Challenge of Renal Protection in Acute Decompensated Heart Failure

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DEFINITION

The term cardiorenal syndrome has repeatedly been used to predict worst outcome when renal failure occurs as a result of ADHF. However, the pathophysiology of kidney disease in Heart Failure (HF) is quite different from the pathophysiology of cardiovascular complications in the setting of CKD. Our focus is on the challenge of renal protection in ADHF.

CARDIORENAL AXIS

Normally, the cross-talk between the heart and the kidneys occurs through atrial-renal reflexes, which contribute to maintaining the total body volume in the normal range. In a nonfailing heart, any increase in atrial pressure diminishes the arginine vasopressin release (AVP) through the Henry-Gauer Reflex, decreases renal sympathetic tone, and increases the atrial natriuretic peptide. All of these increase the urinary sodium and water excretion rate. In HF, however, there is blunting of these reflexes in the low-pressure circulation, probably secondary to being overridden by reflexes initiated in the high-pressure arterial circulation.

PATHOPHYSIOLOGY OF CARDIORENAL SYNDROME

Transrenal perfusion pressure is calculated as mean arterial pressure minus the central venous pressure. Therefore, for the patient with volume overload and heart failure, the combination of increased pulmonary artery or central venous pressure with low systemic pressure may lead to a severe compromise of the net renal perfusion pressure. Therefore, whenever there is an opportunity to reduce the central venous pressure, whether through vasodilation, improved oxygenation or volume reduction, this can result in significant improvements in renal blood flow and urine output.

In the setting of acute decompensated heart failure, there is generally inadequate cardiac output and decreased perfusion pressure and in the presence of risk factors such as diabetes and hypertension, there is further reduction of glomerular filtration. This will further worsen any pre-existing renal dysfunction. (Fig.1)

However, a more important contributor is likely the neurohumoral activation mediated by activation of arterial baroreceptors and intrarenal sensors. These reflexes lead to the activation of the renin-angiotensin system, sympatohadrenal system and arginine-vasopressin system - an intrinsic self-defense system to maintain blood pressure and intravascular volume. All of these factors will lead to peripheral and intrarenal vasoconstriction, further decreasing renal blood flow and GFR, and leading to a decrease in renal function. The consequences also lead to renal hypoxia, inflammation, cytokine release, and progressive structural and functional loss. The net clinical consequences are sodium and fluid retention, and progressive reduction of renal function, initially reversible, but ultimately irreversible damage. (Fig.2)

A recently identified contributing factor is adenosine and the related tubuloglomerular feedback. Adenosine can be locally released in the kidney under stress, and binds to receptors on the afferent arterioles and causes vasoconstriction, thereby reducing renal blood flow. Stimulation of the receptor also increases sodium resorption in the tubules,
Fig. 1: Pathophysiology of acute decompensated heart failure

Fig. 2: Role of decreased baroreceptor sensitivity, and activation of RAAS and SNS in water and sodium retention as well as worsening HF
leading to further sodium and water retention. Acute delivery of sodium to the distal tubules by diuretic therapy in acute decompensated heart failure will in turn stimulate further adenosine release from macula densa, and further reduce glomerular filtration. The aggressive use of diuretics may therefore cause further neuro-hormonal activation, and aggravate systemic and renal vasoconstriction, leading to additional reductions in renal function. The reduction in blood flow and filtration contribute actively to the diuretic resistance.

RISK STRATIFICATION AND PREDICTORS OF MORTALITY IN ADHF

With the advances in medicine in the treatment of ADHF, more cases are being discharged and readmitted with ADHF. Therefore risk stratification of these patients for intensification of diuretic therapy and/or device therapy is based on the patient’s baseline risk or mortality.

Laboratory Parameters

1. Blood urea nitrogen (BUN): Admission BUN of more than 43 mg/dl was found to be the best identifier of inhospital mortality in patients with ADHF.

2. B type natriuretic peptide (BNP): Harrison et al evaluated the prognostic importance of elevated levels of BNP in patients with ADHF. BNP level > 480 pg/ml predicted a 51% chance of death, hospital admission or emergency room visit in 6 months.

