

Pathophysiology, Prevention, and Treatment of Severe Congestive Heart Failure Associated with Progressive Renal Failure

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ABSTRACT

Severe congestive heart failure (CHF) is progressive and almost invariably accompanied by varying degrees of renal failure. A common recommendation is to treat CHF with angiotensin converting enzyme inhibitor (ACEI) or a combination of ACEI and angiotensin receptor blocker (ARB). The result is progression of renal failure giving rise to decreased clearance of sodium and water and hence fluid overload, requiring repeated hospitalization for symptomatic relief. High doses of a combination of diuretics fail to induce adequate diuresis mainly due to very low systolic blood pressure caused by ACEI/ARB drugs. If avoidance of the use of ACEI/ARB drugs is not justifiable, approaches to afford symptomatic relief in a sustainable fashion will be diuretic infusion for 72 to 96 hours, which can be repeated as required. If diuretic response is not optimum, ultrafiltration by intermittent hemodialysis, intermittent peritoneal dialysis, or continuous ambulatory peritoneal dialysis must be initiated to provide symptomatic relief and reduce repeated hospitalization.

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Key words: CHF; CKD; Azotemia; Hyperkalemia

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PATHOPHYSIOLOGY OF RENAL FAILURE, FLUID OVERLOAD, AND ELECTROLYTE IMBALANCE IN SEVERE, CONGESTIVE, HEART FAILURE

Renal failure is a consistent accompaniment of CHF. Renal failure progresses as CHF worsens.

Chronic kidney disease (CKD) is a common comorbidity among the patients with CHF and is independently associated with increased morbidity and mortality^{1,2}. CKD-associated mortality is higher among those with diastolic heart failure than in those with systolic heart failure. A graded association was found between CKD-related deaths and left ventricular ejection fraction (LVED). The hazard ratios for CKD-associated mortality for the LVEF subgroups of <35%, 35%-55%, and >55% were 1.5%³.

Inhibition of renin-angiotensin-aldosterone system (RAAS) is an established approach to the management of patients with severe CHF. Marked decreases in intra-cardiac filling pressures and systemic vascular resistance are found with short and long-term use of ACEI drugs such as captopril or enalapril, and this cardiac improvement is generally followed by alleviation of dyspnea and an increase in exercise tolerance. Despite improvement in heart function, these drugs markedly decrease systemic blood pressure (BP) which reduces renal perfusion and leads to marked azotemia⁴.

Renal blood flow (RBF) decreases in proportion to the decrease in systolic BP. Glomerular filtration rate (GFR) decreases in parallel with RBF. There are multiple causes of decreased BP in heart failure. These are (1) low cardiac output; (2) decreased effective circulating blood volume (ECBV) as a result of excessive use of diuretics meant to promote diuresis; and (3) excessive use of ACEI/ARB drugs meant to improve heart function. Thus pathologically low BP accompanied by progressive decrease in renal function is the hemodynamic basis of inadequate response to diuretic therapy and decreased renal clearance of sodium and water. The result is sustained or recurrent fluid overload which is commonplace in patients with severe CHF and the main cause of frequent hospitalization for temporary relief of increased shortness of breath. A patient is illustrated here to exemplify that. Repletion of ECBV by fluid therapy helps renal function recovery and symptomatic relief⁵.

