"Effective Use of Loop Diuretics in Heart Failure Exacerbation: A Nephrologist's View"

UTSW Internal Medicine Grand Rounds

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This is to acknowledge that Kamalanathan Sambandam, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Sambandam will not be discussing off-label uses in his presentation.

Goal- To provide the audience with the tools to maximize diuresis and mitigate deterioration in renal function during the treatment of acute decompensated heart failure.

Objectives-

- Understand the significance of worsening renal function occurring during the treatment of acute decompensated heart failure.
- Achieve a basic understanding of the determinants of renal function in the setting of decompensated heart failure.
- Understand the means to preserve renal function while achieving effective diuresis in the management of acute decompensated heart failure.

Epidemiology and Clinical Relevance of Worsening Renal Function in Acute Decompensated Heart Failure

There are almost 1 million hospitalizations annually in the United States with a primary discharge diagnosis of congestive heart failure [1]. Underscoring the magnitude of this medical problem and its expense to society is the $12.7 billion spent each year for inpatient management of acute decompensated heart failure (ADHF) [2]. Unfortunately, the therapeutic options for ADHF are limited such that many times, suboptimal outcomes are achieved prior to discharge. Indeed, analysis of outcomes from the Acute Decompensated Heart Failure Registry (ADHERE) reveals that >37% of patients continue to have some symptoms of heart failure at discharge. In fact substantial improvement of congestion is not achieved in many patients: 1/3 of patients lose ≤ 5lbs prior to discharge and up to 15% actually gain weight during their hospitalizations (Figure 1) [3]. These suboptimal endpoints are likely to be a major contributor to the high readmission rates seen after ADHF therapy.

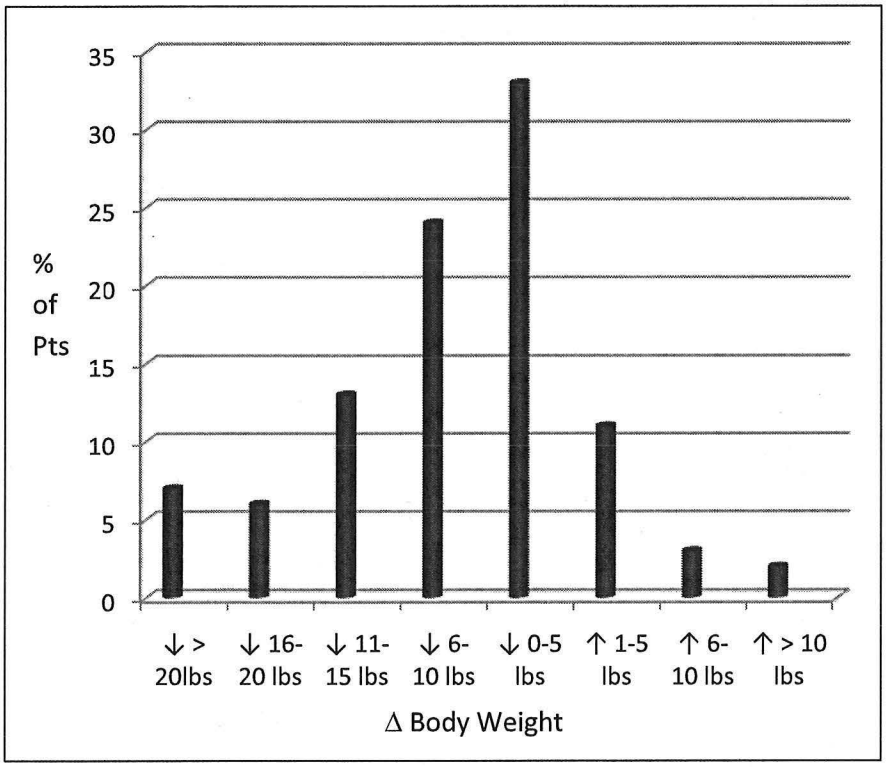

Figure 1. Body weight change at discharge in patients enrolled in the ADHERE database (n = 51013) [3].

The development of worsening renal function during attempts at diuresis in ADHF, the so-called "cardiorenal syndrome," is a main limiting factor in achieving adequate volume removal. In this regard, preserving renal function is an important goal of decongestion therapy, rather than being at odds with it as is often perceived. Beyond these concerns, impaired renal function has potent effects on hard clinical outcomes in ADHF. In fact, renal function is a stronger predictor of mortality than the degree of left ventricular dysfunction [4]. Several studies have consistently found that relatively mild declines in renal function, represented by increases in serum creatinine of just 0.3-0.5 mg/dL, predict increases in mortality and longer hospitalizations. Furthermore, such deteriorations in renal function are unfortunately common, occurring in 1/4 to 1/3 of patients (Table 1).

Despite this risk of worsening renal function, there are clearly some patients who, to the contrary, exhibit an improvement in renal function with ADHF therapy. This is the patient that, as most clinicians who frequently manage heart failure will have had experience with, displays a reduction in the serum creatinine as he is diuresed. We are left then with obvious questions:

How is it that some patients respond with an improvement in renal function during decongestion and others develop worsening function? How do we predict who will display worsening renal function? What therapeutic strategies can be employed to maximize the likelihood of improvement in renal function? Several novel treatment strategies including ultrafiltration, B-type natriuretic peptide, and vasopressin and adenosine antagonists have been investigated, unfortunately without robust positive results. Clearly, our understanding of the pathophysiology of the "cardiorenal syndrome" is incomplete. However, evidence is available that does shed some light on these questions. Limited clinical predictors of worsening renal function do exist and the judicious use of conventional therapeutic tools can provide adequate volume removal and renal protection during the treatment of most patients with ADHF.

