Heart Failure

Diuretic Therapy, Natriuretic Peptides, and Heart Failure

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In many institutions, the primary therapy for acute decompensated heart failure (ADHF) is diuretic-based. Unfortunately, diuretic therapy in congestive heart failure results in a series of negative responses, which may have deleterious effects on clinical outcomes.

Diuretic therapy is associated with activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), which exert negative cardiovascular strain, leading to cardiac remodeling, worsened ventricular function, and increased mortality.[1] Chronic RAAS activation causes glomerulosclerosis, tubulointerstitial fibrosis, proteinuria, and progressive cardiomyopathy.[2,3] See Table 1.

Although helpful in clearing pulmonary congestion, early use of IV loop diuretic monotherapy further activates the RAAS and SNS, leading to elevations in serum creatinine in many patients.[4] Elevations in serum creatinine that can occur in a diuretic-based approach to ADHF therapy often indicates worsening renal function. Most often, these elevations are ignored and, with diuretic resistance, increases in diuretic doses are employed. Unfortunately, even small increases in serum creatinine in at-risk heart failure patients are associated with higher mortality rates.[5] The most common intravenous vasodilators used in acute heart failure therapy are nitroglycerin and nesiritide (recombinant human b-type natriuretic peptide [rhBNP]). Nitroglycerin exerts no significant effect on renal function, whereas there is data to support benefit in patients treated with nesiritide.[6]

Brain Natriuretic Peptide Enhances Renal Actions of Furosemide and Suppresses Furosemide-Induced Aldosterone Activation in Experimental Heart Failure.

Cataliotti A, Boerrigter G, Costello-Boerrigter L, et al. *Circulation.* 2004;109:1680-1685.

Table 1
Adverse Consequences of Chronic Systemic and Tissue Level RAAS Activation

Kidney	Heart
• Hypoxia/vasoconstriction	• Adverse left ventricular remodeling
• Intra-glomerular hypertension	• Left ventricular hypertrophy
• Proteinuria/increased nephrin	• Myocardial fibrosis
• Glomerulosclerosis	• Endothelial dysfunction
• Tubulointerstitial fibrosis	• Coronary atherosclerosis vasoconstriction
	• Prothrombotic effects/ increased plasminogen activator inhibitor

RAAS, renin-angiotensin-aldosterone system
Reproduced from McCullough et al.[4]

Table 2
Cardiorenal Hemodynamics

	Baseline	Low Dose	High Dose	Recovery
MAP, mm Hg				
Fs	105 ± 8	108 ± 8	100 ± 7	96 ± 7
Fs + BNP	104 ± 1	107 ± 3	98 ± 3	102 ± 4
RAP, mm Hg				
Fs	6.2 ± 1.6	5.5 ± 1.6	5.2 ± 1.7	5.0 ± 1.9
Fs + BNP	6.0 ± 1.2	4.9 ± 1.2	4.2 ± 1.1	4.9 ± 0.9
PAP, mm Hg				
Fs	21 ± 3	20 ± 3	21 ± 3	22 ± 3
Fs + BNP	23 ± 2	21 ± 3	19 ± 3	22 ± 2
PCWP, mm Hg				
Fs	16 ± 3	14 ± 2	14 ± 2	15 ± 2
Fs + BNP	18 ± 2	15 ± 2	13 ± 3*	14 ± 2
CO, L/min				
Fs	2.0 ± 0.1	1.9 ± 0.2	1.6 ± 0.2*	1.6 ± 0.2*
Fs + BNP	2.1 ± 0.1	2.0 ± 0.1	1.7 ± 0.1*	1.9 ± 0.1
SVR, mm Hg•L^{-1}•min^{-1}				
Fs	49 ± 5	55 ± 5	61 ± 6*	64 ± 7*
Fs + BNP	48 ± 2	53 ± 3	56 ± 3	57 ± 5
RVR, mm Hg•L^{-1}•mm^{-1}				
Fs	0.81 ± 0.16	0.77 ± 0.15	0.82 ± 0.17	1.04 ± 0.27
Fs + BNP	0.71 ± 0.16	0.61 ± 0.16	0.51 ± 0.10	0.63 ± 0.13
RBF, mL/min				
Fs	151 ± 35	168 ± 40	148 ± 36	128 ± 38
Fs + BNP	170 ± 36	220 ± 53*	224 ± 51*	187 ± 43