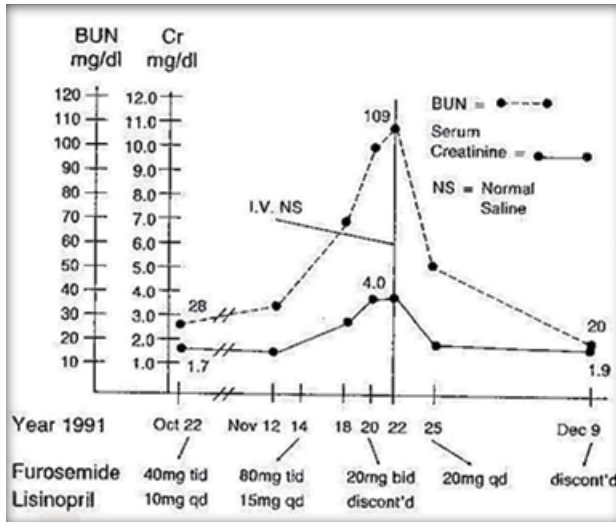


Figure 1 75-year-old white male was admitted with a history of severe shortness of breath and swelling of the legs. Within 3 weeks of initiation of high dose of furosemide (FURO) (240 mg/day) and lisinopril (LIS) (15 mg/day), BUN and serum creatinine (Scr) levels rapidly increased. BUN and Scr levels decreased rapidly upon discontinuation of LIS, and with infusion of normal saline (NS). FURO was continued in a reduced dose until BUN and Scr returned to baseline levels. FURO was then discontinued. Adapted from Mandal AK, Markert RJ, Saklayen MG, Mankus RA, Yokokawa K. Diuretics potentiate angiotensin converting enzyme inhibitor - induced acute renal failure. Clin Nephrol 1994; 42: 170-174 with permission^[3].

Patients with severe CHF typically show slight elevation of serum creatinine in the early stage but disproportionately more elevation of blood urea nitrogen (BUN) and elevated BUN/Scr ratio, as will be found in the figure (BUN/Scr 100/4=25) and in another patient presentation with severe CHF which will be found later (Patient #1). The greater elevation of BUN is the result of excessive reabsorption of urea facilitated by slow urine flow, and further prompted by increased level of antidiuretic hormone (ADH) which is common in CHF due to hypoxic stimulation of the hypothalamus. Markedly, elevated BUN commonly noted in patients with CHF and treated with ACEI/ARB drugs is responsible for poor appetite, nausea or vomiting, and consequently hypoalbuminemia and anemia.

There is a constant struggle between the cardiologists and nephrologists in managing patients with severe CHF which is associated with variable degrees of renal failure. Cardiologists arduously attempt to promote heart function by increasing the dosage of ACEI/ARB drugs and on top of that by adding aldosterone antagonists, such as spironolactone. Nephrologists generally take a neutral stand allowing the cardiologists to manage the patients until the cardiologists determine that conservative management is no longer tenable, and dialysis therapy is justifiable to maintain fluid and electrolyte balance.

This author takes a completely different stand, recognizing that RAAS inhibition causes progressive renal failure associated with moderate to severe hyperkalemia in CHF. This author discontinues these drugs to minimize the progression of CKD and developing symptomatic renal failure warranting urgent dialysis. In CHF, distal tubules exert a more dominant role than the proximal tubules in the retention of sodium and water prompted by the high level of aldosterone. This will be found later in patient #2 showing very low urinary Na and 8 times more urinary K (ratio Na/K=0.1 Normal=Na/K ratio 1.5). High aldosterone levels also enhance urinary potassium loss, as already shown in Patient #2, causing hypokalemia which is common in CHF unless and until ACEI/ARB drugs are added in

the regimen which reverses hypokalemia to severe hyperkalemia associated with suppression of aldosterone blunting urinary potassium loss and changing functional renal insufficiency to pathological renal failure, thereby further aggravating hyperkalemia. Author discontinues spironolactone if hyperkalemia persists.

Slow urine flow, decreased delivery of diuretics to the renal tubules, and increased ADH activity together promote excessive water and urea reabsorption in the collecting tubules, thereby further aggravating fluid overload, hyponatremia, and more azotemia. A previous study has shown that hyponatremia (serum Na <135 mmol/L) in CHF patients not only increases the risk of symptomatic hypotension, but is likely to cause functional renal insufficiency during ACEI therapy^[6]. On the other hand, other investigators have reported that ACEI given with a loop diuretic may have the additional advantage of raising the plasma sodium concentration in patients with CHF and hyponatremia^[7].

In summary, although inhibition of the angiotensin converting enzyme is of established value in the management of severe heart failure, this therapeutic approach is commonly accompanied by systemic hypotension and functional renal insufficiency, which may limit the utility of this treatment in some patients^[8]. Diuretic therapy constitutes an important part of medical management in severe CHF. However, response of diuretic therapy declines in parallel with the decrease in renal function, mainly due to decreased delivery of diuretics at the site of action in the tubules. Concomitant hypoalbuminemia due to malnutrition (inability to eat due to dyspnea) and urinary protein loss attenuates the binding of diuretics to albumin, which is essential for the delivery of diuretics in the loop of Henle^[9].