	Chittineni 2007 [5]	Cowie 2006 [6]	Forman 2004 [7]	Krumholz 2000 [8]
Study Design	Retrospective, N = 509, ARF = ↑Cr 0.5mg/dL	Prospective, N = 299, ARF = ↑Cr 0.3mg/dL	Retrospective, N = 1004, ARF = ↑Cr 0.3mg/dL	Retrospective, age > 65, N = 1681, ARF = ↑Cr 0.3mg/dL
Incidence of AKI	21%	33%	27%	28%
Mortality	In-hospital- 9.35% vs 4.3% (p = 0.049)	30d- 15% vs 5% (p = 0.03)	In-hospital- RR 7:5 (CI 2.9-19.3)	In-hospital- 7% vs 4% (p < 0.05)
Duration of Hospi-talization	9d vs 7d (p < 0.0001)	13d vs 9d (p < 0.001)	>10d: RR 3:2 (CI 2.2-4.9)	9d vs 7d (p < 0.001)

Table 2. Summary of studies describing the incidence and clinical significance of acute kidney injury, variously defined, developing during the inpatient treatment of acute decompensated heart failure. Rates of mortality and duration of hospitalization are presented as outcomes data in patients with acute kidney injury versus stable renal function, respectively. AKI- Acute kidney

Mechanisms of Interaction Between the Failing Heart and Kidney

Characteristics that portend an increased risk of acute kidney injury (AKI) during the treatment of ADHF are provided in Table 2. Several attributes have been shown across multiple studies to carry some predictive value. Unsurprisingly, preexisting renal dysfunction is a consistent predictor of worsening renal function in this population, as it is in many other disease settings. Diabetes also seems to carry significant weight, with even the Chittineni study suggesting a positive correlation, though this did not reach statistical significance as in the other studies. Uncontrolled hypertension on admission may predispose to the development of AKI through the drop in renal perfusion that occurs with aggressive blood pressure lowering, as is often prescribed in this setting. Two characteristics which are notably poor predictors of renal dysfunction include the use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) on presentation and the degree of impairment in left ventricular systolic function. A conclusion that can be drawn from this data is that, more often than not, the pathophysiology of AKI during treatment of ADHF involves significant underlying renal disease, not simply pump failure, except in the case of frank cardiogenic shock. The clinical predictors highlighted here correlate strongly with vasculopathy, the substrate for impaired renal autoregulation. This primacy of impaired renal autoregulation is likely the reason that the

cardiorenal syndrome is much less commonly seen in young patients with even quite profound systolic dysfunction.

Risk Factor (AKI vs no AKI)	Chittineni 2007 [5]	Cowie 2006 [6]	Forman 2004 [7]	Krumholz 2000 [8]
Admit serum Cr	Mean- 1.74 vs 1.41mg/dL ($p < 0.001$)	Mean- 1.77 vs 1.5mg/dL ($p = 0.0025$)	Cr ≥1.5- 56% vs 28% ($p < 0.001$)	Cr ≥1.5- 49% vs 37% ($p < 0.001$)
Diabetes	NS	Insulin requiring- 21% vs 9% ($p = 0.01$)	25% vs 19% ($p = 0.05$)	44% vs 36% ($p = 0.005$)
Peripheral vascular disease		NS	18% vs 11% ($p = 0.005$)	
↑BP on admission			Systolic BP > 160- 39% vs 30% ($p = 0.008$)	Systolic BP > 200- 13% vs 7% ($p <0.001$)
Pulmonary edema		60% vs 42% ($p = 0.02$)	NS	NS
Admit serum Na	Mean- 133 vs 139mEq/L ($p <0.001$)	NS	NS	
Admit hematocrit	NS	NS	Hct < 30%- 17% vs 11% ($p = 0.03$)	Hct ≤ 30%- 16% vs 12% ($p < 0.01$)
Female gender	NS	NS	NS	63% vs 56% ($p = 0.01$)
Degree of ↓LVEF	NS	NS	NS	NS
ACEi/ARB use	NS	NS	NS	NS

Table 2. Summary of studies describing admission clinical characteristics which predict the development of acute kidney injury (defined as ↑creatinine of 0.3-0.5mg/dL) during therapy for acute decompensated heart failure. Either the risk factor's prevalence in those patients with versus without acute kidney injury, or the mean laboratory values for each of the two groups are presented. NS refers to no significant difference between the two groups. AKI- Acute kidney injury, ACEi/ARB- angiotensin converting enzyme inhibitor or angiotensin receptor blocker, BP- blood pressure, Cr- creatinine concentration, Hct- hematocrit, ↓LVEF- left ventricular dysfunction, Na- sodium concentration.

To further explore the causes of worsening renal function during diuresis in ADHF, one must appreciate the complex interactions that exist between the failing heart and the kidney (Figure 2). Poor cardiac function elicits several secondary neurohormonal responses which increase vascular tone and ventricular filling in an attempt to preserve tissue perfusion. The reduction in cardiac output is sensed by baroreceptors which increase catecholamine release from the sympathetic nervous system and adrenal glands. This increase in sympathetic activity, and the reduced cardiac output itself, elicit release of renin from granular cells in a specialized region of the nephron, the juxtaglomerular apparatus (JGA). Renin cleaves angiotensinogen to angiotensin I, which angiotensin converting enzyme converts to angiotensin II (AngII). AngII

elicits positive feedback on the sympathetic nervous system (SNS), facilitating further catecholamine release [9]. Both AngII and catecholamines induce glomerular arteriolar vasoconstriction and thus decrease renal plasma flow (RPF). Yet AngII has a disproportionate vasoconstrictive effect on the efferent arteriole and tends to preserve the glomerular filtration rate (GFR) despite this reduction in RPF. If however, AngII levels and/or catecholamine levels are very high, the reduction in RPF and filtration pressure is too great and GFR falls. Studies in various heart failure populations reveal consistent reductions in RPF to levels much lower than the normal 450mL/min. However, GFR does not start to fall until RPF falls below approximately 200mL/min [10, 11, 12].

