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

Author

*Kamalanathan K. Sambandam, MD*

Editor

*Biff F. Palmer, MD*

**Abstract:** Unfortunately, patients with congestive heart failure suffer frequent admissions for the management of fluid overload. Loop diuretics are pivotal in the management of this common clinical problem. Although loop diuretics have been in clinical use since the 1960s, we still do not understand how to optimally administer these drugs. It is unknown why some decompensated heart failure patients exhibit improvements in renal function with diuresis, whereas others display renal function deterioration, limiting attainment of euvolemia. Here the physiologic interactions between the failing heart and kidneys are reviewed. A conceptual framework is presented that emphasizes the balance between tubuloglomerular feedback and venous congestion in determining renal function during loop diuretic use in heart failure. Within this framework, guidelines are derived that seek to maximize the chance for achieving adequate volume removal while maintaining stable or improved renal function during the treatment of acute decompensated heart failure.

**Key Indexing Terms:** Heart failure; Loop diuretics; Renal insufficiency. **[Am J Med Sci 2014;347(2):139–145.]**

## RELEVANCE OF WORSENING RENAL FUNCTION IN ACUTE DECOMPENSATED HEART FAILURE

There are almost 1 million hospitalizations annually in the United States for congestive heart failure. Analysis of the Acute Decompensated Heart Failure Registry reveals that 1/3 of the patients admitted for acute decompensated heart failure (ADHF) lose ≤5 lbs before discharge and up to 15% gain weight.[1] Worsening renal function during attempts at diuresis in ADHF, the so-called "cardiorenal syndrome," is a main limitation in achieving adequate volume removal. Furthermore, studies have consistently found that relatively modest declines in renal function, represented by serum creatinine elevations of just 0.3 to 0.5 mg/dL, predict longer hospitalizations and increases in mortality. Unfortunately, such deteriorations in renal function are common, occurring pounds in 1/4 to 1/3 of patients.[2–5]

Despite this risk of worsening renal function, there are clearly some patients with ADHF who, as most clinicians who manage heart failure have observed, display improvements in renal function during diuresis. An obvious question arises: How can we maximize the likelihood of an improvement in renal function? Several novel therapies including ultrafiltration, B-type natriuretic peptide, and vasopressin and adenosine antagonists have been investigated, unfortunately without clear benefit. First, this discussion explores the physiology between the failing heart and kidney. Then, from this context, guidelines for loop diuretic–based therapy are presented that seek to achieve adequate volume removal and renal protection during ADHF management.

## INTERACTIONS BETWEEN THE FAILING HEART AND KIDNEY

To further explore the causes of worsening renal function during diuresis in ADHF, one must appreciate the complex interactions between the failing heart and the kidney (Figure 1). The reduction in cardiac output is sensed by baroreceptors that 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 the juxtaglomerular apparatus (JGA) of the nephron. Renin cleaves angiotensinogen to angiotensin I, which angiotensin-converting enzyme converts to angiotensin II (AngII). AngII elicits positive feedback on the sympathetic nervous system, facilitating further catecholamine release. Both AngII and catecholamines induce glomerular arteriolar vasoconstriction, decreasing renal plasma flow (RPF). Yet AngII has a disproportionate vasoconstrictive effect on the efferent arteriole, preserving the glomerular filtration rate (GFR) despite reduced RPF. However, if AngII levels and/or catecholamine levels are very high, the reduction in RPF and filtration pressure is too severe and GFR falls.

