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Renal Dysfunction in Acute Heart Failure

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ABSTRACT

During treatment of acute heart failure (AHF), worsening renal function is often complicated and results in a complex clinical course. Furthermore, renal dysfunction is a strong independent predictor of long-term adverse outcomes in patients with AHF. Traditionally, the predominant cause of renal dysfunction has been attributed to impairment of cardiac output and relative underfilling of arterial perfusion. Recently, emerging data have led to the importance of venous congestion and elevated intra-abdominal pressure rather than confining it to impaired forward cardiac output as the primary driver of renal impairment. Relief of congestion is a major objective of AHF treatment but therapy is still based on the administration of loop diuretics. The results of the recently performed controlled studies for the assessment of new treatments to overcome resistance to diuretic treatment to protect kidneys from untoward effects have been mostly neutral. Better treatment of congestion in heart failure remains a major problem. **(Korean Circ J 2011;41:565-574)**

KEY WORDS: Acute heart failure; Kidney function; Cardiorenal syndrome.

Introduction

Acute heart failure (AHF) is a major source of hospitalization and mortality. Patients with AHF usually present with severe dyspnea due to pulmonary congestion which is the hallmark of AHF. Therefore, elimination of excess fluid should be the primary target of treatment. Also, there is substantial evidence that fluid accumulation is associated with morbidity, mortality, and readmission with heart failure (HF).[1-4] Kidney is the main exit of congestion, but many numbers of AHF patients have accompanying renal dysfunction or experienced worsening of renal function during hospitalization. The heart and kidney are very closely related. Thus derangement of cardiac function can make renal dysfunction, recently referred to as "cardiorenal syndrome (CRS)" or inversely as "renocardiac syndrome". In 2008, Ronco et al.[5] classified CRS

into 5 subtypes, as showed in Table 1, by primarily affected organ (heart or kidney) and course of injury (acute or chronic). By this classification, type 1 CRS, which is the development of renal dysfunction in clinical situation of AHF, is the topic of our discussion and has been found to be more prevalent in hospitalized AHF patients.

Although, it is well established that patients who are admitted with AHF and renal dysfunction have worse outcomes, there is limited data for evidence-based therapeutic approaches.[6-8] This is most likely because AHF is not a specific clinical-pathologic event and is not caused by a well-defined pathophysiologic mechanism (like acute coronary thrombosis), but instead results from various factors. AHF patients may manifest either 1) rapid accumulation of fluid in the lung, 2) progressive systemic congestion, or 3) clinical findings associated with reduced cardiac output. In addition, it is very difficult to test the impact of specific interventions, because these patients are inherently unstable and there are so many available treatment options and lack of appropriate target endpoints. For these reasons, there is a paucity of useful clinical trial evidence in patients with AHF, which results in a situation where most guideline recommendations for managing this syndrome are derived from "expert" opnions, unsupported by solid outcome data.[9-11]

However, there is continuous accumulation of clinical data from well-controlled clinical trials for the diagnosis and mana-

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Table 1. Classification of CRS

Type	Character	Proposed mechanism	Clinical setting
Type 1	Acute CRS	Abrupt worsening of cardiac function leading to kidney injury	Acute cardiogenic shock, acute decompensated HF
Type 2	Chronic CRS	Chronic cardiac abnormalities causing progressive chronic kidney injury	Chronic heart failure cause chronic renal hypoperfusion
Type 3	Acute renocardiac syndrome	Abrupt worsening of renal function causing acute cardiac disorder	ARF, Acute GN cause acute pulmonary edema, arrhythmia
Type 4	Cronic renocardiac syndrome	Chronic kidney disease contributing to decreased cardiac function	Chronic renal disease cause cardiac hypertrophy, decreased cardiac function
Type 5	Secondary CRS	Systemic condition causing both cardiac and renal dysfunction	Diabetes, sepsis

CRS: cardiorenal syndrome, HF: heart failure, ARF: acute renal failure, GN: glomerulonephritis

gement for AHF and accompanying renal dysfunction. In this review, we discuss the pathophysiology of renal dysfunction associated with AHF, early detection modalities, and finally, current therapeutic strategies. We used the terminology "renal dysfunction in AHF" rather than "CRS". As noted above, some authors used the "CRS" in a variable clinical situation, but our point of discussion is focused on renal dysfunction in the setting of AHF, especially worsening during AHF treatment.