It is needless to reiterate that renal failure is not as much worrisome as hyperkalemia induced by ACEI/ARB therapy in CHF. There are abundant reports on severe to life threatening hyperkalemia associated with the above drugs in the literature including those of our own^[10,15]. It is evident that hyperkalemia invariably occurs associated with use of ACEI drug therapy and resolves after discontinuation of the drug but requires the prescription of potassium-binding resin or aldosterone analog, like fludrocortisone. The latter is very effective provided patient is not oliguric or anuric. However, life threatening hyperkalemia develops and patient is often brought to Emergency room with chest pain when aldosterone-antagonist such as spironolactone is added to treatment with ACEI/ARB drugs. The Randomized Aldactone Evaluation Study (RALES) has demonstrated that^[11]. In that study spironolactone prescription rate was 34 per 1,000 patients in 1994 and after the publication of RALES, prescription rate increased to 149 per 1,000 patients by 2001 ($p<0.001$). The rate of hospitalization for hyperkalemia rose from 2.4 per 1,000 patients in 1994 to 11.0 per 1,000 patients in 2001 ($p<0.001$), and the associated mortality rose from 0.3 per 1,000 to 2.0 per 1,000 patients ($p<0.001$). Publication of RALES was not associated with significant decreases in the rates of readmission for heart failure or death from all causes^[11]. Other authors have stressed the serious risk of severe hyperkalemia with the use of a combination of ACEI drugs and aldosterone antagonists^[10].

PREVENTION AND TREATMENT

A combination of risks consisting of sustained hypotension, renal failure, hyponatremia, and hyperkalemia associated with use of RAAS inhibitor drugs with or without use of aldosterone antagonist in CHF logistically contradicts the use of these therapies in CHF. Ignoring these risks and continuing these therapies will subject the patient to dialysis and high morbidity and mortality.

Investigators also noted that patients with CHF and renal dysfunction; using vasodilator drugs like hydralazine and nitrates were not receiving ACEI/ARB drugs. This finding suggested that intolerance to ACEI/ARB drug therapy may have led to the use of alternative vasodilator therapy. However, even among patients with severe kidney disease, the rate of hydralazine and nitrate use was only 22%^[16].

On the other hand, use of combination of loop diuretic such as furosemide or bumetanide and distal tubule diuretic such as hydrochlorothiazide or metolazone is likely to induce diuresis, and afford symptomatic relief. However, in the presence of renal failure (eGFR <30 mL/min or serum creatinine >2.5 mg/dL), diuretic therapy orally may not produce optimal diuresis such as five liters of urine per day. On the other hand, bumetanide infusion (12 or 24 mg in 500 mL normal saline if serum Na less than 135 mmol/L) at a rate of 21 mL/hour for 72 hours can produce 20 liters or more urine with disappearance of edema and marked relief of shortness of breath. Renal function decreases due to rapid loss of fluid, but recovers if replacement fluid in the form of normal or half normal saline is given when the diuresis peaks. This diuretic infusion is similar to venovenous hemofiltration except it is a simple procedure and can be repeated again and again with a short-term hospital admission.

Two patients are illustrated here to exemplify the effectiveness of bumetanide infusion.

Patient #1 An 82 year, Caucasian female was admitted into a local hospital in April of 2009 with a diagnosis of anasarca, CHF, lung cancer treated with chemotherapy, and chronic and acute renal failure. She was unable to move her legs because of massive edema. She was treated with Lisinopril 10 mg daily, and furosemide 40 mg PO twice daily. Initial laboratory showed BUN/serum creatinine 84/2.32 mg per dL, eGFR 21 mL/min ($n \geq 60$ mL/min), and albumin 2.6 g/dL. Upon hospital admission, Lisinopril and furosemide were discontinued, bumetanide 12 mg in 500 mL 5% dextrose in water was started at 21 mL/hour for 5 days. She received replacement fluid from Day 2.

Table 1 Total fluid loss 51055 mL=51.55 Kg=113.41 pound weight loss, She was then able to move her legs.