Two other determinants of renal function in ADHF deserve discussion: tubuloglomerular feedback (TGF) and the degree of hemodynamic congestion present. In TGF, distal chloride delivery is sensed by the loop diuretic sensitive sodium/potassium/2 chloride cotransporter (NKCC2) in a specialized region at the end of the loop of Henle, the macula densa. The macula densa, by virtue of the hairpin orientation of the loop of Henle, is in close proximity to the vascular pole of the glomerulus where it interacts with the other elements of the JGA, the afferent arteriolar vascular smooth muscle cells and the renin secreting granular cells. When volume expansion or increased GFR leads to increases in chloride delivery to the macula densa, TGF results in vasoconstriction of the afferent arteriole and decreased renin release. The drop in afferent blood flow and the vasodilation of the efferent arteriole from the fall in AngII release results in a fall in GFR. Though still not completely understood, adenosine seems to be a major mediator of this cascade of events in the JGA. In heart

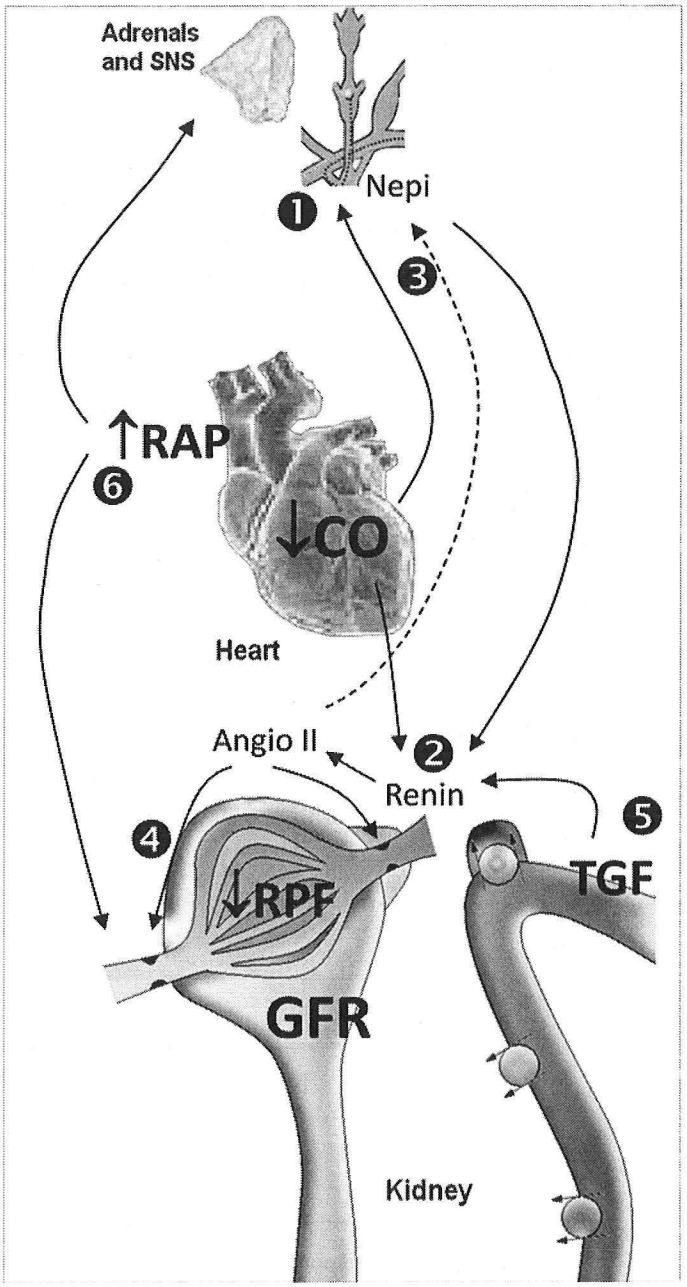

Figure 2. Simplified representation of interactions between the failing heart and kidney. Decreased cardiac output stimulates the release of catecholamines from the adrenals and sympathetic nervous system (1). The reduction in cardiac output and increased sympathetic activity leads to the release of renin from the juxtaglomerular apparatus (2). Renin generates angiotensin II which further promotes sympathetic activity (3) and which constricts the afferent and efferent arterioles, the latter to a greater degree (4). A reduction in distal solute delivery initiates tubuloglomerular feedback which feeds forward to fuel more renin release (5). The severity of congestion affects renal function through increases in right atrial pressure and worsening neurohormonal derangements (6), as further described in the text. Angio II- angiotensin II, CO- cardiac output, GFR- glomerular filtration rate, Nepi- norepinephrine, RAP- right atrial pressure, RPF- renal plasma flow, SNS- sympathetic nervous system, TGF- tubuloglomerular feedback.

failure, high AngII and catecholamines levels increase reabsorption of solute in the proximal nephron. This reduces distal chloride delivery and the opposite downstream events occur: the afferent arteriole vasodilates and renin release increases, leading to increased efferent arteriolar tone. If sympathetic tone is not too great (remember that AngII feeds forward to the SNS), the net effect will be an increase, or at least a preservation, in GFR.

Loop diuretics modulate tubuloglomerular feedback through blockade of the sensor of distal chloride delivery in the macula densa, NKCC2 (Figure 3). Though solute delivery to the late loop of Henle is dramatically increased by the inhibition of upstream NKCC2 transporters, loop diuretics also prevent the transport of chloride into the cells of the macula densa. The downstream effects would mimic the situation in which these cells sense low distal chloride delivery. Afferent arteriolar tone would fall and efferent tone will rise, the latter the result of increased renin and AngII levels. The net result would be fall in RPF but stable or increased GFR. This is in contrast to the effect of diuretics that act on different nephron segments such as the proximal or distal convoluted tubules in which RPF and GFR fall [13]. From purely this mechanistic consideration, it is predictable that adenosine blockade would not alter the incidence of worsening renal function with conventional loop diuretic-based therapy in ADHF, as has been corroborated in the largest trial of this novel intervention [14]. Loop diuretics decrease TGF and would therefore tend to reduce, not elevate, adenosine levels in the juxtaglomerular apparatus.