Prevalence and Prognosis

Accompanying renal dysfunction

American College of Cardiology/American Heart Association guidelines for "HF data standard" suggested that chronic renal disorder can be categorized in to 4 groups as mild, moderate, severe renal insufficiency and chronic renal failure by using the estimated glomerular filtration rate (eGFR); 60-89, 30-59, 15-29, <15 mL/min/1.73 m² respectively.[9] Although, GFR can be estimated by various formulas, simplified Modification of Diet in Renal Disease (MDRD) formula (186.3× sCr$^{-1.154}$×age$^{-0.203}$, female: MDRD×0.742, Black or non-white: MDRD×1.212) is simple, and only serum creatinine and age are needed for calculation. It is also a reliable predictor for prognosis in HF patients.[12] It is not appropriate to use a single measurement of serum creatinine for the evaluation of renal function, because serum creatinine levels can be largely influenced by age, muscle mass etc. However, many clinical trials and registry data used serum creatinine levels for the diagnosis of renal dysfunction.

In large nationwide registry data in USA and Europe, 20.4% of patients had serum Cr >2.0 mg/dL in Acute Decompensated Heart Failure National Registry (ADHERE), and 18% in EURO-Heart survey (40% in old EU). In Korean Heart Failure (Kor-HF) registry, 15.2% of AHF patients showed level of serum Cr >2.0 mg/dL.[1)2)13] In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), the proportion of patients with an eGFR <60 mL/min was 31.4%.[14]

Accompanying renal dysfunction is one of the main independent risk factors for prolonged hospitalization, rehospitalization, and short- and long-term mortality.[6-8] In patients with HF, compared to left ventricular ejection fraction (LVEF) or NYHA functional class, baseline GFR has been demonstrated to be a stronger predictor for all-cause mortality. Likewise, a decrease in GFR is directly associated with the rate of in-hospital mortality. In a meta-analysis, Smith et al.[15] reported that, annual mortality rates were 26% in patients without renal dysfunction, 41% in the patients with any impairment of renal function and 51% (p<0.001) in patients with moderate to severe impairment (p<0.001).

Worsening renal function

Patients hospitalized for AHF often develop worsening renal function. It occurs in 25-30% of acute HF admissions and is more likely in patients with renal dysfunction at baseline, diabetes and previous HF.[16-19] In Kor-HF registry, worsening of renal function, defined as increasing serum creatinine levels more than 1.5 times baseline, happened in 21.5% of AHF patients.[13] Although there is no concrete criteria, worsening renal function is often defined as an increase in sCr ≥0.3 mg/dL from baseline value. In a meta-analysis, prior mentioned, of 16 studies including 80,098 patients, worsening renal function was associated with a 47% increase in one-year mortality, with a 33% increase in mortality for every 1 mg/dL increase in sCr.

Forman et al.[16] reported that from 1,004 AHF patients, worsening renal function was related with 7.5 times higher relative risk ratio for in hospital death and 2.1 times higher for complication. In Kor-HF registry, in-hospital mortality was significantly higher (13.2% vs. 5.4%, p<0.01) and duration of intensive care unit (ICU) stay and hospitalization were prolonged in patients with worsening renal function.[13]

Sometimes, worsening renal function dose not persist, but in two-thirds of this condition could to be persist and associated with worse outcomes. Due to confounding factors (etiology, co-morbidities, medications etc.) and baseline renal func-

tion, the real impact of worsening renal failure on prognosis is unclear. Additionally, the lack of a clear definition of worsening renal function, and heterogeneity of currently available biomarkers of renal function provide a limitation for the interpretation of these results.

Pathophysiology

Heart failure is characterized by complex cardiac, renal, and vascular interactions, mediated through both hemodynamic and neurohumoral mechanisms (Fig. 1). Increased vascular stiffness limits the ability of the intravascular space to accomodate salt and fluid loads. Endothelial dysfunction contributes to vasoconstriction and increased afterload. Renal dysfunction may limit sodium excretion and drives activation of the renin-angiotensin-aldosterone axis. Although, it is not yet clearly identified the mechanism of progressive renal dysfunction in AHF, following factors are proposed as pathophysiologic alterations of this syndrome.