Urine Output	
Day 1	3800 mL
Day 2	7300 mL
Day 3	9000 mL
Day 4	6600 mL
Day 5	11050 mL

Table 2 Laboratory Study. Her breathing improved and she started to eat well. Her diuresis continued with bumetanide 2 mg PO twice daily.

	Before Infusion	After Infusion
BUN (mg/dL)	84	75
Scr (mg/dL)	2.32	1.41
eGFR (mL/min)	21	38
Albumin (g/dL)	2.6	2.6

Patient #2 65 year white male was admitted into a local hospital in early January of 2014, secondary to being poorly responsive and hypothermic. He was in circulatory shock. His blood pressure (BP) was very low to almost undetectable. Significant past history included extensive coronary artery disease status post coronary artery bypass graft in 1990 and 1999, history of ischemic cardiomyopathy, CHF, automatic implantable cardioverter/defibrillator and chronic obstructive pulmonary disease. He is a heavy smoker and still does. After resuscitative measures, he regained consciousness and blood pressure (BP) increased to 90/60 mmHg. He gave history of the

swelling of the lower extremities and genitalia. Electrocardiogram revealed normal sinus rhythm at 93 beats/minute, possible old anterior myocardial infarct and persistent nonspecific ST and T wave abnormalities. Cardiac enzymes were abnormal, Troponin levels were elevated. Eight hourly troponin levels were 0.41 ng/mL, 1.87 ng/mL, and 6.82 ng/mL but decreased to 4.67 ng/mL 24 hours later. A CT scan of the brain without contrast was unremarkable. Arterial blood gas showed pH 7.4, PCO₂ 40 mmHg, PO₂ 156 mmHg, HCO₃ 24.8 mmol/L and O₂ saturation was 98.9%. Serum chemistry showed BUN 45 mg/dL, Serum creatinine (Scr) 1.38 mg/dL, eGFR 55mm/min, Na 136 mmol/L, K 4.7 mmol/L, glucose 133 mg/dL, and BNP 2788 pg/mL. An echocardiogram showed left ventricular ejection fraction of 10%. Nephrology consultation was requested and seen by the author 4 days after admission to the hospital. Visit with the patient revealed severe orthopnea, repeatedly begging to help him sit at the edge of the bed for breath, generalized edema, and ascites which required one paracentesis with removal of 2 liters of clear fluid, chest auscultation revealed rales bilaterally, systolic BP ranged between 90 and 100 mmHg. Comprehensive laboratory studies on the day of nephrology consultation revealed Na⁺ 133 mmol/L, K⁺ 4.3 mmol/L, chloride 97 mmol/L, CO₂ 26 mmol/L, glucose 161 mg/dL, BUN 75 mg/dL, Scr 1.48 mg/dL, BUN/Scr ratio of 51, eGFR 51 mL/min, serum phosphorous of 4.4 mg/dL, uric acid 10 mg/dL, BNP 3933 pg/mL, albumin 2.9 g/dL. Thus this patient demonstrated clinical evidence of severe CHF (NYHA class IV) and renal failure with markedly elevated BUN and high BUN/cr ratio. A supporting evidence of severe CHF is markedly elevated BNP. On the day of nephrology consultation however, troponin level reduced to 1.78 ng/mL. Thus he had myocardial infarction on top of CHF. Chest X-ray revealed CHF, bilateral pleural effusion and pulmonary edema consistent with CHF. Since hospital admission, he was treated with furosemide (Lasix[®]) 40 mg iv Q 12 hour. Curiously, a urine electrolytes panel on the day of nephrology consultation revealed: Na 7 mmol/L, K 59 mmol/L, Cl 26 mmol/L, creatinine 85.8 mg/dL. This type of low urine Na and high urine K is typically seen in edematous condition such as CHF associated with low ECBV. He was immediately started with bumetanide (Bumex[®]) infusion at a dose of 24 mg in 500 mL of 0.45% saline solution at a rate of 21 mL/hour for 96 hours. Furosemide bolus injections were discontinued.

Table 3 Response to bumetanide infusion shown by urine output (mL) from Day 1 to Day 6.

Urine	Output with	Balance (Output-Intake)
Day 1	1850	+2042
Day 2	8250	-5793
Day 3	10850	-9616
Bumetanide infusion reduced to 15 mL/hour		
Day 4	8820	-7040
Bumetanide infusion discontinued		
Day 5	3350	-1722
Bumetanide 2 mg PO BID started		
Day 6	950	-110

Total fluid loss=24281 mL=24.3 liters.