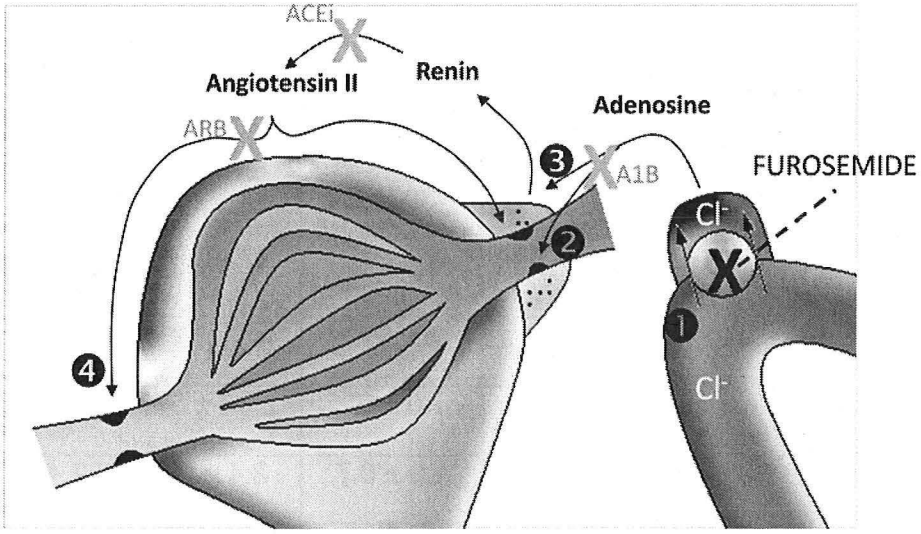

Figure 3. Tubuloglomerular feedback. Distal chloride delivery is sensed by the cells of the macula densa via the sodium/potassium/2-chloride cotransporter (1). Adenosine (and perhaps adenosine tri-phosphate) is released by the macula densa and binds its receptors in specialized mesangial cells and smooth muscle cells. The result is afferent arteriolar vasodilation (2) and release of renin from granular cells (3). Renin release results in increased angiotensin II which causes efferent and, to a lesser extent, afferent arteriolar vasoconstriction (4). Furosemide inhibits the first step in signal sensing as shown. The points at which adenosine receptor blockers (A1B), ace-inhibitors (ACEi) and angiotensin receptor blockers (ARB) inhibit steps downstream are also shown.

The last mediator of renal function in ADHF that will be discussed is the severity of hemodynamic congestion present. Congestion may lead to changes in renal function through alterations in renal vein pressures and through effects on the neurohormonal environment. Increasing right atrial pressure while maintaining constant arterial pressures would be expected to reduce renal perfusion pressure and thus reduce RPF. Increases in renal interstitial pressures in this setting of "renal congestion" may also contribute to a reduction in renal function. Such effects of venous hypertension have been described in animal studies as early as 1931 [15, 16]. Studies in humans with heart failure in which renal vein pressures were

assessed reveal that the measured reduction in perfusion pressure would predict a fall in RPF of only about 15%, not the 50% reduction that is normally seen [17]. Therefore, the lion's share of the fall in RPF is a result of the increase in glomerular arteriolar tone that develops as described above. However venous hypertension may be additive to this and provoke a significant decline in renal function. Evidence for the significance of elevated right atrial pressures in the worsening renal function observed in some patients with ADHF comes from a prospective observational study from the Cleveland Clinic. The severity of illness was high in this cohort of 145 ADHF patients who were treated in an intensive care unit with pulmonary artery catheter monitoring. Mean baseline characteristics included an ejection fraction of 20%, cardiac index of 1.9L/min/m^2, wedge pressure of 24mm Hg, and creatinine of 1.66mg/dL. Patients who developed worsened renal function during treatment had higher baseline (18 ± 7 vs 12 ± 6 mmHg, $p < 0.001$) and follow-up (11 ± 8 vs 8 ± 5 mmHg, $p = 0.04$) right atrial pressures than those who did not. Cardiac index, wedge pressure, and systolic blood pressure had no predictive value for the development of renal dysfunction [18].

Metrics	Severe Disease (n = 10)		Intermediate Disease (n = 9)		Mild Disease (n = 13)	
	Baseline	After UF	Baseline	After UF	Baseline	After UF
Total UF (mL)		3024 ± 1388		3105 ± 1013		1622 ± 797
MAP (mmHg)	85 ± 12	83 ± 13	100 ± 24	96 ± 19	82 ± 7	82 ± 12
PCWP (mmHg)	29 ± 6	21 ± 7*	31 ± 7	18 ± 5*	19 ± 9	10 ± 7*
RAP (mm Hg)	19 ± 7	10 ± 6*	18 ± 5	10 ± 5*	8 ±4	4 ± 3*
CI (L/min/m^2)	2.0 ± 0.6	1.9 ± 0.7	2.4 ± 0.6	2.4 ± 0.5	2.8 ± 0.5	2.3 ± 0.6*
NE (pg/mL)	3483 ± 1259	1835 ± 827*	1165 ± 640	1034 ± 431	380 ± 482	579 ± 436*
Renin (ng/mL/h)	40.3 ± 19.4	24.6 ± 12*	7.6 ± 6.9	10.7 ± 11.7	2.5 ± 3.9	7.4 ± 7*
Aldo (pg/mL)	1038 ± 517	515 ± 288*	270 ± 100	236 ± 115	133 ± 81	359 ± 348*
Creatinine (mg/dL)	2.8 ± 1.6	2.8 ± 2.2	1.7 ± 1.5	1.8 ± 1.3	1.5 ± 0.6	1.5 ± 0.6
BUN (mg/dL)	163 ± 72	168 ± 71	75 ± 48	85 ± 49*	52 ± 29	70 ± 44*
UOP (mL/d)	370 ± 350	2195 ± 1032*	1785 ± 624	1785 ± 569	1875 ± 644	1030 ± 440*

Table 3. Summary of baseline and follow up variables in 32 chronic heart failure patients subjected to extracorporeal ultrafiltration until right atrial pressure decreased by 50%. At data analysis, the patients fell into 3 groups based on severity of symptoms, neurohormonal derangements, and renal function at baseline and at follow-up. Aldo- aldosterone, CI- cardiac index, MAP- mean arterial pressure, NE- norepinephrine, PCWP- pulmonary capillary wedge pressure, RAP- right atrial pressure, SVR- systemic vascular resistance, UF- ultrafiltration, UOP- urine output. *Differences from baseline significant at $p < 0.05$ [19]. Modified from reference 19.

Whether greater hemodynamic congestion leads to renal dysfunction through a reduction in renal perfusion pressure as described above, or through a greater severity of neurohormonal derangements is not known. An argument for the latter comes from a prospective analysis of 32 chronic heart failure patients who underwent ultrafiltration with invasive hemodynamic and neurohormonal monitoring until the right atrial pressure fell by 50% (Table 3) [19]. The use of an extracorporeal means for volume removal eliminated the confounding effect of diuretics on neurohormone levels. Analysis revealed that the patients stratified into three separate groups. Those patients that by hemodynamic measurements and symptomatology had the greatest degree of congestion at baseline exhibited the highest baseline levels of norepinephrine, renin, and aldosterone and the worst renal function. Furthermore, after ultrafiltration this group manifested a reduction in these maladaptive neurohormone levels and a dramatic improvement in urine output with stable renal function. There was no change in cardiac index to explain the improvement in diuresis. Those patients with the mildest baseline symptoms, renal dysfunction, and perturbation in neurohormones actually exhibited a worsening in neurohormone levels and urine output. The last group of patients had a moderate baseline severity of disease and displayed an outcome that was intermediate between the other two. These data suggest that the relief of severe congestion can reduce vasoconstrictive and antidiuretic neurohormones when they are profoundly deranged and that this may result in favorable renal effects in the treatment of ADHF.