Hemodynamic abnormalities

Low cardiac output

Patients with HF may progress to a chronic low cardiac output state with systemic and renal hypoperfusion and cause activation of rennin-agiotensin-aldosterone system (RAAS) and sympathetic sympathetic nervous system (SNS) leading to sodium retention, volume expansion and ventricular remodeling.[20][21] Theoretically, the progressive impairment of renal function may result from inadequate renal perfusion secondary to reduced cardiac output. However, several data suggest that hemodynamic alteration from low cardiac output is not the only determinant of reduced GFR, and management of patients with CRS based only on improvement of renal blood flow does not lead to a better prognosis.[22] This hypothesis is supported by the observation that renal dysfunction occurs at similar rates in patients with either systolic or diastolic dysfunction.[23]

Elevated central venous pressure

Basically, the pressure gradient between glomerular afferent and efferent arterioles makes the drive force for glomerular filtration. In HF patients, increased central venous pressure (CVP) can be transmitted to the glomerular efferent arteriole with a reduction of the glomerular filtration pressure gradient and cause a fall of GFR. Additionally, it was postulated that transmitted pressure to the renal vein causes increased renal interstitial pressure and this may lead to renal parenchymal hypoxic state. In practical terms, Mullens et al.[24] reported that in 145 patients of AHF, only the CVP was the most important determinant of the development of worsening renal function. In addition, Damman et al.[25] found that CVP was the most important determinant of renal dysfunction and the most important independent predictor of mortality in 2,557 patients hospitalized for cardiac catheterization. Notably, elevated jugular venous pulsations on physical examination and baseline right atrial pressure are related with elevated baseline serum creatinine.[26] Recently, further studies have demonstrated that CVP has a close relationship with renal dysfunction in patients with HF.[27][28]

Adenosine

Adenosine is released in response to increased sodium loading in the distal tubule, and via A1-receptors in the proximal tubule and afferent arterioles, mediates constriction of afferent arterioles and reduction of renal blood flow and GFR. Additionally, activation of A1 receptors induces release of rennin and enhances sodium re-absorption at the proximal tubule and reduces diuresis.[29] Thus, adenosine may be an important mediator for renal dysfunction after intensive diuretic treatment with high dose loop diuretics for AHF. Unfortunately, studies with type 1a-adenosine receptors blocking agents have failed to demonstrate a significant beneficial effect in renal function in AHF.[30]
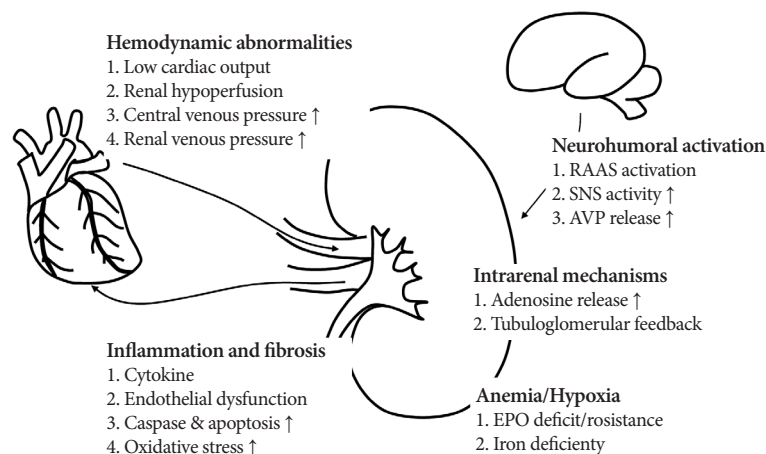

Hemodynamic abnormalities
1. Low cardiac output
2. Renal hypoperfusion
3. Central venous pressure ↑
4. Renal venous pressure ↑

Neurohumoral activation
1. RAAS activation
2. SNS activity ↑
3. AVP release ↑

Intrarenal mechanisms
1. Adenosine release ↑
2. Tubuloglomerular feedback

Inflammation and fibrosis
1. Cytokine
2. Endothelial dysfunction
3. Caspase & apoptosis ↑
4. Oxidative stress ↑

Anemia/Hypoxia
1. EPO deficit/rosistance
2. Iron deficienty

Fig. 1. Pathophysiological mechanisms of worsening renal function in acute heart failure.

Neurohumoral mechanism

When HF develops, RAAS and SNS are activated as a protection mechanism for renal hypoperfusion.[31)32)] This is essential in dangerous situations like gastrointestinal bleeding or trauma. However, in the case of chronically stimulated state, the consequence of these conditions is deleterious on the heart and kidney.

