Targeting the Kidney in Acute Decompensated Heart Failure: Conventional Diuretics and Renal-Acting Vasodilators

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A mainstay of therapy for congestive heart failure has been the use of potent diuretic agents, such as furosemide, that target the kidney to enhance sodium and water excretion. Although furosemide is widely used to treat the symptoms of acute decompensated heart failure (ADHF), the consequent activation of the renin-angiotensin-aldosterone system may limit the natriuretic response by reducing the glomerular filtration rate. In addition, excessive diuresis may reduce cardiac preload and result in systemic hypotension, which reduces renal perfusion pressure and prerenal azotemia and raises levels of blood urea nitrogen. In order to preserve and/or enhance renal function in ADHF, especially with agents such as conventional diuretics and vasodilators, an understanding of intrarenal factors that may protect the kidney may provide a direction for optimal use of current therapies and also lead to newer therapeutic strategies. Vasodilators, especially those that are linked to cGMP activation, may provide an alternative approach.
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Key words: Acute decompensated heart failure • Renin-angiotensin-aldosterone system • Diuretics • Renal function • Vasodilators

A hallmark of congestive heart failure (CHF) is avid sodium and water retention, with edema and its multiple complications related to congestion. Braunwald and colleagues[1] stated in 1965 that "the inability to excrete ingested sodium and water is one of the most fundamental abnormalities of CHF. Indeed, most of the physical signs and symptoms in CHF result in large measure from retention of salt and water by the kidney, leading to congestion." Thus, a mainstay of therapy for CHF has been the use of potent diuretic agents that target the kidney to enhance sodium and water excretion, thus improving

the symptoms of congestion and the well-being of the patient.

In this review, we will first address the activation of the renin-angiotensin-aldosterone system (RAAS) by diuretics, which can contribute to a worsening of renal function. We will also discuss the use of vasodilators linked to the important second messenger cyclic 3′,5′ guanosine monophosphate (cGMP), and consider their actions on the kidney and their relationship to diuretic therapy, especially as it involves the cardiac natriuretic peptide (NP), B-type natriuretic peptide (BNP). Thus, we will attempt to provide a unifying understanding of these renal-active agents as they relate to the therapeutics of CHF, with a special focus on acute decompensated heart failure (ADHF).

Diuretic Therapy in Heart Failure

As stated above, the use of diuretics, such as furosemide, remains a standard therapy for dyspnea, edema, and other symptoms of CHF. Although furosemide is widely used to treat the symptoms of ADHF, the consequent activation of the RAAS may limit the natriuretic response by reducing the glomerular filtration rate (GFR). In addition, excessive diuresis may reduce cardiac preload and result in systemic hypotension, which reduces renal perfusion pressure and prerenal azotemia and raises levels of blood urea nitrogen (BUN). The Acute Decompensated Heart Failure National Registry (ADHERE) reported that BUN is the most important predictor of long-term survival in patients hospitalized in the United States for ADHF; an elevated BUN predicts increased mortality in ADHF better than any other factor.[2] Other studies have established that the GFR is also an important predictor of long-term survival in patients with CHF, even surpassing parameters of cardiac function such as left ventricular ejection fraction and New York Heart Association Class.[3,4]

To further explore the deleterious renal actions of furosemide in patients with CHF, we sought to define the importance of angiotensin II (ANG II), which is activated by furosemide and is a key mechanism of reduced renal function and activation of aldosterone.[5] We utilized a pharmacologic approach to understand how ANG II, and the angiotensin-1 (AT-1) receptors to which ANG II binds in the kidney, mediate the detrimental renal actions of furosemide.[5,6] The AT-1 receptor antagonist losartan was used because it effectively binds to specific renal ANG II receptors. In this study, furosemide increased sodium excretion but reduced both renal blood flow and GFR, in association with a marked activation of aldosterone. We concluded that this response was related to activation of ANG II because AT-1 blockade with losartan preserved the GFR and renal blood flow and reduced plasma aldosterone. Thus, the study underscored the pathophysiological role of the AT-1 receptor in mediating the detrimental renal and adrenal properties of acute diuretic therapy in patients with CHF. It should be stressed that AT-1 receptors are abundant in the kidney and are localized to the renal vasculature, glomeruli, proximal and distal tubules, and medullary interstitial cells. The predominant receptor subtype is the AT-1 receptor that, when activated, mediates mesangial contraction, renal vasoconstriction, and increased tubular sodium reabsorption. Activated AT-1 receptors in the adrenal glands release aldosterone, contributing further to sodium retention and congestion.

