by GFR and reabsorption of filtered fluid through the tubular system. As filtered fluid passes through the tubular system, fine-tuning of electrolyte and volume balance takes place.[49] GFR and tubular reabsorption are regulated at the single nephron level through tubuloglomerular feedback (TGF), a homeostatic mechanism by

which each nephron senses tubular fluid electrolyte concentrations and changes single nephron GFR to keep tubular fluid and salt load constant.[56] In the setting of volume overload, each nephron in the renal system has a fluid and salt load beyond capacity. At this point, TGF also inhibits renin, reducing total body volume and subsequently total renal GFR.[49] Importantly, adenosine regulates volume status through these mechanisms via A1 receptor activation. With increased salt load in a single nephron, adenosine levels increase in the tubular system to stimulate proximal tubular reabsorption. Simultaneously, the macula densa senses elevated salt load and transmits adenosine as the mediator of TGF to cause afferent glomerular vasoconstriction. The sum effect of tubular reabsorption and afferent glomerular vasoconstriction is increased volume and decreased GFR. In volume overload states, adenosine released for TGF inhibits renin and thus exerts negative feedback on its mainly volume avid effects.[56]

Selective adenosine A1 receptor antagonists may, therefore, benefit patients with cardiorenal syndrome by alleviating the volume dysregulation that contributes to worsening HF and by preventing further renal dysfunction. Adenosine-receptor antagonists can increase GFR and promote diuresis by simultaneously blocking glomerular afferent vasoconstriction and tubular reabsorption. By blocking TGF, adenosine antagonists uncouple communication between the glomerular and tubular system, so that the glomerular is unable to compensate for the tubular system in the setting of diuretic therapy. With improvement of renal function and volume status, there may be an improvement in diuretic responsiveness. With selective A1-receptor blockade, preserved A2 activity can promote renal blood flow through vasodilation and prevent renal ischemia that may contribute to renal dysfunction.

Although a number of selective A1 receptor antagonists have been developed for basic investigation, 3 agents have undergone significant clinical development to target cardiorenal syndrome: KW-3902 (rolofylline), BG9719 (formerly known as CVT-124), and BG9928. Rolofylline, an intravenously administered adenosine antagonist with high affinity for the A1 receptor, is not yet approved in the US or Canada.[57] In 32 patients with stable HF but with baseline renal impairment, Dittrich et al[58] administered intravenous rolofylline or placebo in a double-blind, crossover study to assess effects on GFR, renal plasma flow (RPF), and diuresis. All patients received intravenous furosemide during study drug infusion. At 8 hours post-infusion, rolofylline increased GFR by 32% over baseline and increased diuresis by 500 mL compared with placebo. Prior to the second treatment period, a crossover effect was observed such that the patients who received rolofylline first had an increase in GFR of 9 ± 3.0 mL/min while those receiving placebo first had a decrease in GFR of 2.6 ± 4.5 mL/min. Thus, rolofylline may have salutary effects on renal function that last longer than expected based on pharmacokinetics. Givertz et al[59] studied the cardiorenal effects of rolofylline in 2 hospitalized HF populations: patients with AHFS and creatinine clearance of 20-80 mL/min and patients with diuretic resistance with a creatinine clearance averaging 34 mL/min. In the AHFS protocol, 146 patients were randomized to receive 1 of 4 doses of rolofylline (2.5 mg, 15 mg, 30 mg, and 60 mg) or placebo administered intravenously over 2 hours daily for up to 3 days. On Day 1, rolofylline increased urine output at all doses compared to placebo (Figure 1A), and on Day 2, it decreased serum creatinine. In addition, intravenous furosemide dosing tended to be lower in the rolofylline groups (Figure 1B). In the diuretic-resistant protocol, a single dose of rolofylline (10 mg, 30 mg, or 60 mg) increased hourly urine volume and estimated creatinine clearance compared with placebo, and peak effects occurred at 2-3 hours and 24 hours, respectively. PROTECT (Placebo-controlled Randomized study of Rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment

Figure 1. Effects of rolofylline on urine volume (A) and daily furosemide dose (B)[1]



A. Cumulative urine volume (mean ± standard error of the mean [SEM]) 6 hours after initiation of placebo or KW-3902 in acute decompensated heart failure patients with renal impairment (*P=0.02 vs. placebo).
B. Daily dose of intravenous (IV) furosemide (mean ± SEM) administered to the placebo and 4 KW-3902 groups over the first 3 days of the study (*P<0.05 vs. placebo).

Table 2: Optimizing patient outcomes in acute heart failure syndromes (AHFS) and cardiorenal syndrome (CRS): looking ahead

Study	Agent	Question
ASCEND-HF	Nesiritide	Can nesiritide be shown to be safe and effective in 7000 patients?
PROTECT TRIDENT Solvay 2B	Rolofylline BG9929 SLV320	Will adenosine A1 receptor antagonists preserve or improve renal function? Can they lead to sustained reductions in death and rehospitalization?
DOSE-AHF	Furosemide	Bolus vs drip? High vs low-dose?
CARRESS	Ultrafiltration	What role does UF have in managing CRS? Who are "target" patients?
BALANCE	Lixivaptan	Can vasopressin antagonists safely be used to treat hyponatremia AHFS?
IGNITE	Istaroxime	A safer inotrope and lusitrope?
NILE-2B	CD-NP	A safer natriuretic peptide? Can it improve symptoms and preserve renal function without hypotension?
PILL-CVD	Education	Can predischarge counselling and medication reconciliation reduce serious medication errors?
GALLANT	Blood NGAL	Can a novel renal marker be used for early risk assessment?

Effect on Congestion and renal function) is an ongoing Phase III clinical trial in which 2000 patients with AHFS and renal impairment are randomized 2:1 to receive rolofylline (30 mg) or placebo in addition to intravenous loop diuretics for 3 days. In a dose-finding pilot study of PROTECT,[60] a total of 301 patients hospitalized for AHFS with an estimated creatinine clearance of 20-80 mL/min were enrolled within 24 hours of presentation to placebo or rolofylline (10 mg, 20 mg, or 30 mg) administered as 4-hour infusions for 3 days, in addition to loop diuretics. Compared with placebo, rolofylline produced a trend towards more patients with marked or moderately improved dyspnea and fewer patients with worsening heart failure or renal function. Serum creatinine increased in patients receiving placebo and remained stable or tended to decrease in those receiving rolofylline. Treatment with 30 mg, the dose selected for the pivotal trials, was associated with a trend toward reduced 60-day mortality or readmission for cardiovascular or renal cause (hazard ratio, 0.55; 95% confidence interval, 0.28-1.04). The primary endpoint of PROTECT will be treatment success or failure at 7 days based on signs and symptoms of HF, readmission, and death. Morbidity and mortality will also be tracked through Day 60. The recruitment of PROTECT has already been completed.

Conclusion

AHFS and the cardiorenal syndrome represent an ominous and frequent development in the natural history of patients who suffer from HF. The understanding of the underlying mechanisms remains rudimentary, and effective therapies are lacking. Fortunately, this problem has captured the attention of investigators, industry, and authorities responsible for setting research priorities, as illustrated by the number of ongoing studies, which are summarized in Table 2.

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