Increased renin secretion is demonstrated in HF and generation of angiotensin II from angiotensin I is enhanced by rennin. Angiotenin II is a potent constrictor of arterioles and therefore increases the afterload resulted in decreased cardiac output. Angiotenin II stimulates the SNS and aldosterone release as well, and these cause further constriction of renal vasculature. Constriction of afferent arterioles by angiotensin II and SNS reduces renal blood flow and GFR, and causes increased proximal tubular sodium reabsoprtion.[32)33)]

Activation of SNS initially has a protective role for maintaining cardiac output by positive chronotropic and inotropic effects. Like RAAS activation, chronic activation of SNS also resulted in numerous deleterious effects on the cardiovascular system and kidneys.[34)] In the kidney, activation of SNS also causes further activation of RASS and leads to inadequate fluid and sodium retention. Reduced renal perfusion pressure during HF causes constriction of afferent arterioles, and a further decrease in renal blood flow and GFR. When HF develops, these effects are more exaggerated due to higher release and lower clearance of catecholamines.

Arginine vasopressin (AVP) is released by osmotic stimuli, blood pressure, and cardiac factors. In usual situations, low osmolarity suppresses AVP release, but in HF state, due to non-osmotic baroreceptor mechanisms, there is a marked increase in AVP release even with hyponatremia. AVP activates the V2 receptor in the collecting duct and increases the permeability of water channels resulting in water retention. AVP stimulates the V1a receptors of the vascular smooth muscle that results in vasoconstriction of the arterial and venous system.[35-37)]

Evaluation of Renal Dysfunction

Conventional markers (blood urea nitrogen, creatinine)

Usually, evaluation of renal dysfunction is based on change of serum creatinine (sCr). However, there are many limitations in using sCr as a marker of renal dysfunction. Serum creatinine is largely influenced by age and related to other variables including sex and muscle mass.[38)39)] Additionally, sCr level is not sensitive for the detection of renal injury. It is demonstrated that, kidney damage can occur without producing a change in eGFR calculated by sCR. The amount of changes in serum creatinine after renal injury is highly dependent on baseline kidney function: in case of normal baseline renal function, sCr levels start to increase at advanced stage of renal injury, whereas when renal dysfunction is already present, it can be overestimated due to the sCr level changing a relatively large amount (e.g., 50% increase in sCr with baseline level 1.0 mg/dL and 2.0 mg/dL result in 1.5 mg/dL and 3.0 mg/dL respectively).[40)] Also, there is an exponential relationship between sCr level and estimated GFR, therefore, worsening renal function may be better defined by either an absolute increase from baseline and a percent increase. Recently, it has been reported that renal dysfunction defined as both a ≥0.3 mg/dL increase plus ≥25% increase from baseline values was an independent prognostic factor, whereas it had no independent prognostic value when defined only by absolute changes from baseline.[19)]

Because sCr has slow kinetics, marked reduction in eGFR may cause relatively small changes in sCr levels in the early stage of acute kidney injury (24-48 hours). In addition, sCr kinetics are dependent on baseline renal function so that the time interval from kidney injury to 50% increase in sCr ranges from 4 hours with normal baseline renal function to more than 1 day with underlying advanced renal dysfunction.[41)] More importantly, sCr level is a marker of renal function rather than kidney injury, so, increased sCr levels are not always representative of kidney injury.

Blood urea nitrogen (BUN) was shown to be an important predictor of morbidity and mortality in patients with HF.[8)42-44)] The major difference between sCr and BUN is related to the reabsorption of BUN in the renal tubules. It is mediated by AVP, sympathetic nervous activity, renin-angiotensin-aldosterone system and to sodium reabsorption with volume status.[45)] Therefore, intensive diuretic treatment, enhance urea reabsorption and increase BUN. Recently, Testani et al.[46)] reported that, in Beta-blocker Evaluation of Survival trial, elevated serum BUN level with high dose loop diuretics was associated with high mortality in chronic HF (Fig. 2). BUN is also dependent on nitrogen production and in conditions causing an increase in protein catabolism, such as cachexia and gastrointestinal hemorrhage.[47)]