As can be seen from the above discussion, there are several determinants of renal function in the heart failure patient. The delicate balance between venous hypertension and afferent and efferent vascular tone, as influenced by systemic and local neurohormonal factors, determine whether glomerular filtration is maintained or deteriorates in the setting of impaired cardiac output. Notably absent in this account is an invocation of changing cardiac output to explain changes in renal function during ADHF therapy, despite this being the most often explanation offered at the bedside. It is often said that decongestion improves cardiac output by resetting to a more favorable point

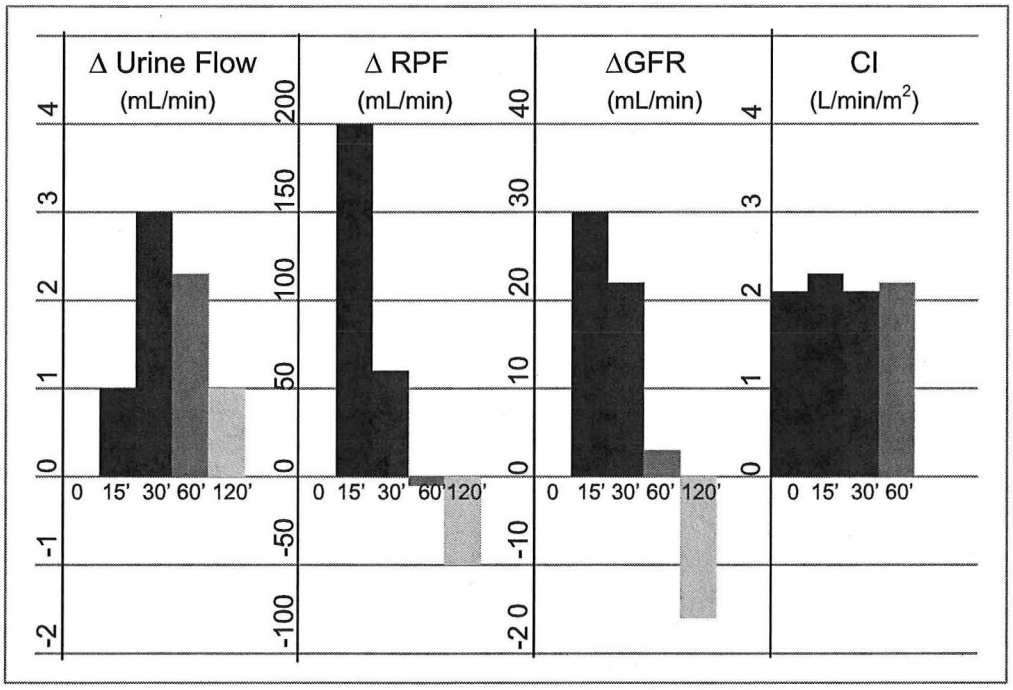

Figure 4. Change in urine output, renal plasma flow (RPF), glomerular filtration rate (GFR), and cardiac index (CI) at 15, 30, 60, and 120 minutes after a bolus of 0.5-1mg/kg furosemide in 20 patients admitted with acutely decompensated heart failure and myocardial infarction. Modified from reference 21.

on Starling's curve. Improved cardiac function with volume removal might occur in certain special conditions such as when left ventricular filling is impeded by a bulging intraventricular septum in severe right ventricular volume overload or when mitral regurgitation is exacerbated by a stretched mitral valve apparatus. However these situations are not common and the bulk of evidence reveals that cardiac output remains unchanged or declines with diuresis [20]. This discordance between improving renal function and cardiac output is most elegantly described in 20 patients presenting acutely with myocardial infarction and decompensated left ventricular failure [21]. RPF and GFR were accurately measured by para-aminohippurate and inulin clearances and a pulmonary artery catheter was used to obtain hemodynamic measurements before and after a bolus of furosemide. Increases in RBF and GFR were apparent within 15min of the dose of furosemide with no change in cardiac output. From the above concepts, possible explanations for these observations include the vasorelaxing effect on the afferent arteriole by loop diuretics via modulation of TGF and/or the effect of relief of severe congestion.

Strategies to Optimize Loop Diuretic Therapy in Acutely Decompensated Heart Failure

Now that some of the interactions between the failing heart and kidneys have been described, these concepts can be used to derive practical methods to maximize outcomes during the treatment of ADHF. The goal of these interventions is to achieve adequate volume removal with loop diuretic therapy while preserving renal function. Even better, it is hoped that the optimal outcome of improved renal function with diuresis may be more frequently realized. This discussion assumes compliance with medications and a low-sodium, fluid-restricted diet.

Rule 1- Maximize GFR.

Any intervention that results in a decline in GFR will tend to reduce natriuresis. This concept is obvious when one understands the dependence of natriuresis on GFR and fractional sodium excretion. With normal renal function, the proportion of the total mass of sodium that is filtered across the glomerulus (the product of the serum sodium concentration and GFR), avoids reclamation by renal tubular transport, and exits the body is very small. This "fractional excretion of sodium" (FENa) is usually significantly less than 1%. By blocking NKCC2 transporters in the thick ascending limb of Henle, loop diuretics increase the FENa. Let us suppose that with effective loop diuretic dosing, an identical rate of diuretic is delivered to the thick ascending limb of the loop of Henle in two identical ADHF patients A and B. Assuming identical sodium handling in the remaining tubular segments of the two patients, the measured FENa would be equal, perhaps around 3%. Let us now calculate the total daily natriuresis of these two patients if patient A has a GFR of 120mL/min (173L/d) and patient B has a GFR that is 80mL/min (115L/d):

- Natriuresis = Serum sodium concentration X GFR X FENa
- Patient A: 140mEq/L X 173L/d X 0.03 = 726mEq of sodium excretion/d
- Patient B: 140mEq/L X 115L/d X 0.03 = 483mEq of sodium excretion/d

Despite an equivalently effective loop diuretic dose, there is a 33% decline in total natriuresis. This fall in GFR would correspond to a rather small change in serum creatinine from 0.6 to 0.9 mg/dL in a 60 year-old male. For this reason, every attempt should be made to preserve GFR

and avoid nephrotoxic insults during ADHF therapy. Identification of patients at risk for worsening renal function using the predictors outlined in Table 2 may be helpful in this regard.

