Neurohormonal Activation Rapidly Decreases After Intravenous Therapy With Diuretics and Vasodilators for Class IV Heart Failure

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OBJECTIVES  
This study was designed to determine whether therapy with vasodilators and diuretics, designed to normalize loading conditions in decompensated heart failure (HF), reduces neurohormonal activation in the short term.

BACKGROUND  
Elevated vasoactive neurohormone levels in chronic HF have adverse prognostic impact and may be targeted by specific therapies.

METHODS  
Endothelin-1, catecholamines, renin, aldosterone, angiotensin and atrial natriuretic peptides (ANP, N-ANP and BNP) were measured in 34 patients with advanced HF before and after hemodynamically guided therapy with vasodilators and diuretics. The therapy was designed to reduce filling pressures and systemic vascular resistance (SVR) without inotropic therapy. Blood was drawn before therapy (A), after initial diuretic and nitroprusside therapy to optimize hemodynamics (B, mean 1.4 days) and after transition to an oral regimen designed to maintain improved hemodynamics (C, mean 3.4 days).

RESULTS  
Mean pulmonary wedge pressure fell from 31 to 18 mm Hg, right atrial pressure from 15 to 8 mm Hg, and SVR from 1,780 to 1,109 dynes/s/cm². Cardiac index increased from 1.7 to 2.6 l/min/m² without intravenous inotropic agents (all p < 0.05). Average endothelin levels declined by 30%, from 7.7 to 5.5 pg/ml, and remained low at time point C, 5.2 pg/ml (p < 0.01). Norepinephrine was 858 at time A, 817 at time B, and fell by time C to 608 pg/ml (p < 0.05). The mean plasma BNP level fell by 26% after only 1.4 days and by 53% at time C (p < 0.001).

CONCLUSIONS  
Neurohormonal activation rapidly decreases after short-term therapy tailored to decrease severely elevated filling pressures and SVR without inotropic agents. Therapy designed to address neurohormonal activation should include therapy to improve severe resting hemodynamic compromise. (J Am Coll Cardiol 2002;39:1623–9) © 2002 by the American College of Cardiology Foundation

Symptomatic chronic heart failure (HF) is associated with an elevation of vasoactive plasma neurohormone levels, including norepinephrine, endothelin, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). This neurohormonal activation is emerging as an important prognostic marker in patients with HF (1–5). Atrial natriuretic peptide and BNP are endogenous vasodilators, whereas norepinephrine and endothelin exert vasoconstrictor effects. Many of the current strategies for HF therapy are specifically targeted to decrease aspects of neurohormonal activation. Long-term treatment with neurohormonal antagonists improves neurohormonal profiles in patients with HF (6–8). Direct hemodynamic improvement with a left ventricular (LV) assist device lowered plasma levels of norepinephrine and ANP over a three-month period (9).

Although these long-term alterations have been demonstrated in response to therapy, it is less clear to what extent the neurohormonal profile can be modified acutely by improving the hemodynamics. This may be most relevant in New York Heart Association (NYHA) class IV patients, where resting hemodynamics are markedly abnormal. Intensive HF therapy tailored to reduce filling pressures and systemic vascular resistance has been associated with an acute decrease in mitral regurgitation and an increase in forward cardiac output. The hypothesis of this study is that intensive medical therapy designed to normalize loading conditions in decompensated HF acutely reduces neurohormonal activation, decreasing plasma levels of norepinephrine and endothelin as well as BNP and ANP.

METHODS  
Study population. Consecutive patients with chronic HF who were admitted for treatment of decompensation using hemodynamic monitoring were identified. Subjects were excluded if: 1) their ejection fraction was >35% or their symptoms had been present <6 months; 2) they had...
untreated thyroid disease, myocardial infarction within six months or a history of drug or alcohol abuse; or 3) they required intravenous inotropic therapy. All patients except one with intolerance were receiving enalapril or captopril. None was taking beta-blocking agents at the time of admission. All participants gave written, informed voluntary consent. The study was approved by the Human Research Committee of Brigham and Women’s Hospital.

Therapy for hemodynamic goals. Treatment of these patients began with empiric diuresis to reduce obvious volume reservoirs such as anasarca and ascites when present. Subsequently, a pulmonary artery catheter was inserted into an internal jugular or subclavian vein under sterile conditions and local anesthetic (1% lidocaine). Baseline measurements were made to document systemic blood pressure, right atrial pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, cardiac output, systemic vascular resistance and pulmonary vascular resistance. A combination of nitroprusside and diuretics was used to approach the following hemodynamic goals: right atrial pressure ≤8 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg and systemic vascular resistance between 1,000 and 1,200 dynes/s/cm², while maintaining a systolic blood pressure ≥80 mm Hg (10). Angiotensin-converting enzyme (ACE) inhibitors were not administered during nitroprusside titration. As these goals were approached, nitroprusside was weaned and oral vasodilators were reintroduced and up-titrated to maintain the hemodynamics achieved. Initially, captopril was given at a dose of 6.25 mg orally every 8 h and titrated upwards to 25 to 75 mg every 6 to 8 h as guided by optimal hemodynamics defined earlier, as the nitroprusside was weaned. If necessary to maintain optimal loading conditions, oral isosorbide dinitrate was added 10 mg three times daily and increased as necessary. Hydralazine was initiated, if necessary, to supplement vasodilation. The dosing regimens established at the end of therapy closely approximated the patients’ regimens at discharge from the hospital.