Novel markers

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is the most promising emerging biomarker for acute kidney injury. In humans, NGAL is a small 25 kDa 178 amino acid chain, expressed by neutrophils and other epithelial cells in the proximal collecting tubule.[48)] The physiological role of NGAL in renal ischemia or toxin induced kidney injury, may be to decrease injury by reducing apoptosis and increasing the normal proliferation of kidney tubule cells. It is freely filtered by the glomerulus and completely reabsorbed in the tubules. Several studies in various clinical settings have demonstrated
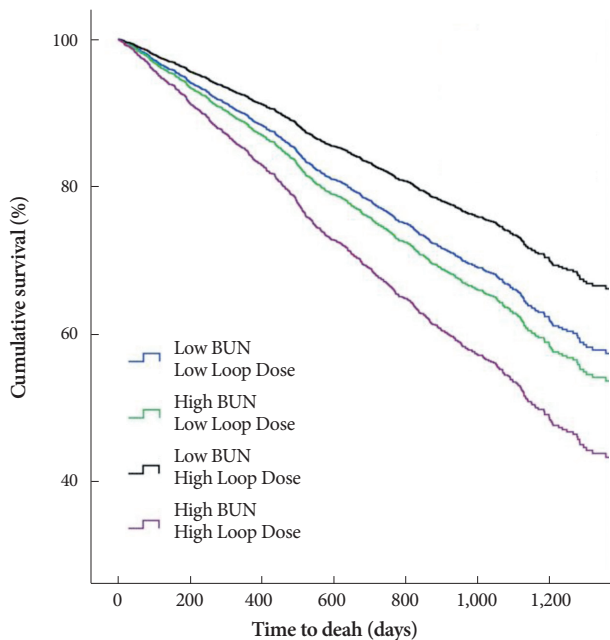
Fig. 2. Adjusted survival plots grouped by BUN and high dose loop diuretics use.[46]

the ability of NGAL to allow early identification of acute kidney injury, including cardiac surgery, contrast studies, ICUs and the emergency department.[49] In patients with acute HF, NGAL can predict worsening renal function more accurately in an earlier stage than sCr. Aghel et al.[50] reported that in 91 patients admitted for AHF, worsening renal function was observed in 38% within 5 days of follow-up. Patients who developed worsening renal function had significantly higher median serum NGAL levels (194 ng/mL vs. 128 ng/mL, p=0.001) at admission and it was associated with an increase in risk of developing worsening renal function.[50] Levels of urinary NGAL may be more sensitive as makers for tubular damage than serum levels. However, more studies are needed to confirm its usefulness in clinical practice and provide exact cut-off levels for different clinical settings.

Cystatin C

Cystatin C (CysC) is a 13.3 kDa, 122-amino acid protein, member of the superfamily of cysteine protease inhibitors, and is synthesized by all nucleated cells at a constant production rate. It is freely filtered by the glomerulus, and not secreted but slightly metabolized by tubular epithelial cells. Compared with sCr, CycC has been demonstrated to be independent of age and sex.[51)52)] Thus, serum CysC would be one of the ideal markers to estimate GFR. It has been demonstrated that CysC is a more sensitive marker than SCr for small changes in GFR and could be an earlier indicator of mild renal failure. In patients with AHF, CysC is an independent factor for longer length of hospitalization (p=0.01) and higher in-hospital and post-discharge mortality. Interestingly, elevated serum CysC is associated with higher mortality at

12 months in patients with normal sCr level (p<0.0001).[53]

Other biomarkers

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed in proximal tubule cells during renal diseases associated with either proteinuria, toxic or ischemic damage. It is expressed in post-ischemic kidneys while remaining undetectable in healthy subjects, and showing that it expresses during tubule-interstitial injury and inflammation. Urinary KIM-1 levels correlate with tubular KIM-1 expression in experimental models and in human renal disease.[54] In chronic HF, KIM-1 demonstrated a correlation with plasma N-terminal pro-brain natriuretic peptide (BNP) levels and, independently of GFR values, was associated with an increased risk of death or HF hospitalizations. KIM-1 is highly sensitive to acute tubular injury but in the setting of acute HF its role is still unsettled.[56]

N-acetyl-beta-D-glucosaminidase (NAG) is produced in the proximal tubule and after tubular injury, released into the urine. In patients with HF, urinary NAG levels, as KIM-1, were associated with plasma N-terminal pro-BNP levels and increased risk of death or HF hospitalizations regardless of GFR.[55] In addition, NAG levels were correlated with GFR (p=0.001) and effective renal plasma flow (p=0.006), suggesting that this marker can detect decreased renal perfusion in patients with low cardiac output As for KIM-1, data in AHF are lacking. The accuracy of this marker in acute kidney injury suggesting its usefulness in the acute setting and further studies are needed in order to define its role in AHF. Other novel protein biomarkers for the early detection of kidney are listed and briefly introduced in Table 2.

Treatment

In patients with acute HF, markedly activated neurohormonal axis and worsening renal function ultimately ensue to venous congestion and elevated CVP, which results in a vicious cycle. Thus, the focus of the treatment should be on reducing the congestion with as little hemodynamic compromise as possible.