Rule 2- Avoid overly aggressive afterload reduction.

Vasodilators are often employed to reduce afterload and improve cardiac function in patients admitted for ADHF. However this population has a heavy burden of vascular disease, and is therefore at increased risk of impaired renal autoregulatory response to abrupt changes in systemic arterial pressures. Such patients may not be able to maintain RPF if blood pressures are rapidly reduced with aggressive vasodilator therapy. Recall that elevated blood pressures on admission may predict worsening renal function (Table 2), perhaps through this mechanism. Worsening renal function would inhibit natruiresis as described above. Furthermore, a drop in RPF from a decline in renal perfusion pressure, even if not accompanied by a fall in GFR, generally results in reduced natruiresis as well.

Rule 3- Administer low doses of angiotensin system inhibitors.

The evidence for the effectiveness of ACEis and ARBs to increase natriuretic response after loop diuretic dosing is somewhat variable. This is not surprising given the delicate balance that one must achieve to realize a positive effect. Recall from the relationships in Figures 2 and 3 that after a dose of loop diuretic there is an increase in renin release from the juxtaglomerular apparatus and an increase in circulating AngII. This, in combination with the increase in sympathetic tone AngII elicits, would lead to vasoconstriction of the afferent and efferent glomerular arterioles, and a reduction in RPF would ensue. The degree of reduction in RFP and the balance in afferent and efferent tone will determine whether GFR is maintained or falls. In addition, cardiac hemodynamics may also suffer from the increase in these neurohormones. Such a phenomenon has been prospectively observed during invasive monitoring after the dosing of furosemide in 15 severely decompensated ADHF patients without ACEi exposure [22]. Renin, norepinephrine, and vasopressin levels rapidly rose following a furosemide bolus and remained elevated for 2hrs. There was a concomitant fall in stroke volume that was not explained by a drop in preload since left ventricular end diastolic pressure and systemic vascular resistance rose simultaneously, consistent with an increase in afterload. The administration of an ACEi or ARB with the loop diuretic would blunt the rise in AngII and catecholamines and might thereby prevent a decline in RPF, GFR, and cardiac output. In a placebo controlled, double blind, crossover study in a small number of heart failure patients, RPF and GFR were

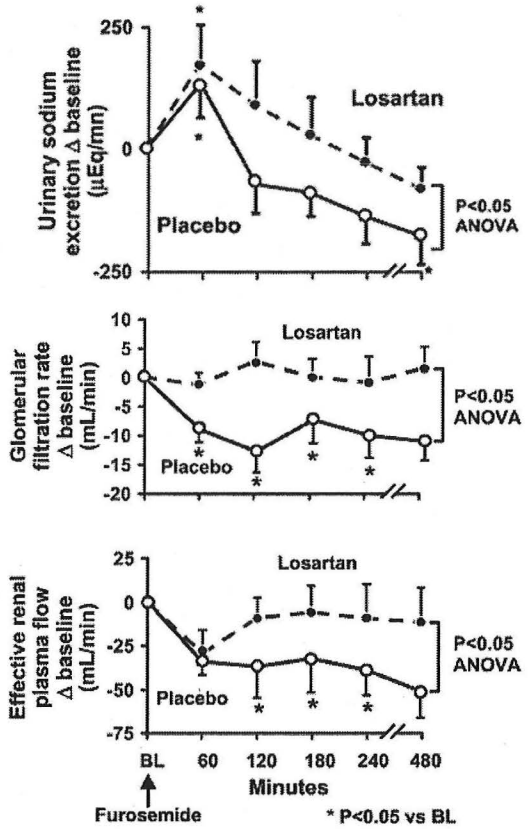

Figure 5. Renal response to furosemide plus losartan 50mg or placebo in 10 patients with congestive heart failure. Taken from reference 23.

measured accurately through para-aminohippurate and inulin clearances during the administration of furosemide and study drug [23]. The addition of losartan to furosemide resulted in augmentation in natruiresis and blunting in the decline in GFR and RPF compared to furosemide alone. Cardiac output was not measured. The renal response to angiotensin system blockade will depend on the degree to which baseline renal plasma flow is reduced and GFR is relying on efferent arteriolar tone. Evidence would suggest that relatively low doses of ACEi or ARB be used [24, 25]. If sufficient dose is given to raise the serum creatinine, however small, natriuresis would be impeded by the mechanism described above.

Rule 4- Employ a sufficiently frequent dosing interval of loop diuretic.

It has been proven that the bolus administration of furosemide to an individual elicits a transient period of natruiresis, lasting 6hrs if renal function is normal, followed by a longer period of increased renal tubular sodium avidity [26]. The mechanisms of this response are several and include an increase in AngII and catecholamines from the blockade of TGF and reduction in effective circulating volume, a fall in atrial natriuretic peptide, and an increase in distal convoluted tubule [27] and thick ascending limb transporters [28]. The result of these responses is that no net natriuresis is achieved with once daily dosing of loop diuretic, unless sodium intake is maintained at exceedingly low levels. Thus in order to achieve effective volume removal in AHDF, a setting in which anti-natriuretic factors are already increased, bolus dosing of loop diuretic must be administered two to four times per day.

The strategy of continuous dosing of loop diuretic is simply an extrapolation of this concept in which the interval time between dosing is reduced to zero. In this instance, there is no period during the day in which anti-natriuretic responses overwhelm the natriuretic effect of the loop diuretic and thus net negative sodium balance is sustained throughout the day. There is no evidence however that this dosing strategy results in more effective volume removal or less renal dysfunction than an intelligently prescribed bolus dosing regimen. This was proven by the findings of the only large, double blind, randomized controlled trial to study this question, the Diuretic Optimization Strategies Evaluation (DOSE) trial [29]. The results did reveal that patients receiving bolus dosing more often required a protocol-allowed dose increase at 48 hours than those receiving continuous infusions (21% vs 11%, p = 0.01). Indeed, at the bedside it is axiomatic that equivalent diuresis will be achievable if one is allowed to increase the bolus at will should one not be satisfied with the initial. This finding has little practical significance since the cost of furosemide is small.