The well-documented activation of RAAS by furosemide may have implications even beyond the kidney. Most recently, an elegant study was performed in an experimental model of CHF.[7] Groups were randomized to chronic furosemide therapy or placebo. The investigators tested the novel hypothesis that furosemide accelerates the progression of left ventricular systolic dysfunction in CHF. Their findings supported the hypothesis: furosemide shortened the time to the onset of left ventricular dysfunction. By the second week of the study, the patients treated with furosemide had plasma aldosterone levels that were markedly activated and higher, which is characteristic of severe heart failure. Serum sodium was also reduced in the furosemide-treated group compared with the control group. In isolated cardiac myocytes, furosemide significantly increased basal sodium calcium exchange currents and depressed catecholamine responsiveness. The authors concluded that chronic use of furosemide accelerated the progression of experimental heart failure from both contractile and metabolic perspectives. This effect was characterized by worsening ventricular systolic dysfunction, further elevated serum aldosterone levels, and altered calcium handling.

The well-documented activation of the renin-angiotensin-aldosterone system by furosemide may have implications even beyond the kidney.

The controversy regarding the use of diuretic therapy in heart failure continues to be a focus of attention. The Clinical Research Heart Failure Network, a new program supported

by the National Heart, Lung, and Blood Institute, will include a prioritized, multicenter, National Institutes of Health–supported trial that will examine this issue. The Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF) trial will study the use of diuretic therapy in CHF by comparing high and low doses with continuous and acute bolus administration. Further trials, particularly those that randomize subjects to diuretic or nondiuretic strategies to treat volume overload, continue to be discussed but have not yet been planned.

Cyclic GMP-Based Vasodilator Therapy in ADHF: Protecting the Kidney

In order to preserve and/or enhance renal function in ADHF, especially with agents such as conventional diuretics and vasodilators, an understanding of intrarenal factors that may protect the kidney may provide a direction for optimal use of current therapies and also lead to newer therapeutic strategies. This approach is relevant to the use of vasodilators, especially those that are linked to cGMP activation, such as nitroglycerin (NTG), sodium nitroprusside, and nesiritide, which is the cardiac hormone BNP.

From an integrated cardiorenal physiological view, ADHF involves acute cardiac overload with release of atrial natriuretic peptide (ANP) and BNP. Release of these peptides activates the particulate guanylyl cyclase (pGC) NP receptor-A, resulting in the generation of the second messenger cyclic cGMP and the effector protein kinase G.[8] NP receptor-A is also the target of the intrarenal natriuretic peptide urodilatin that, like ANP and BNP, is being developed for the treatment of acute heart failure. Infusion of these 3 NPs in animals and people results in natriuresis, diuresis, and—at certain doses—an increase in the GFR.[9,10] These NPs possess other actions, including suppression of the RAAS, inhibition of fibrosis and cardiomyocyte hypertrophy, and positive lusitropism. In severe experimental or human CHF, NP may induce renal hyporesponsiveness, partly because of excessive hypotension as well as upregulation of phosphodiesterase V activity, which degrades NP-generated cGMP.[11-13] The importance of the NPs and the NP receptor-A in renal regulation is underscored by studies of genetic and pharmacologic receptor disruption characterized by impaired renal sodium handling and, often, hypertension.[14-16]

Cardiac volume overload, as seen in ADHF, may result in the release of ANP and BNP. However, the associated reduction of arterial pressure that may occur activates the intrarenal nitric oxide (NO) pathway, in which NO stimulates the soluble guanylyl cyclase (sGC) that is localized to the cell cytosol. sGC is a cGMP activator, distinct from the ANP and BNP cGMP pathway, that involves activation of pGG that is membrane-bound and linked to NP receptor-A, to which ANP and BNP bind.