3. Troponins: Approximately 40% of patients who are admitted to the hospital with ADHF have plasma elevation of Troponin that are not associated with any ECG changes or findings of acute coronary syndrome. According to the finding of the ‘EFFECT trial’ it has been observed that the cardiac troponin I elevation (>0.5 microgram/litre) was a strong and independent predictor of all cause mortality.

4. Hypotension: Not only is a lower sodium concentration associated with higher mortality during hospitalization and post discharge but it also correlates with a higher risk of readmission within 6 months. This is supposed to be due to increased vasopressin level in heart failure.

5. Anemia: Anemia is common finding in patients with heart failure. The mechanism of anemia in CHF is multifactorial. Al Ahmed et al. have shown that with every decrease in haematocrit of 1%, the mortality rate rises by 2.7%.

Clinical Parameters

1. Renal insufficiency: A number of patients with ADHF may have baseline renal insufficiency. yet perhaps more important is the change of renal function during hospitalization. Gottlieb et al. have shown that even a small increase in serum creatinine will worsen the outcome. In the ADHERE registry the mortality rate is 4% for all the patients but the mortality of patients with significant renal insufficiency (serum creatinine > 3.0 mg/dl) is 9.4%. The CHARM investigators have found that 10ml/min decrease in GFR increased the adjusted hazard ratio of cardiovascular death or readmission by 10%.

2. Blood Pressure: Gheorghiade et al. in an examination of OPTIMIZE HF registry cohort have shown that systolic hypertension is not only common in acute HF but is inversely correlated with inhospital mortality regardless of admission LV systolic function. For admission systolic blood pressure readings <160 mm of Hg the Hazard Ratio for inhospital deaths increased 21% for every 10 mm of Hg fall.

3. Hypothermia: Angiotensin II regulates body temperature through AT I receptors. According to ACTIV in CHF trial an oral body temperature of less than 35.8 degree C was associated with an increased incidence of mortality (9.4% versus 5.9%).

4. Coronary Artery Disease (CAD): A recent analysis of OPTIMIZE-HF demonstrated a 14% higher in-hospital mortality in patients with CAD as compared with patients who do not have CAD (3.7% versus 2.9%). Post discharge mortality at 60 to 90 d was also increased by 37% (9.2% versus 6.9%, HR 1.46, 95% CI 1.14 to 1.85, P < 0.002) in the presence of CAD (76). These effects were independent of LV function. Lastly, CAD patients who had coronary revascularization had the same mortality as ADHF patients without CAD. Thus, it is important to appreciate the importance of CAD in patients who are admitted for ADHF as it relates to potential coronary intervention.

CHALLENGES IN PATIENT MANAGEMENT WITH CARDIORENAL SYNDROME

Managing the patient with cardiorenal syndrome often involves making recommendations or choices of therapies that are mutually contradictory. Because one is attempting to treat volume overload and congestion, the aggressive use of diuretics and volume depletion directly worsens renal function. On the other hand, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, while being cardiorenal protective, can lead to temporary worsening of renal function. To preserve renal function, it is preferable to replete intravascular volume and provide a salt load,
but these measures directly worsen cardiac congestion. Cardiologists and nephrologists often provide contradictory recommendations that are mutually incompatible for the attending medical team, reflecting the difficult choices that have to be made. Many patients end up being discharged from hospital either still volume loaded or markedly worse in terms of renal function. There is a high readmission rate for patients recently discharged from hospital with heart failure or renal failure. This dilemma at least partially accounts for the worsening clinical outcomes for patients recently admitted with heart failure and the cardiorenal syndrome.

**OPTIONS OF MANAGEMENT FOR CARDIORENAL SYNDROME**

**Optimize heart failure therapy**
The acute management of the patient with symptomatic congestion often focuses on symptomatic relief and the rapid removal of volume. However, to date, no therapies focused mainly on symptomatic relief or volume removal have demonstrated any benefit on improving survival or attenuating disease progression. This refocuses the importance of instituting or optimizing disease-modifying therapy for the symptomatic patients as soon as possible. These include, where appropriate, optimal doses of angiotensin modulators, beta-blockers and/or aldosterone antagonists. All of these therapies, when used judiciously, will help to improve the patient’s survival and reduce hospitalization. However, their effect on renal function and blood pressure during acute decompensation will need to be monitored very closely, initially on a daily and later on a biweekly basis following discharge. Much of this has been outlined in the Canadian Cardiovascular Society’s Heart Failure consensus guidelines updates21. The specific recommendations related to patients with heart failure and renal dysfunction appear in the 2007 guidelines, and are outlined in Table I.