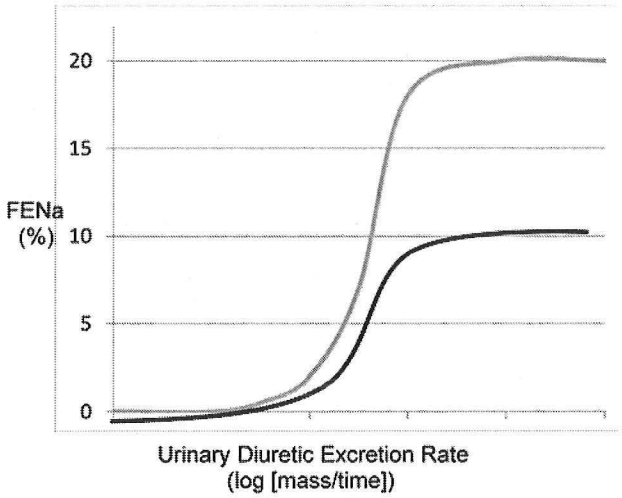

Figure 6. Relationship between the natriuretic response and the amount of loop diuretic reaching the tubular lumen. The darker curve represents the shift downward from normal that is typical in the context of heart failure [30],

Rule 5- Employ a sufficiently high dose of loop diuretic.

Conventional descriptions of effective loop diuretic dosing strategies stress the need to administer an adequate dose. The goal is to reach "threshold", the steep part of the dose-response curve at which point much a higher

FENa is achievable with modest increases in furosemide dose (Figure 6). Simple calculations as performed above will reveal that transiently reaching a high FENa a few times per day can achieve more total daily natruiresis than staying on the low, flat part of the curve with low doses administered more frequently. In addition to this often invoked aspect of loop diuretic physiology, more novel suggestions of how aggressive diuretic dosing might be helpful in the special case of ADHF are explored below. It should first be disclosed that several observational studies suggest that higher loop diuretic doses are associated with worse clinical outcomes in ADHF [31, 32]. However, these studies are limited by bias since patients with more severe disease and underlying renal insufficiency require higher diuretic doses. When evaluated in a randomized, prospective fashion in the DOSE trial, a high dose strategy compared to low doses was associated with a small increase in the risk of an elevation in creatinine greater than 0.3mg/dL (23% versus 14%, p = 0.04). This did not however, translate into an increased risk of adverse clinical outcomes.

The patient displaying hemodynamic congestion and worsened renal function, either on presentation or after attempts at diuresis, is the type of difficult patient to which the following discussion pertains. DOSE does not specifically address this clinical scenario. In DOSE, the average daily quantitiy of furosemide administered in the high dose arm was 260mg (about 80mg TID or 10mg/hr). A much higher dose may be needed in this class of patient. The presence of renal insufficiency alone necessitates a higher dose of loop diuretic to achieve equivalent drug delivery to the active site, and thus to achieve the same FENa as a patient with normal renal function. But beyond this fact, it is the author's experience that when the loop diuretic dose is aggressively titrated upward so that a net 1-2.5kg of fluid per day is removed (while also attending to the other rules above), the patient often responds with stability or improvement in renal function. This is often true even in the patient who has been exhibiting worsening renal function with lesser amounts of fluid removal. For most patients with access to three meals per day, this requires 3-5L/d of urine output. Frequent reassessment and dose titration is required to ensure that the goal will be achieved that day. Indeed, the argument will be made that achieving a lesser diuretic response,

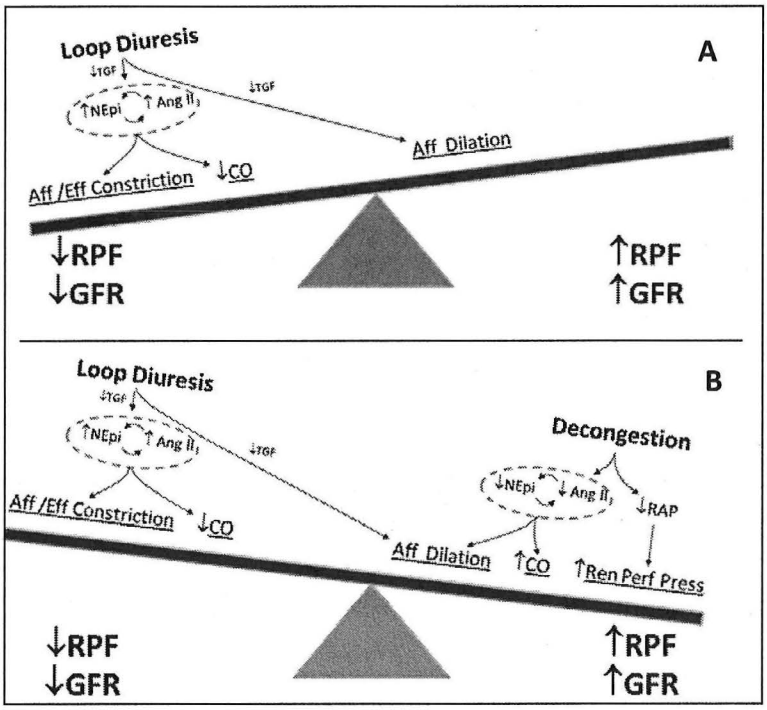

Figure 7. (A) Proposed mechanism by which a more conservative diuretic strategy can lead to worsening renal function in a heart failure patient with tenuous renal function. Vasoconstricting influences predominate through tubuloglomerular feedback. (B) More aggressive volume removal may offset the maladaptations of tubuloglomerular feedback and promote improved renal perfusion from a reduction in vasoconstrictors and improvement in renal venous hypertension. Aff- afferent arteriole, Ang II- angiotensin II, CO- cardiac output, Eff- efferent arteriole, GFR- glomerular filtration rate, NEpi- norepinephrine, Ren Perf Press- renal perfusion pressure, RPF- renal plasma flow, TGF- tubuloglomerular feedback.

may paradoxically increase the risk of further renal dysfunction. Quite large doses of loop diuretic may be required to achieve this rate of volume removal. With profound renal dysfunction, maximal FENa can be achieved with intravenous bolus furosemide doses of 200mg [33], though even higher doses may be warranted to ensure that effective natriuresis is sustained for longer periods. Progressive increases in continuous infusions of furosemide of up to 160mg/hr have been studied in ADHF patients with resistance to high doses of loop diuretics [34]. Despite these massive doses, further increases in FENa were achieved in some patients as the drug was titrated upward. Furthermore, as long as the GFR was greater than 30mL/min, blood furosemide levels remained below the theoretically ototoxic range of 100μg/mL. When ototoxicity did occur, it was manifested as tinnitus which was transient and completely reversible.