Values are expressed as mean ± SEM.
*P < .05 vs baseline.
MAP, mean arterial pressure; RAP, right atrial pressure; CO, cardiac output; SVR, systemic vascular resistance; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RVR, renal vascular resistance; RBF, renal blood flow.
Reproduced with permission from Cataliotti et al.

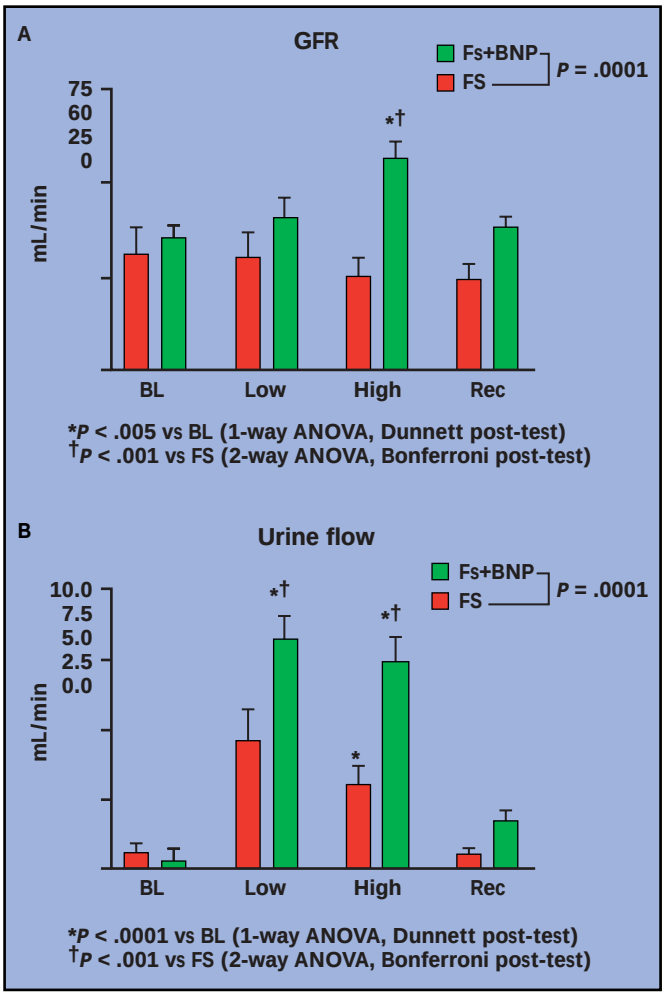

Figure 1. *Glomerular filtration rate (GFR)* **(A)** *and urinary flow rate* **(B)** *in the furosemide (Fs) vs Fs + brain natriuretic peptide (BNP) groups. Low dose = 2 pmol/kg^{-1}/min^{-1}; High dose = 10 pmol/kg^{-1}/min^{-1}. BL, baseline; Rec, recovery. Reproduced with permission from Cataliotti et al.*