Sample collection and analysis. Neurohormonal measurements were made before the initiation of nitroprusside, with each patient maintaining his/her baseline oral regimen until the morning of catheterization, except for intravenous diuretics (time point A), after optimal hemodynamics were approximated on intravenous medication (time point B) and again after patients had been converted to an oral vasodilator regimen (time point C). On average, the time from A to B was 1.4 ± 0.2 (mean ± standard error) days. The time from A to C was 3.4 ± 0.4 days. All 34 subjects had samples obtained at time point A, 22 of those had samples obtained at time point B, and 28 at time point C. All subjects had at least two measurements. Measurements were missed because of patient request, lack of access to sample preparation room during off-hours or unplanned discontinuation of the catheter.

All blood samples were drawn at least 2 h after catheter placement, with the subject supine and resting quietly for at least 30 min. Samples were drawn from the right atrial port. Those for ANP, BNP, N-ANP, endothelin and norepinephrine were placed in chilled tubes containing ethylenediaminetetraacetic acid and immediately placed on ice. They were centrifuged at 4°C within 30 min, quick frozen and stored at −70°C until analyzed. Atrial natriuretic peptide and the N-terminal fragment of the ANP prohormone (N-ANP) were measured by radioimmunoassay as previously described (3); BNP was measured by a commercially available immunoradiometric assay (Shionoria BNP kit, Shionogi and Co., Ltd.) (11). Plasma endothelin levels were measured by a commercially available radioimmunoassay as previously described (4). Norepinephrine was determined by radioenzymatic assay (12). Serum sodium, plasma renin activity and aldosterone were also measured to assess the activity of the renin-angiotensin-aldosterone system. Plasma renin activity was assessed by radioimmunoassay measurement of angiotensin I generation (13). Aldosterone was measured by radioimmunoassay (Cost–A–Count, Diagnostic Products, Los Angeles, California). Blood urea nitrogen and creatinine were measured to assess the impact of therapy on renal function.

Statistical analysis. Data are expressed as mean ± standard error. Changes in central hemodynamic measurements were compared using a paired, two-tailed Student t test with a Bonferroni correction for multiple comparisons. Neurohormone levels were compared using a one-way analysis of variance with repeated measures. Only subjects with data available at both of the indicated time points were included in each comparison. Statistical significance was accepted at the 95% confidence interval (p ≤ 0.05).

RESULTS

Characteristics of the study population. The participants included 34 patients with HF, 28 men and 6 women, age 52 ± 2 years. All were admitted to the hospital for intensive medical therapy. Each patient had symptoms of HF for more than six months. Twenty-three patients were NYHA class IV, and 11 patients were class III/B. The average LV ejection fraction was 20% ± 1%, determined by echocardiography. Two patients had mild mitral regurgitation, 31 had moderate regurgitation, and one had severe regurgitation as estimated by the color flow Doppler technique. In the 20 patients able to perform an exercise test within 48 h of baseline hemodynamics, the average peak oxygen consump-
tion was 10.2 ± 0.8 ml/min/kg. The etiology of LV dysfunction was coronary artery disease in 13 patients, idiopathic cardiomyopathy in 16 patients, familial cardiomyopathy in three patients, valvular disease in one patient and peripartum cardiomyopathy in one patient (Table 1).

**Hemodynamic response to therapy.** Medical therapy tailored to reduce filling pressures resulted in a fall in pulmonary capillary wedge pressure from 31 ± 1 to 18 ± 1 mm Hg, right atrial pressure from 15 ± 1 to 8 ± 1 mm Hg, systemic vascular resistance from 1,780 ± 94 to 1,109 ± 50 dynes/s/cm² and mean systemic arterial pressure from 84 ± 2 to 77 ± 2 mm Hg (all p ≤ 0.05). Although they were not specific targets of therapy, pulmonary vascular resistance decreased from 316 ± 37 to 174 ± 22 dynes/s/cm², and cardiac index increased from 1.70 ± 0.08 to 2.58 ± 0.09 l/min/m² (Table 2). The mean doses of captopril before and after tailored therapy were 77 ± 14 mg/day and 134 ± 18 mg/day, respectively (p = 0.002), and the mean doses ofisosorbide dinitrate before and after therapy were 10 ± 5 mg/day and 50 ± 7 mg/day, respectively (p < 0.01) (Table 2). Four subjects began to receive hydralazine during treatment. No patient received an intravenous inotropic agent or a beta-receptor antagonist at baseline or during the study.