Sodium nitroprusside and NTG are widely used for the treatment of ADHF, and they are both sGC activators and potent vasodilators. Again, this mechanism is in contrast to that of ANP and BNP, which target pGC. We recently employed NTG and a novel direct activator of sGC, BAY 41-2272, in a model of ADHF. There was potent renal vasodilation without natriuresis, diuresis, or changes in GFR, although both treatments produced a significant reduction in arterial pressure together with cardiac unloading.[17] Importantly, genetic or pharmacologic disruption of the NO/cGMP system also involves alteration of the physiological control of cardiorenal function, which is most often characterized by hypertension secondary to systemic and renal vasoconstriction.[18,19]

Knowledge of the compartmentalization of cGMP signaling in cells has been advancing, particularly in regard to the heart. Studies show that pGC and sGC have distinct roles in cardiomyocyte function.[20,21] Furthermore, Airhart and colleagues[22] have reported that the pGC agonist ANP, but not the sGC agonist S-nitroso-L-acetyl penicillamine, stimulates the translocation of protein kinase G to the plasma membrane of renal cells, augmenting the NP receptor-A to which ANP, BNP, and urodilatin bind. These observations strongly support in vitro, distinct, functional roles for pGC and sGC in the kidney, meaning that a natriuretic peptide like BNP could have different renal actions from NTG or sodium nitroprusside despite the fact that they all activate the second messenger cGMP.

Comprehension of the role played by the NP/cGMP and NO/cGMP pathways in the control of renal function in ADHF patients would advance our knowledge of renal adaptations in this syndrome and help guide the therapeutic use of agents such as BNP (nesiritide) and NTG. Therefore, we used a large, in vivo animal model of ADHF produced by rapid ventricular pacing to discern the physiological properties of the endogenous NP/cGMP and NO/cGMP pathways in the control of renal hemodynamic and excretory function.[23] We hypothesized that each pathway would play a specific role in the maintenance of renal function in ADHF that is reflective of their distinct guanylyl cyclase enzymes.

Indeed, we observed differential but complementary roles for these 2 endogenous cGMP-activating systems in ADHF. The endogenous NPs

appeared to play a greater role in the preservation of GFR and sodium excretion, whereas the endogenous NO system was more important in the control of renal blood flow. Thus, the preservation of renal function in experimental ADHF is mediated by dual cGMP systems that activate both pGC and sGC enzymes.

As discussed above, both NTG and sodium nitroprusside, which activate sGC, are used as potent vasodilators to unload the heart in patients with ADHF. One might conclude that such agents are renal vasodilators, but that they would not necessarily enhance GFR or sodium excretion. This idea has been confirmed in studies of experimental ADHF using NTG or a direct sGC activator.[17] Therefore, it is tempting to speculate that an optimal renal therapeutic strategy in ADHF would be the use of nonhypotensive doses of a pGC agonist such as ANP or BNP together with a direct sGC activator. Such a strategy would then target the glomeruli, the renal vasculature, and the renal tubules. Phosphodiesterase V inhibition potentiates the renal actions of BNP in experimental CHF. Potentiation of the dual cGMP system with a phosphodiesterase V inhibitor should also maximize cGMP signaling and warrants further investigation.[13]

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A Strategy to Enhance Renal Function With BNP in ADHF