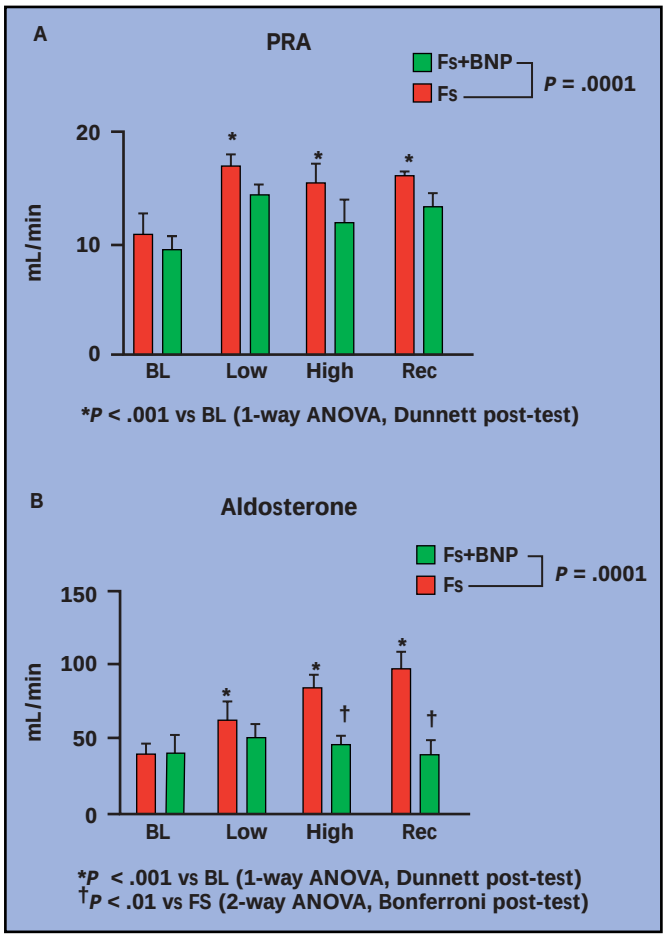

Figure 2. *Plasma renin activity (PRA)* **(A)** *and plasma aldosterone* **(B)** *in the furosemide (Fs) vs Fs + brain natriuretic peptide (BNP) groups. Low dose = 2 pmol/kg^{-1}/min^{-1}; High dose = 10 pmol/kg^{-1}/min^{-1}. BL, baseline; Rec, recovery. Reproduced with permission from Cataliotti et al.*

Cataliotti and associates conducted a study to test the hypothesis "that exogenous BNP enhances the renal diuretic and natriuretic actions of furosemide (Fs) and retards the activation of aldosterone in a model of CHF [congestive heart failure]." Heart failure was induced in 2 groups of dogs by means of ventricular pacing. One group received a continuous infusion of Fs and the second group received an infusion of Fs and a 45-minute infusion of low-dose (2 pmol/kg/min) BNP, followed by a 45-minute infusion of high-dose (10 pmol/kg/min) BNP (Fs + BNP). Though Fs increased urine output, there was greater increase in the Fs + BNP group.

Relative to the dogs receiving Fs, those that received nesiritide, particularly in higher doses, exhibited increased renal blood flow and reductions in pulmonary capillary wedge pressure and right atrial pressure. Fs alone led to increases from baseline systemic vascular resistance. (Table 2)

In the dogs receiving infusions of nesiritide, increases in glomerular filtration rates from baseline were observed at the higher doses whereas there were trends toward reductions in the Fs-only group (Figure 1). In addition, there were much greater increases in urine flow in dogs receiving nesiritide at both the high and low dose and plasma renin and aldosterone levels were lower in dogs receiving the nesiritide compared to the diuretic only group, at either dose (Figure 2).

The authors conclude that the study "demonstrates that coadministration of BNP and furosemide unloads the heart and inhibits the activation of aldosterone while maximizing natriuresis and preserving renal function in this model of experimental heart failure."

From a clinical viewpoint, it seems that coadministration of nesiritide with diuretics will provide for more rapid diuresis in heart failure patients. This should lead to more rapid symptom improvement and perhaps yield shorter hospital stays. Avoidance of exacerbations of renal function and resultant higher mortality that are associated with elevations of serum creatinine in a primary diuretic approach, as well as increased levels of aldosterone and angiotensin that may lead to negative ventricular remodeling and diuretic resistance, seems attributable to the use of nesiritide. The ideal approach in eligible ADHF patients may be to initiate intravenous nesiritide and Fs early in their presentation, ideally in the emergency department. ■

References

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