**Responses of renal function, the renin angiotensin system, norepinephrine and endothelin.** Sodium levels were not significantly different after therapy (137 ± 1 mmol/l before and 136 ± 1 mmol/l after therapy, p = 0.07). Serum creatinine and blood urea nitrogen were also unchanged (1.2 ± 0.1 to 1.1 ± 0.1 mg/dl, p = 0.63; and 27 ± 2 to 28 ± 2 mg/dl, p = 0.62, respectively). Angiotensin-converting enzyme inhibitors were withheld between time points A and B then re-introduced between time points B and C. Aldosterone levels increased significantly between time points A and B, from 16.5 ± 3.4 to 28.8 ± 5.9 ng/dl (p = 0.02), but they then decreased to baseline levels at time point C, 16.3 ± 3.2 ng/dl. As subjects underwent progressive diuresis, plasma renin activity increased from 15.4 ± 2.2 ng/ml/h at time point A to 30.4 ± 1.8 ng/ml/h at time point B (p = 0.0006) and remained elevated at time point C, after ACE inhibitors had been re-introduced, 32.0 ± 1.4 ng/ml/h (p < 0.0001) (Fig. 1).

Norepinephrine levels were not significantly different between time points A (858 ± 96 pg/ml) and B (817 ± 97 pg/ml) (p = 0.60) after 1.4 days. By 3.4 days (time point C), however, norepinephrine levels were significantly lower (608 ± 47 pg/ml, p = 0.005) (Fig. 2). Mean dopamine and epinephrine levels were unchanged after therapy.

Endothelin levels declined by 30% with intravenous therapy from 7.7 ± 0.6 to 5.5 ± 0.5 pg/ml (p = 0.004) and remained low at time point C, 5.2 ± 0.3 pg/ml (p < 0.001) (Fig. 3).

**Response to therapy of the natriuretic peptides.** As expected from a large reduction in filling pressures, plasma ANP levels fell by 52% from 201 ± 30 to 96 ± 14 pmol/l (p = 0.001) after intravenous therapy, and they remained low, at 74 ± 12 pmol/l (p < 0.001), after titration to an oral regimen. Levels of N-ANP also fell from 3,882 ± 326 to 2,790 ± 333 pmol/l at time point B (p < 0.001) and to 2,575 ± 295 pmol/l at time point C (p = 0.007). The mean plasma BNP level rapidly fell by 26%, from 175 ± 22 to 126 ± 20, after only 1.4 days of therapy (p < 0.001) and fell further to 82 ± 13 pmol/l at time point C (p < 0.001) (Fig. 4). It was not possible to demonstrate correlation between the decrease in BNP and the amount of change in weight or right atrial pressure, as all parameters improved in all patients studied.

**DISCUSSION**

This study demonstrates that intervention to improve hemodynamic status with diuretics and vasodilators acutely modifies markers of neurohormonal activation in patients with a severe degree of resting hemodynamic compromise. Endothelin and natriuretic peptide levels rapidly decrease after medical therapy designed to reduce filling pressures.
Norepinephrine levels also show a decline in hospital but are slightly delayed. Heart failure is characterized by activation of a broad range of neurohormonal systems. Elevated levels of vasoconstrictor hormones adversely affect remodeling and disease progression. Vasodilator hormones may provide a counter-regulatory influence. Current treatment of HF focuses on direct antagonism of neurohormonal systems in an effort to attenuate progression of disease, whereas the main benefit of therapy that improves hemodynamics is often considered to be relief of symptoms. The data presented here highlight the importance of optimizing hemodynamics, a strategy specifically directed at decreasing elevated filling pressures and vascular resistance, not only to relieve symptoms but also to attenuate intense neurohormonal activation.

**Sympathetic nervous system activation and response.** Plasma norepinephrine levels, markers of sympathetic nervous system activation, increase in HF (14) and correlate inversely with prognosis (2), contributing to progression of HF by a variety of potential mechanisms including direct myocardial toxicity, renal sodium and water retention, peripheral vasoconstriction, induction of apoptosis, activation of the renin-angiotensin system or stimulation of arrhythmias. In subjects with HF, norepinephrine levels decreased coincident with the symptomatic improvement associated with diuresis alone over a one-month period (15), and they decreased also with long-term administration of ACE inhibitors and beta-blocking agents (6–8). Hemodynamic therapy resulting in lower filling pressures has also been shown to decrease norepinephrine concentrations after three months or more (9,16).