Relief of congestion

Diuretics

Current practice guidelines recommend loop diuretics as the mainstay of therapy in patients with congestive symptoms in the setting of AHF.[11] In ADHERE registry, 88% of patients receive loop diuretics, mainly intravenously.[1] There are no randomized controlled trials to evaluate the beneficial effects of loop diuretics. However, it is evident that congestion correlates with mortality, therefore, patients with AHFS should be treated for the relief of congestion. In patients who have se-

Table 2. Protein biomarkers for the early detection of acute kidney injury

Biomarker	Associated injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
N-GAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α-GST	Proximal tubule injury, acute rejection
π-GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokines	Ischemia and graft function

GST: glutathione S-tranferase, KIM: kidney injury molecules, L-FABP: L-type fatty acid binding protein, NGAL: neutrophil gelatinase-associated lipocalin, NHE: sodium-hydrogen exchanger

Table 3. Causes of resistance to furosemide

Inadequate diuretic dose
Excess sodium intake
Delayed intestinal absorption of oral diuretics
Delayed diuretic excretion into the urine
Na+ reabsorption at diuretic-insensitive site in the nephron

vere congestion and renal dysfunction, diuresis may improve kidney function, possibly through relieving the central venous congestion. What is more beneficial for controlling congestion intermittent versus bolus, or high dose versus conventional dosage of loop diuretics is a recurring question. The Diuretic Optimization Strategies Evaluation (DOSE) trial is the first randomized, controlled exploration of a management strategy in loop diuretics in AHFS patients. In this study, there was no statistically significant difference in symptom relief or renal function at 72 hours between intermittent versus continuous infusion or low dose versus high dose strategy.[56]

There are several mechanisms for diuretic resistance: inadequate dose, excess sodium intake, delayed intestinal absorption, decreased excretion of diuretics at action site, vigorous sodium reabsorption at other sites of nephron (Table 3). Experts recommend switching from intravenous to continuous infusion in patients who seem to be nonresponsive to diuretics. Although, for the relief of congestion and symptoms, loop diuretics are very effective, it should be considered that there are serious adverse effects associated with loop diuretics.[57] Electrolyte abnormalities mainly hyponatremia, hypokalemia and hypomagnesemia are frequently developed with these agents. The loop diuretics can cause increased release of renin and further stimulation of neurohormones and acute vasoconstriction after administration, so, even though urine output is substantially increased GFR can be reduced by loop diuretics induced vasoconstriction.[58] Another approach to overcome diuretic resistance is limitation of total daily sodium intake to less than 2 gm, and fluid restriction of less than 2 liters. When moderate hyponatremia (<130 mEq/L) exists, the patient should be educated for more aggressive fluid restriction. The pharmacologic approach to overcome resistance is to add another diuretic that acts in distal tubule, such as a thiazide or metolazone. Continuous infusion of loop diuretics may avoid rebound absorption of sodium that occur when serum levels of loop diuretics are low or reduce ototoxicity. But, as stated above, in the DOSE trial, there was no difference in outcome of mortality.

Vasopressin antagonist

Patients with acute decompensated HF often have an activation of AVP release. AVP causes water retention via vasopressin type 2 (V2) receptors in the collecting duct. The V2 receptor antagonists-"vaptans"-can induce free water diuresis and correction of hyponatremia in patients with HF. In Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan trial, the efficacy of the selective V2 receptors antagonist, tolvaptan has been evaluated with 4,133 patients with HF for the outcomes, and symptoms/signs of HF. Compared to placebo, tolvaptan was associated with greater improvement of symptoms, but no benefit on outcomes. There was no derangement of renal function throughout the study.[59] Other studies conducted on subjects with chronic HF showed neutral effects of vasopressin antagonists on renal function compared with furosemide.[60] Therefore AVP antagonists can be applied in the limited setting of HF patients with hyponatremia. However, antagonists for V2 receptors are not yet available in Korea.