Two other determinants of renal function in ADHF deserve discussion: tubuloglomerular feedback (TGF) and severity of hemodynamic congestion. In TGF, distal chloride delivery is sensed by the loop diuretic–sensitive sodium/potassium/2 chloride cotransporter (NKCC2) in the macula densa at the end of Henle's loop. The hairpin orientation of the loop of Henle allows for close proximity of the macula densa with the other elements of the JGA, the afferent arteriolar smooth muscle cells and the renin-secreting granular cells at the glomerular vascular pole. When volume expansion or increased GFR results in increased chloride delivery to the macula densa, TGF mediates afferent arteriolar vasoconstriction and decreased
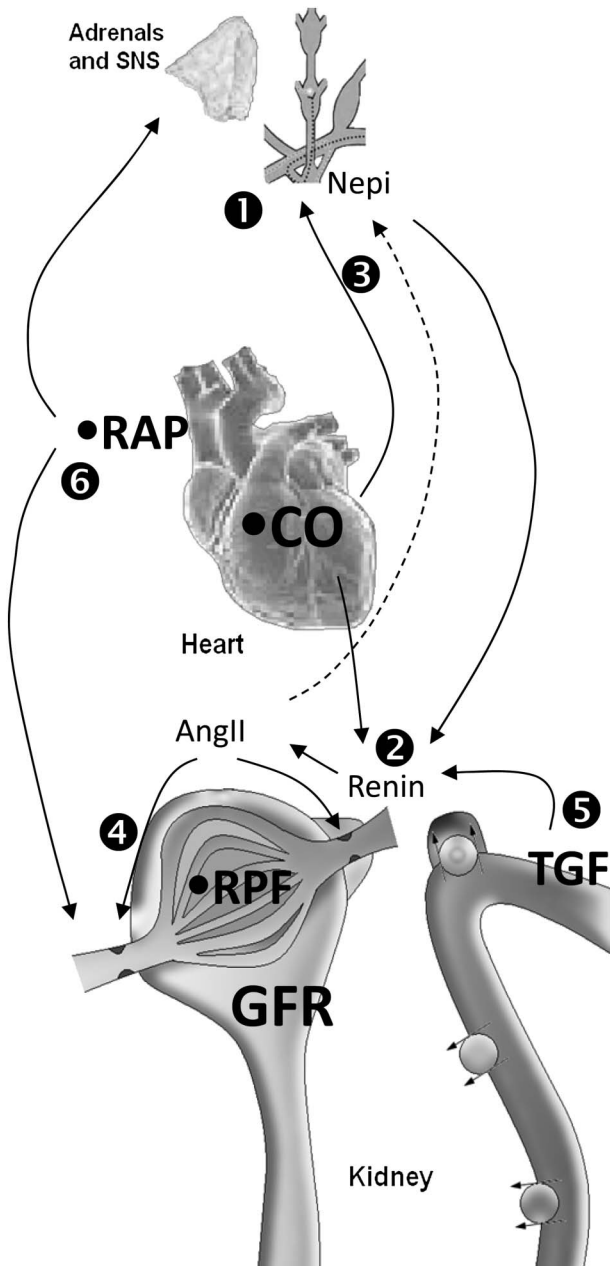
FIGURE 1. Interactions between the failing heart and kidney. Decreased cardiac output stimulates catecholamine release from the adrenals and SNS (1). The reduction in cardiac output and increased sympathetic activity induces renin release from the JGA (2). Renin generates AngII, which further promotes sympathetic activity (3) and which constricts the afferent and efferent arterioles, the latter to a greater degree (4). A reduction in distal solute delivery influences TGF to fuel more renin release (5). Hemodynamic congestion affects renal function through increases in right atrial pressure and worsening neurohormonal derangements (6), as described in the text. AngII, angiotensin II; CO, cardiac output; GFR, glomerular filtration rate; JGA, juxtaglomerular apparatus; Nepi, norepinephrine; RAP, right atrial pressure; RPF, renal plasma flow; SNS, sympathetic nervous system; TGF, tubuloglomerular feedback.

renin release. This afferent vasoconstriction, with efferent arteriolar vasodilation from the fall in AngII, decreases GFR. Although not completely understood, adenosine appears to mediate this cascade of events in the JGA. In heart failure, high AngII and catecholamine levels increase proximal tubular reabsorption of solute. 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, the net effect will be maintenance of GFR despite reduced cardiac output and RPF.

Loop diuretics modulate TGF through blockade of NKCC2, the sensor of distal chloride delivery in the macula densa (Figure 2). Although solute delivery to the late loop of Henle is dramatically increased by inhibiting upstream NKCC2 transporters, loop diuretics also prevent chloride transport into macula densa cells, mimicking a state of low distal chloride delivery. Afferent arteriolar tone falls and efferent tone rises, the latter the result of increased renin and AngII levels. The net result is an increase in GFR with variable effects on RPF. This is in contrast to the effect of diuretics acting on the proximal or distal convoluted tubules, in which RPF and GFR fall.[6] From purely this mechanistic consideration, it is predictable that adenosine blockade would not alter the incidence of renal dysfunction with loop diuretic therapy in ADHF, as has been corroborated in the largest trial of this intervention.[7] Loop diuretics decrease TGF and therefore reduce adenosine levels in the JGA.

The last determinant of renal function in ADHF that will be discussed is severity of hemodynamic congestion. Congestion may alter renal function through changes in renal vein pressures and through effects on the neurohormonal environment. By the first mechanism, increasing right atrial and renal vein pressure while maintaining constant renal arterial pressures would reduce net renal perfusion pressure and thus reduce RPF. Increases in renal interstitial pressures in this setting of "renal congestion" may also contribute to renal dysfunction. Such effects of venous hypertension have been described in animal studies as early as 1931.[8] Evidence in humans for the significance of elevated right atrial pressures comes from a prospective
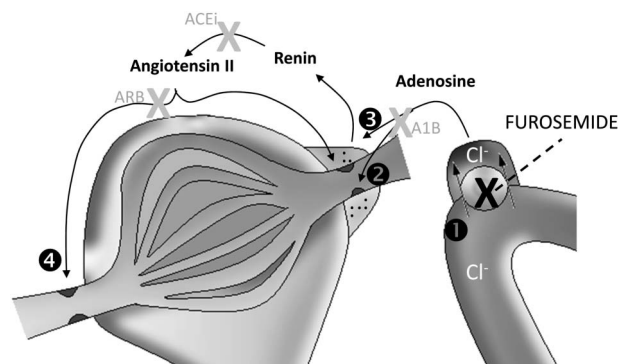


FIGURE 2. The effect of loop diuretics on TGF. Sensing of chloride delivery is inhibited by loop diuretic blockade of the sodium/potassium/2-chloride cotransporter in the macula densa (1). Adenosine release by the macula densa falls, leading to afferent arteriolar vasodilation (2) and increased renin release from granular cells (3). Renin increases Angiotensin II that causes efferent and, to a lesser extent, afferent arteriolar vasoconstriction (4). The points at which adenosine receptor blockers (A1B), ACEi and ARB inhibit steps downstream are also shown. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; TGF, tubuloglomerular feedback.