As previously discussed, loop diuretics are powerful natriuretic agents and are considered first-line therapy in the management of CHF patients with volume overload. Indeed, the use of diuretics in the Systolic Hypertension in the Elderly Program (SHEP) trial reduced the development of CHF in elderly patients with hypertension.[24] Despite the widespread use of diuretics in CHF, studies have reported detrimental actions. Over time and in patients with severe CHF, sensitivity to diuretics may be reduced, requiring an increase in the dose administered. In addition, chloride depletion, as may occur with furosemide, may render the receptor for BNP hyporesponsive.[25] Loop diuretics can reduce GFR and activate the RAAS both acutely and chronically. The importance of furosemide-mediated reductions in GFR is underscored by recent studies reporting that GFR is a key predictor of mortality in CHF.[26,27] Therefore, new therapeutic strategies are warranted both to minimize adverse effects of conventional diuretics and to potentiate their renal actions, which might permit use of lower dosages.

Based upon the renal actions of the endogenous natriuretic peptide/cGMP system in experimental ADHF, BNP continues to emerge as an important renal-acting vasodilating therapy for ADHF. Such a therapeutic strategy has been supported by Marcus and colleagues,[28] who reported beneficial renal actions of BNP—specifically, increased sodium excretion in CHF patients. However, Jensen and coworkers[29] observed a blunted natriuretic response without an increase in GFR in CHF patients after BNP administration. In addition, in the Vasodilation in the Management of Acute Congestive heart failure (VMAC) study, in which BNP was administered to patients with acute CHF, the authors reported a greater increase in creatinine in patients receiving BNP, although this subgroup had more severe CHF compared with the NTG groups.[30] Moreover, Wang and colleagues[31] reported that BNP had no effect in patients hospitalized with ADHF, as demonstrated by a lack of diuretic response.

Observation of BNP use in patients with CHF has prompted the question of how BNP and diuretics interact. We addressed this question by using furosemide in a model of experimental CHF.[32] We observed that BNP and furosemide together had favorable cardiovascular hemodynamic actions as compared with furosemide alone. Both furosemide and BNP together increased GFR and resulted in more profound diuresis and natriuresis responses without renin and aldosterone activation. These and other data have resulted in a new approach, which is to optimize the renal actions of BNP in patients with ADHF by using a different strategy from the one currently employed.

The recommended dose of nesiritide is a bolus of 2 μg/kg followed by infusion of 0.01 μg/kg/min. As discussed above, preclinical studies have demonstrated the renal-enhancing effects of systemic intravenous administration of BNP. Yet, as also mentioned, the clinical trials that led the Food and Drug Administration to approve BNP for the management of acute CHF have offered conflicting results in regard to the renal-enhancing properties of BNP. A meta-analysis of BNP clinical trials suggests that nesiritide may even be detrimental to renal function in patients with acute decompensated CHF.[33] One possible mechanism for the disparity between the preclinical and clinical data could be, in part, that the dose used in the clinical

studies resulted in significant decreases in blood pressure and, therefore, renal perfusion pressure, which attenuated the renal-enhancing effects, especially in the setting of preexisting renal disease. Supporting this hypothesis is our previous study in experimental CHF, which demonstrated that a low-dose, subcutaneously administered BNP, which did not lower blood pressure, had a more beneficial renal hemodynamic profile than a higher dose that did lower blood pressure.[34]

To address this question, we performed a retrospective review on consecutive patients admitted to the Mayo Clinic Heart Failure Hospital Service, Rochester, MN, for ADHF who received nesiritide at doses lower than the standard.[35] We identified patients who received 0.005 μg/kg/min and 0.0025 μg/kg/min of nesiritide without bolus. We compared the results with those from a group of patients who did receive the standard dose of nesiritide (2 μg/kg bolus followed by 0.01 μg/kg/min) and from a group of patients who received diuretic therapy without nesiritide, matching for ejection fraction and calculated creatinine clearance. The patients who received low-dose nesiritide had lower baseline systolic blood pressure compared with patients who received standard-dose nesiritide or no nesiritide. Systolic blood pressure did not significantly decrease with low-dose nesiritide. It did decrease with standard-dose nesiritide and no nesiritide. The low-dose nesiritide group had improved plasma creatinine associated with a decrease in BUN. Renal function, as measured by plasma creatinine, and BUN did not improve in the standard-dose nesiritide and no-nesiritide groups. Patients in the low-dose nesiritide group received less furosemide than patients in the standard-dose nesiritide and no-nesiritide groups. All 3 groups achieved similar diuresis during the intravenous therapy period.