**Optimize diuretic therapy**
Furosemide infusion, taking an estimated total daily dose and infusing it over 2 h to 4 h, may offer more effective diuresis and greater safety profile, in contrast to bolus injections. However, the studies to date are generally small in size, and the design not optimal, thus precluding a definitive first-line recommendation. Combination diuretics, where the loop diuretic (eg, furosemide) is preceded by an ascending tubular agent (eg, thiazides such as hydrochlorothiazide or metalazone), can be used to produce a more effective diuresis, overcome some diuretic resistance and increase fractional sodium excretion. However, patients on this combination need to be very carefully monitored for adverse events such as hypokalemia, worsening renal function and dehydration. The combination should be terminated as soon as the volume status has been restored to avoid long-term complications.

**Table I. Pulse Wave Pattern: Disease Progression of Left Ventricular Diastolic Dysfunction**

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<th>Recommendations</th>
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<tr>
<td>Heart failure patients with stable renal function (serum creatinine levels less than 200 µmol/L) should be monitored for serum potassium and creatinine if combination therapy is used or in the presence of potential dehydration (class I, level B).</td>
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<tr>
<td>Patients with heart failure with increasing serum creatinine should be assessed for reversible causes such as concomitant medications (e.g., nonsteroidal anti-inflammatory drugs), hypovolemia, hypotension, urinary tract obstruction or infection (class I, level C).</td>
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<td>In oliguric heart failure patients who are hemodynamically stable, diuretics, ACE inhibitors, ARBs spironolactone and nonheart failure drugs that can impair renal function should be reviewed daily (class I, level C).</td>
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<td>In stable heart failure patients who are not oliguric but have increasing serum creatinine levels of more than 30% from a previous stable baseline, the dose of diuretics, ACE inhibitors, ARBs and spironolactone may be reduced until renal function stabilizes (class 1, level C).</td>
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<td>In heart failure patients not responding adequately to more than 240 mg intravenous furosemide daily, treatment options include:</td>
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<td>More frequent or higher doses of intravenous boluses of diuretic (class IIb, level C);</td>
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<td>Combination with thiazide diuretic, eg, hydrochlorothiazide or metolazone (class IIA, level B); or</td>
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<td>Continuous intravenous furosemide infusion (class IIA, level B).</td>
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**Vasodilator therapy**

Vasodilators such as intravenous nitroglycerin or nesiritide (recombinant human B-type atrial natriuretic peptide) have been shown to be much less detrimental to renal function, particularly when used at low doses that do not decrease blood pressure. Vasodilators can rapidly reduce ventricular filling pressures and central venous pressures, and decrease myocardial oxygen consumption. They can also decrease systemic vascular resistance, decrease ventricular workload, increase stroke volume and improve cardiac output under the right circumstances. Intravenous nitroglycerin is a vasodilator commonly used to relieve pulmonary congestion in patients with decompensated heart failure. While it is an effective vasodilator, frequent dose titration of intravenous nitroglycerin is necessary to produce the desired hemodynamic effects and symptomatic relief. The reduction in venous pressure may be beneficial in reducing transrenal perfusion pressure. While intravenous nitroglycerin is effective in reducing symptoms and pulmonary congestion, it is not clear whether this has long-term benefits in terms of renal function or survival.

**Recombinant human B-type natriuretic peptide (nesiritide)**

Recombinant human B-type natriuretic peptide, or nesiritide, is an effective vasodilator with mild diuretic effects. It has been shown in moderate-sized controlled trials and registries to be effective in reducing symptoms when compared with placebo, with a reasonable safety profile. However, subsequent meta-analyses suggested that administration of nesiritide at the variety of doses tested (0.01 µg/kg/mL to 0.03 µg/kg/mL) in the setting of acute heart failure may increase the risk of worsening renal function.