As urine output progressively increased, his breathing improved in parallel, he was able to lie flat in bed, and rest and sleep. After 48 hours of bumetanide infusion he developed hypokalemia and metabolic alkalosis with a pH 7.51, PCO₂ 52 mmHg, PO₂ 80 mmHg and HCO₃ 41.5 mmol/L.

In order to reduce plasma HCO₃ hence pH, he received acetazolamide (Diamox[®]) 500 mg intravenously $\times 3$ doses. In addition to bumetanide infusion and boluses of acetazolamide, he also received normal saline with KCl infusion, high doses of spironolactone (Aldactone) 50 mg PO Q 6 hour and digoxin 0.25 mg PO daily.

Table 4 Laboratory before and after bumetanide infusion.

	Before Infusion	After Infusion
BUN (mg/dL)	75	58
Scr (mg/dL)	1.48	1.38
eGFR (mL/min)	51	58
Na (mmol/L)	133	130
K (mmol/L)	4.3	5.5
CO ₂ (mmol/L)	26	43
Albumin (g/dL)	2.9	3.9

The latter two drugs either alone or both resulted in hyponatremia and hyperkalemia. Spironolactone was discontinued. By the way he was receiving regularly losartan (as Cozaar®) 50 mg daily which was discontinued on the day of nephrology consultation.

An echocardiogram done day after discontinuation of bumetanide infusion revealed mildly dilated left ventricle with multiple wall abnormalities. Overall left ventricular ejection fraction was 20% with an increase from 10% in the past. Moderately elevated systolic pulmonary artery pressure at 44 mmHg and mildly dilated left atrium were noted. He is a heavy smoker requiring nicotine patch 14 mg every 24 hours in the hospital. Finally his serum hemoglobin increased from 10.2 g/dL at the time of hospital admission to 13.2 on the last day of bumetanide infusion. This increase in hemoglobin concentration is most likely due to hemoconcentration from massive loss of fluid. He was discharged home with the advice to continue bumetanide 2 mg PO BID, metoprolol (Lopressor®) 12.5 mg PO BID and digoxin 0.124 mg PO once daily. He will be followed up in the office soon.

Thus it is evident from the presentation of these two patients that bumetanide infusion for three to five days is associated with remarkable symptomatic relief of dyspnea and orthopnea, decreased swelling and increased sense of well being with removal of 25 to 50 liters of fluid. Very little information is available on the efficacy of furosemide or bumetanide infusion in CHF. Nevertheless, from the examples presented here, bumetanide infusion should be considered effective in reducing fluid overload and ensuring symptomatic relief.

If diuretic infusion fails to yield adequate urine output and afford symptomatic relief, contemplation of dialysis is a legitimate consideration. Of the different modes of dialysis therapy, maintenance hemodialysis (HD), intermittent peritoneal dialysis^[17] or continuous ambulatory peritoneal dialysis (CAPD) were tried in CHF. CAPD was tried most^[18]. While intermittent peritoneal dialysis removes a large amount of fluid using 4.25% dextrose solution^[17], CAPD offers the opportunity to continue ultrafiltration on an out-patient basis in patients in whom CHF did not improve after short-term ultrafiltration. CAPD has unique advantages as a method for ultrafiltration compared to HD. Fluid can be removed slowly and continuously, thus avoiding a decrease in BP which is often a problem with rapid method of fluid removal by HD. The disadvantages of CAPD include that it is done by the patient at home requiring a support system and peritonitis. This study, as well as others, has found that CAPD consistently improves the quality of life, reduces hospitalization and is thus, cost effective^[19]. Other authors have reported significantly reduced hospitalization by treating refractory CHF patients with CAPD. Peritonitis or exit site infection should not be a deterrent to recommend CAPD in patients with severe CHF refractory to conservative therapy. Some studies have noted improvement in heart function as well^[20]. A recent study from Germany has stated that in patients with chronic refractory CHF, volume overload and renal failure, peritoneal dialysis should be the therapy of choice^[21].