What is the mechanism of the improvement in renal function observed in the low-dose nesiritide group? Most likely, it is multifactorial, and we hypothesized that the improvement was due in part to the fact that systolic blood pressure was not reduced in this group. The significant reduction in systolic blood pressure that was observed in the standard-nesiritide and no-nesiritide groups may have activated counter-regulatory mechanisms, such as the sympathetic system and the RAAS, thus attenuating the renal-enhancing properties of nesiritide. In a study by Brunner-La Rocca and colleagues,[36] the sympatho-inhibitory effects of BNP were greater with low-dose (0.003 μg/kg/min) infusion, which did not alter hemodynamics, as compared with a higher-dose (0.015 μg/kg/min) infusion. These data, in part, support our hypothesis. Based upon these observations, a prospective, randomized, controlled study is warranted to test the efficacy of nonhypotensive low-dose nesiritide. Results from our small, retrospective study are now supported by 2 additional studies in which nesiritide was administered preoperatively for cardiorenal protection at either a low dose (0.05 μg/kg/min for 48 hours) or without the bolus in patients undergoing cardiopulmonary bypass surgery who had chronic renal disease or ventricular dysfunction.[37,38] Both studies demonstrated improved renal function as compared with standard therapy.

Main Points

- The use of diuretics, such as furosemide, remains a standard therapy for dyspnea, edema, and other symptoms of CHF.
- Furosemide activates the renin-angiotensin-aldosterone system, which may limit the natriuretic response by reducing the glomerular filtration rate (GFR), a key predictor of mortality in congestive heart failure.
- In a recent model of acute decompensated heart failure, nitroglycerin and a novel direct activator of soluble guanylyl cyclase, BAY 41-2272, achieved potent renal vasodilation without natriuresis, diuresis, or changes in GFR. However, both treatments produced a significant reduction in arterial pressure together with cardiac unloading.
- In a study of experimental congestive heart failure, a low-dose, subcutaneously administered B-type natriuretic peptide, which did not lower blood pressure, had a more beneficial renal hemodynamic profile than a higher dose that did lower blood pressure.
- Another emerging concept that supports the use of low-dose B-type natriuretic peptide therapy is the design of novel chimeric peptides that are renal-enhancing but less hypotensive because they target natriuretic peptide receptor-B in the venous system and avoid excessive arterial vasodilation.

Lastly, another emerging concept that supports the use of low-dose BNP therapy is the design of novel chimeric peptides that are renal-enhancing but less hypotensive because they target natriuretic peptide receptor-B in the venous system and avoid excessive arterial vasodilation, which occurs with ANP and BNP.[39] A phase I clinical trial of one such peptide, CD-NP, has recently been completed, and shows its safety in healthy subjects and its favorable cGMP-activating, natriuretic, and diuretic actions.[40]

Summary

The kidney plays a key role in ADHF. The challenge remains of how to optimize renal function in this syndrome and how best to utilize conventional diuretics to obtain their beneficial natriuretic and diuretic properties without their adverse effects, such as overactivation of the RAAS. The natriuretic peptides such as BNP and the next-generation peptides hold promise as demonstrated in experimental and human studies of ADHF. Another challenge is to understand how best to administer these important peptides with cardiorenal actions so as to fully realize their favorable biologic properties of renal enhancement and protection. ■

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