However, subsequent studies of nesiritide under somewhat different circumstances contradicted the earlier meta-analysis in terms of renal function. A study of the Follow-Up Serial Infusions of Nesiritide trial (FUSION I) demonstrated that in a heart failure population at high risk for cardiorenal syndrome, infusion of nesiritide at two doses (0.005 µg/kg/mL or 0.01 µg/kg/mL) was well tolerated with no worsening of renal function.

**Dialysis or ultrafiltration**

Ultrafiltration is a mechanical process that directly removes plasma water across a semipermeable membrane that maintains the same osmolality as the plasma. On the other hand, hemodialysis aims to remove solutes from blood across the membrane down a concentration gradient, allowing customization of target electrolytes and solutes. Recent improvements in ultrafiltration devices allow flexible low-flow catheters to be inserted in the antecubital vein for venous-venous filtration. This is a relatively simple procedure, and obviates the need for intensive care admissions and monitoring.

Therefore, ultrafiltration can potentially address the clinical conundrum of worsening renal function, decreased urine output despite escalating doses of diuretics or diuretic resistance in severe heart failure.

**Vasopressin antagonist**

Vasopressin or antidiuretic hormone is secreted by the posterior pituitary gland in response to hyperosmolality or volume depletion. The release of vasopressin engages the V1a (vascular) and V2 (renal) receptors, which leads to vasoconstriction and water reabsorption through aquaporin channels in the tubules. Selective V2 antagonists, such as tolvaptan, can effectively mobilize free water clearance, hence aquaresis, and would end up increasing the serum sodium in those who are hyponatremic.

In the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist (ACTIV) trial, patients with acute heart failure showed a greater reduction in body weight at 24 h receiving tolvaptan compared with those receiving placebo or standard therapy. There was also an increase in urine output at 24 h, and a slight increase in serum sodium in the group treated with tolvaptan.

**Adenosine antagonist**

Adenosine antagonists are novel agents that have the effect of activating adenosine (A1) receptors and promoting diuresis. In the setting of impaired tubular glomerular filtration, adenosine is released and binds to A1 receptors to induce constriction of the afferent arterioles. This decreases renal blood flow and enhances sodium resorption by the proximal tubules. Adenosine antagonists have the potential to improve renal blood flow and increase sodium excretion. The safety and efficacy of adenosine antagonists are currently being evaluated in larger clinical trials to determine their net effect on renal function, and potential cardiovascular outcomes.

**Inotropes**

Short-term inotropic infusion, although frequently used to improve hemodynamics and symptoms in ADHF,
remains controversial. When patients present with profound circulatory collapse, inotropes may be absolutely required. For patients with ADHF who have evidence of end-organ hypoperfusion or diuretic resistance, but no frank hypotension, the use of inotropic agents is not well supported. Dobutamine is a synthetic catecholamine with mainly β1-receptor agonist and some β2-receptor activity, characteristics that make it an inotropic vasodilator. Use of milrinone, a phosphodiesterase III inhibitor, results in elevated levels of cyclic adenosine monophosphate in the myocardium and smooth muscle. This leads to increased cardiac contractility and vasodilation. Milrinone works via a different cellular signaling pathway than dobutamine; it therefore can be used simultaneously with catecholaminergic agonists or antagonists.

**Levosemendan**

Levosemendan binds to cardiac troponin C, stabilizing the conformational change of troponin C through binding to calcium thereby improving cross bridging and contractility. However because of reports of increased mortality in ADHF with Levosemendan, at present it is only used in Europe and is not approved by FDA for use in USA.

**COMMON STRATEGIES FOR BOTH THE CARDIOVASCULAR AND NEPHROLOGY TEAMS**

The previous focus on symptomatic treatment with increasing doses of diuretics only met with diuretic resistance. The new focus should be to recognize the cardiorenal syndrome, and treat the whole patient, and treat for long term. The optimization of heart failure therapy also preserves renal function. Newer approaches to diuretic infusion or combination therapy may reduce the degree of renal dysfunction, while vasodilators such as nitroglycerin and particularly nesiritide at low doses may improve transrenal blood flow while protecting renal function. Newer approaches such as ultrafiltration, vasopressin antagonists and adenosine receptor blockade may offer additional opportunities to improve volume regulation while preserving renal and cardiac function.