Adenosine antagonists

As mentioned above, adenosine has a detrimental effect on renal hemodynamics. On the basis of this pathophysiological concept, adenosine A1 receptor antagonists have been investigated in patients with advanced HF. Many relatively small, controlled studies have been conducted for the evaluation of adenosine receptor antagonists including BG9719, KW-3902 (rolofylline), and could find renoprotective effects of A1 receptor blockers. Based on these results a large-scale controlled trial (PROTECT trial) was designed. In this trial, renal function was included among the components of the primary endpoint. Unfortunately, the results of PROTECT were neutral for the primary endpoint (dyspnea relief combined with the absence of worsening HF at 1 week and worsening renal function at 7 and 14 days) and for the pre-specified secondary outcomes (death from any cause or rehospitalization for cardiovascular or renal causes through day 60 and the proportion of patients with persistent renal impairment).[30] In con-

clusion, the administration of rolofylline was not associated with favorable effects on renal outcomes. An important issue in the PROTECT trial was the excess of neurological complications observed in the rolofylline group. Therefore, adenosine receptor antagonist can not be recommended in HF patients with renal dysfunction.

Correction of hemodynamic abnormalities

Dopamine

When administered at low doses (≤2 μg/kg per min), dopamine may selectively improve renal blood flow through its action on DA1 receptors. Also, improvement of diuresis can be expected, even though small but favorable changes in renal function by administration of low dose dopamine occur. At intermediate doses (2-5 μg/kg per min), dopamine interacts with the β1-receptor, producing positive inotropic effects; this increase in cardiac output may be another favorable mechanism of the action of dopamine.[61][62] In the recently completed Dopamine in Acute Decompensated Heart Failure (DAD-HF) trial, 60 patients with acute HF were randomly assigned to continuous 8 hours infusion of high-dose furosemide (20 mg/h) or low-dose furosemide (5 mg/h) plus low-dose dopamine (5 mcg/kg/min). Both strategies had similar effects on hourly diuresis and dyspnea score. Worsening renal function was more frequently observed in the high-dose diuretic group (30%), than in the dopamine group (6.7%) (p= 0.042).[63] Length of hospitalization and 60-day mortality or rehospitalization rates were similar between both groups. Even though the favorable outcome was observed, the small sample size and no favorable effect on major outcome (mortality, rehospitlalization and free from renal replacement therapy), it can not be directly applied as evidence.

Other inotropics

Because renal hypoperfusion due to low cardiac output can contribute to renal dysfunction in acute HF, administration of inotropic agents might be useful. Dobutamine administration has been associated with an increase of diuresis and natriuresis, and these effects are likely caused by the increase in cardiac output.[64] Recently reported data showed that in 88 patients with acute HF randomized to levosimendan or dobutamine, only levosimendan administration was associated with an improvement in measured eGFR (+15 and +45% from baseline after 24 and 72 hours, respectively), whereas there was no change in the dobutamine group.[65] However, these data were obtained in small, single-center studies, and were not confirmed in the large Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial.[66]

There are possible suggestions to improve of renal function not related with increased cardiac output but associated with relief of venous congestion and decreased intra-glomeluar pressure. The absence of clinical benefit associated with increased cardiac index was shown in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study, and in the ESCAPE trial, which found no association between baseline renal function and cardiac index.[8][14] These results seem to confirm that, increased renal venous pressure and intraglomerular pressure, but not low cardiac output, could be the main determinants of renal dysfunction and diuretic resistance, and therefore represent the therapeutic target, whereas inotropic agents should not be the treatment of choice for this condition.

IV vasodilators

Intravenous vasodilators-nitrates and sodium nitroprusside-are frequently administrated, in patients with AHF with normal or high blood pressure. In KoHF registry, 35.8% of patients were treated with intravenous nitrate infusion.[13] At a low dose, nitroglycerin dilates venules and decreases cardiac filling pressures and myocardial oxygen demand; at higher doses, it decreases afterload and augments cardiac output. Sodium nitroprusside acts on vascular smooth muscle, and induce arterial and venous vasodilation.[67][68] Although, in patients with HF, nitrates and sodium nitroprusside do not have a direct influence on fluid overload and do not improve renal blood flow, compared with high doses of furosemide alone, treatment with nitrates added to low doses of furosemide has been shown to be associated with better outcomes in patients with acute HF and normal to high blood pressure. Relaxin causes systemic and renal vasodilatory effects via nitric oxide pathways and the endothelin type B receptor, lead to systemic and renal vasodilation and increased arterial compliance; triggering similar changes could potentially be beneficial in the treatment for patients with HF.[69]

On the basis of small sized data, a preliminary double blind, placebo-controlled, parallel group, dose-ranging study of relaxin for the treatment of patients with acute HF (Pre-RELAX-AHF) was designed to assess the effect of intravenous relaxin compared with placebo in 234 patients with acute HF, and mild-to-moderate renal insufficiency. Despite previous data suggesting favorable effects on GFR and renal blood flow, relaxin did not show a clear effect on renal function, although a greater weight loss with less diuretic use was noted. The ongoing RELAX-AHF study will provide more elements.