Concepts that have already been discussed may explain how more aggressive diuresis can mitigate or improve renal dysfunction in these high-risk ADHF patients (Figure 7). When loop diuretics are administered but ineffective volume removal is achieved, the vasoconstrictive responses of reduced TGF predominate. Increased norepinephrine and Ang II lead to severe reductions in RPF and perhaps even reduced cardiac output from increased afterload. However, when effective decongestion is achieved, the determinants of renal function are tipped in favor of increased RPF and improved GFR. Reduction in congestion limits the rise in norepinephrine and AngII. The rise in glomerular arteriolar tone is mitigated. The reduction in renal venous pressure improves renal perfusion pressure, further supporting RPF. Cardiac afterload falls.

Additional support for the "dose-responsiveness" of loop diuretic-induced improvements in renal function in ADHF with renal insufficiency comes from the author's own unpublished experience as part of an unrelated pilot study. Figure 8 summarizes the clinical course of BP, a 72 year-old female who presented with ADHF (ejection fraction = 25%), renal insufficiency and marked hypervolemia despite home diuretic therapy. Inpatient therapy did not involve inotropes and included intravenous bolus dosing of furosemide of up to 320mg three times daily. Her urine output average between 3-5L/d during the middle portion of her hospitalization and she eventually achieved a total weight loss of 15kg by discharge. Note the correlation between effective volume removal and improving renal function. In preparation for discharge, her diuretics were converted to oral dosing

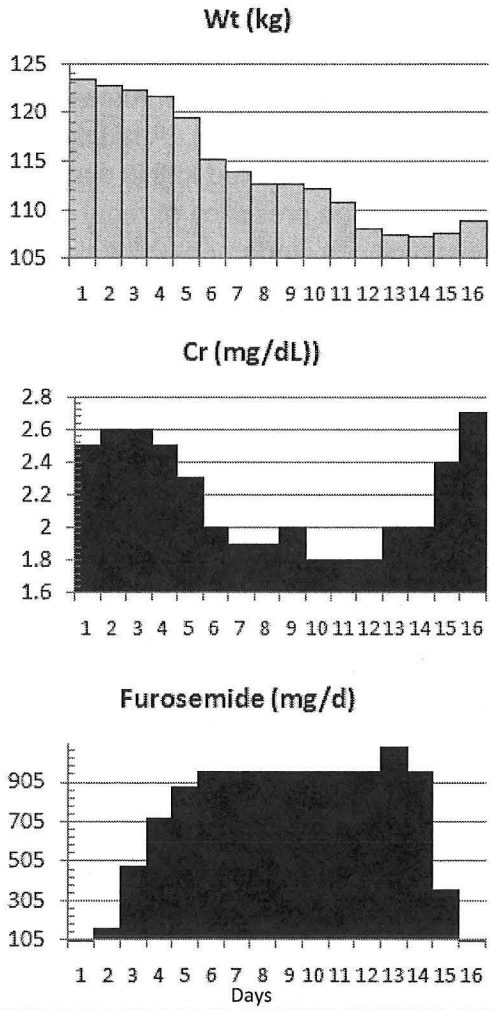

Figure 8. The clinical course of a patient who presented with decompensated heart failure, renal insufficiency, and diuretic resistance. Loop diuretic based therapy was the main means of volume removal. Note the trend in worsening renal function at lower diuretic doses and improving renal function with higher doses. Cr- creatinine, Wt- weight.

on day #15. She developed an abrupt rise in creatinine at this point, despite the fact that accurate weights indicated that she was in net positive fluid balance. Hypovolemia would therefore not provide an adequate explanation for the deterioration in renal function and no hypotension or additional medication changes occurred. Her diuretics were held and eventually her renal function improved. Similar cases have been noted in the literature in which deterioration in renal function occurs despite neutral or even positive fluid balance, when diuretics are rapidly down-titrated [34, 35].

Rule 5- Once loop diuretics have been maximized, add a thiazide diuretic.

Increases in distal thiazide-sensitive solute transport occur immediately upon blockade of upstream NKCC2 with loop diuretics. This occurs because an increase in sodium delivery to this portion of the nephron results in an immediate increase in sodium and chloride flux due to the concentration dependence of the thiazide-sensitive transporter activity [36]. Within 60min of furosemide dosing there is an increase in the number of thiazide sensitive transporters present in the membrane [27]. Later adaptations to increased solute delivery to this segment occur and are apparent from an increase in cell volume and sodium/potassium/ATPase activity [37]. The net effect is a reduction in the natriuretic response to loop diuretics. Once a sufficient dose of loop diuretic is administered to reach dose-response threshold, one can add a thiazide diuretic to augment natriuresis. Earlier dosing of thiazides when suboptimal loop diuretic dosing is employed may forfeit the potential improvements in renal function that are possible with effective TGF blockade. Thiazides do not have this potential favorable effect on renal function. Furthermore, marked potassium wasting is a common side effect from this strategy of sequential blockade. If one does decide to initiate a thiazide to augment diuresis, there is no evidence that metolazone is superior to any other thiazide in this setting.

Conclusions

We still do not fully understand the complex interactions between the failing heart and kidney. Most clinicians who frequently take care of patients with ADHF will have had a wealth of experience with patients who stratify into 3 groups. One group has no change in renal function during therapy. One group demonstrates worsening renal function with attempts at diuresis. The last group reveals improvements in renal function with effective volume removal. Despite this frequent clinical observation, we still do not have a robust means to predict to which group an individual patient will belong. We do not have guidelines to ensure that the best chance for this latter outcome is realized. Here is a proposed conceptual framework with which to approach this question. It is hoped that further investigation will continue and that we will become more skillful in the use of this clinical tool which has been in our armamentarium since the 1960s, the loop diuretic.

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