Although some data are available with regard to effectiveness of peritoneal dialysis including CAPD, very little published data is

available with regard to usefulness and safety of HD in chronic CHF. A patient is presented here to validate the importance of need and safety of HD in CHF (Patient #3).

Patient #3 An 80 year white female was brought to emergency room of a local hospital by her daughter for increased shortness of breath and was admitted into intensive care unit. She had history of hypertension, CHF, atrial fibrillation and myocardial infarction ×2. Prior to hospitalization she was treated as an outpatient with furosemide 40 mg PO BID, ramipril (Altace®) 10 mg PO daily, metolazone 5 mg PO daily, digoxin 0.125 mg PO daily, metochlorpropanide 10 mg PO daily and micro-K 10 mEq PO daily. A serum chemistry at the emergency room revealed BUN 96 mg/dL, Serum creatinine 5.3 mg/dL, glucose 101 mg/dL, Na 129 mmol/L, potassium 8.0 mol/L and CO₂ 22 mmol/L. A repeat serum K was 8.2 mmol/L. An electrocardiogram showed atrial fibrillation. An initial treatment of calcium gluconate, glucose and insulin and sodium bicarbonate was administered. Ramipril and micro-K were discontinued. Hemodialysis was initiated. A chest X-ray prior to hemodialysis showed cardiomegaly, pulmonary congestion and bilateral pleural effusion consistent with CHF. Following hemodialysis, she felt greatly relieved. Hemodialysis was continued on Mondays and Fridays per week for maintenance of fluid and electrolyte control and symptomatic relief. Hemodialysis treatment was put on hold and she was treated conservatively. She felt well. However, hemodialysis was restarted 3 months later for increased shortness of breath and weight gain of 8 kilogram (17.6 Lbs) in 3 months. She continued on maintenance hemodialysis three times a week. One year after her fist hemodialysis, she was completely asymptomatic, lived a comfortable life and frequently traveled long distances with her family. Her 24 hour creatinine clearance increased to 25 mL/min. She maintained a urine volume of 2 liters per day with diuretic therapy. Strangely, her daughter experienced increased difficulties in transporting her to dialysis clinic, and her financial situation did not permit her to reside in a nursing home. Her daughter decided to terminate her dialysis treatment. She died shortly thereafter.

SIMULTANEOUS HEART AND KIDNEY TRANSPLANTATION (HKT) IN PATIENTS WITH CARDIAC AND RENAL FAILURE

Ventricular assist device (VAD) implantation as a bridge to cardiac transplantation is an effective treatment option for end stage heart failure^[22]. This study describes 74 patients who underwent VAD implantation as a bridge to transplant, 28 patients developed renal failure, and of these 28 patients, 6 had simultaneous heart and kidney transplantation. All required hemodialysis prior to transplantation. Immunosuppression consisted of anti-thymocyte globulin followed by triple drug therapy consisted of calcineurin inhibitors, mycophenolate and corticosteroids. At 6 months after HKT, LVEF was 60.2±5.8% and serum creatinine 1.1±0.2 mg/dL. No rejection was noted^[22].

In summary, heart failure is a major public health concern; chronic kidney disease (CKD) is a common accompaniment of CHF. Renal failure progresses as CHF worsens. Patients with CKD has echocardiographic findings of a significantly large left atrial dimension, lower ejection fraction and fractional shortening and shorter deceleration time. A significantly greater proportion of patients with CKD also have moderate-severe mitral and tricuspid regurgitation and grades 2-3 diastolic dysfunction compared to patients without CKD. Multivariate regression analysis indicated

that a low ejection fraction and a low fractional shortening were significantly associated with CKD^[23]. Use of RAAS inhibition is a conventional therapy in CHF in order to increase ejection fraction. However, use of RAAS inhibitor drugs is associated with worsening of renal function and fluid overload; repeated hospitalization and high mortality. Oral diuretic therapy even in combination and in large doses produce less than optimum result but bumetanide infusion for 72 to 96 hours is found to produce massive diuresis even in the presence of CKD, symptomatic relief and even improvement in kidney function. Following infusion, satisfactory diuresis may be maintained with oral diuretic therapy. If diuretic infusion fails, dialysis remains the mainstay of therapy for symptomatic relief.

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