Nesiritide

Nesiritide is a recombinant human BNP and can be categorized as a vasodilator. It enhances peripheral vasodilation, natriuresis, and diuresis through activation of guanylate cyclase pathways; moreover, it antagonizes the effects of the renin-angiotensin system, endothelin, and catecholamines. In the United States and other countries, it is approved for the treat-

ment of congestive symptoms, in addition to diuretics, in patients with acutely decompensated HF. However, a subsequent meta-analyses of randomized trials evidenced untoward effects of nesiritide on renal function and mortality. In particular, patients with acute decompensated HF nesiritide significantly increased the risk of worsening renal function.

Recently, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial was performed to assess the effects of nesiritide on symptoms and outcomes of patients with acute HF. This study included 7,141 patients with acute decompensated HF, randomized to placebo or nesiritide. Unfortunately, it did not meet the pre-specified criteria for statistical significance. However, nesiritide was associated with a small improvement of dyspnea, without significant effects on outcomes. Thus, ASCEND-HF demonstrated that nesiritide is safe, but has only mild effects on symptoms, and no effects on outcomes.[70]

Neurohumoral Blockade

Although, RAAS has an important role in renal dysfunction in acute HF syndrome, the role of the RAAS blockade with ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors, or aldosterone antagonists in acute progressive stage of renal dysfunction is unclear. Additionally, patients with diuretic resistance and advanced HF frequently show intolerance to the hemodynamic and renal effects of RAA antagonists. Moreover, ACE inhibitors and angiotensin receptor blockers can lead to an acute decrease in GFR through the dilatory effect on the efferent arteriole. Thus, in patients with acute decompensated HF, the risk of worsening renal function RAAS blockers were frequently hesitant to initiate them.

However, the benefits of ACE inhibitors are clear, and outcomes are extremely poor in individuals with HF in whom ACE inhibitors are held. In the Cooperative North Scandinavian Enalapril Survival Study, enalapril treated group showed increased mean serum creatinine, but had lower mortality rates.[71] These data suggest that some increase in creatinine and reduction in GFR (up to 30%) using ACE inhibitors should be tolerated even in patients with renal dysfunction.

Ultrafiltration

Excess water can be removed by ultrafiltration using a semipermeable membrane in response to a transmembrane pressure gradient between the blood and filtrate side. The removed fluid by ultrafiltration is isotonic to plasma, and isotonic fluid loss may be a potentially better tool for the treatment of congestion in patients with HF who have an activation of primarily sodium retentive mechanisms. Compared with loop diuretics, relatively more sodium can be removed by ultrafiltration. In case of diuretic resistance, ultrafiltration

have been used to decrease excessive fluid overload and in patients with significantly decreased renal function, to correct abnormalities in electrolyte levels and acid-base status. In the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure there was marked weight loss and relief of HF symptoms, but no improvement of renal function.[72] In the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure trial, there was a marked decrease in body weight, vasoactive drug requirement as well as hospital readmission over 90 days in the ultrafiltration arm.[73] However, this was associated with a trend towards higher-serum creatinine level in the first week of therapy in the ultrafiltration arm. The ongoing Cardiorenal Rescue Study in Acute Decompensated Heart Failure trial will further define the use of this treatment in patients with acute decompensated HF and acute renal dysfunction.

Conclusions

For treatment of patients with acute HF, clinicians are frequently faced with worsening renal dysfunction. The main driver of the pathophysiology and symptomatology is congestion and the focus of treatment should be relieving congestion without hemodynamic compromise. Unfortunately, every modality of treatment has dual effects - beneficial and detrimental - on this aspect. Loop diuretics relieve congestion but stimulate the neurohormones and reduce GFR. Inotropes improve hemodynamics but can potentially increase mortality and arrhythmias. Vasopressin antagonists have not been proven to decrease mortality in a large randomized control trial, although there are no large data sets on mixed receptor blockers. Natriuretic peptides may worsen kidney function and fail to show clinical benefit. Vasodilators can cause substantial hypotension while improving the hemodynamics. Therefore, it might be impossible to provide guidelines containing beneficial treatment modalities based on robust evidence. Accurate assessment for hemodynamic status with clinical parameters combined with newer biomarkers and more appropriate and effective interventions would help us to achieve optimal hemodynamic status and outcome of patients with acute HF syndrome.

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