The current data indicate a trend toward a rapid fall in venous plasma norepinephrine concentration that is apparent after $3.4 \pm 0.4$ days. Importantly, the time course over which norepinephrine falls may be longer than that for the endogenous vasodilator hormones. The earlier fall in vasodilator substances before a decline in norepinephrine may impact short-term responses to therapy for severe HF. It is possible that some patients tolerate these short-term reductions in filling pressures poorly because of the initial persistence of norepinephrine elevation, as endogenous vasodilators such as the natriuretic peptides are attenuated more rapidly.

**The endothelin system and HF.** Endothelin is a potent endogenous vasoconstrictor peptide that is elevated in a number of disease states, including pulmonary hypertension and HF, in which the plasma levels have been correlated with prognosis and central hemodynamics (17–19). Catecholamines, angiotensin II and arginine vasopressin all stimulate endothelin synthesis (20,21), and endothelin clearance is decreased in HF (22). Endothelin, like the catecholamines, may help support blood pressure for the acutely failing heart, but it contributes to myocardial remodeling and causes vasoconstriction in coronary, pulmonary and peripheral vascular beds (23–26). Endothelin also may stimulate endogenous production of ANP, which may modulate cardiac and vascular effects of endothelin (27).

This study of advanced HF showed that intensive hemodynamic therapy focused on lowering intracardiac ventricular filling pressures significantly lowered circulating endothelin-1 levels over $3.4 \pm 0.4$ days in severely compromised patients, although it is not clear whether the change reflects decreased production or increased clearance, both of

**Figure 1.** Effect of therapy on plasma aldosterone levels (left) and plasma renin activity (right) before intervention (A), after intravenous vasodilators and diuretics (B) and after transition to an oral regimen, including captopril (C). *p < 0.05 compared to A.

**Figure 2.** Effect of therapy on plasma norepinephrine levels before intervention (A), after intravenous vasodilators and diuretics (B) and after transition to an oral regimen (C). *p < 0.05 compared to A.

**Figure 3.** Effect of therapy on plasma endothelin levels before intervention (A), after intravenous vasodilators and diuretics (B) and after transition to an oral regimen (C). *p < 0.05 compared to A.
which may contribute (28). Reduction of endothelin may also contribute to lower natriuretic peptide levels.

The regulation of the renin–angiotensin–aldosterone system. In HF, increased plasma renin activity is associated with institution of diuretic therapy (29). Many studies in patients with LV dysfunction have shown decreased mortality with ACE inhibition (30–32). The intensive therapy studied here includes significant diuresis and vasodilation to optimize loading conditions. As expected, initial cessation of ACE inhibition and simultaneous diuresis resulted in higher plasma renin activity and aldosterone levels at time point B. With additional diuresis and reinstatement of converting enzyme inhibition by time point C, plasma renin activity remained elevated, but aldosterone levels fell to their baseline values. The net change in this system is complex and may also reflect changing natriuretic peptide levels and later enhanced dosing of ACE inhibitors. In spite of diuresis, vasodilation and marked lowering of filling pressures, there was no evidence of enhanced activation of the renin–angiotensin–aldosterone system.

Natriuretic peptide regulation in HF. Atrial natriuretic peptide and BNP are vasoactive peptides produced chiefly by atrial myocytes and ventricular myocytes, respectively, in normal humans (33). Both are released in response to chamber wall tension and have important natriuretic and vasodilatory effects (33–37). Plasma ANP and BNP are increased in HF and correlate with atrial filling pressures and disease severity (33,36,38). In addition to vasodilator effects, ANP and BNP have been shown to suppress renin release and decrease angiotensin II and aldosterone production (39).

The vasodilatory effect of natriuretic peptides is blunted in both animal and human studies of severe HF (34,40), perhaps through alterations of receptor density, increased local clearance or uncoupling of intracellular signaling transduction pathways (41–43). Our data indicate that in patients with severe, decompensated HF, natriuretic peptide levels can be rapidly reduced with therapy designed to lower ventricular filling pressures, as has been shown with the bedside BNP assay (38). This could cause transient impairment of natriuresis and systemic vasodilation, and this effect must be considered when achieving rapid normalization of filling pressures. It is not known whether a longer-term reduction of circulating natriuretic peptide levels may normalize receptor density or function, and volume responsiveness (44).

The rapid changes in natriuretic peptides with reduction of filling pressures lend support to the evolving concept that these levels may be useful in evaluating a given patient’s hemodynamic status during therapeutic interventions (44). However, the brisk decline of these vasodilator and natriuretic peptides, which occurs more rapidly than the decline in norepinephrine, may lead to a period of relative systemic and regional hemodynamic instability with deficient endogenous vasodilation while awaiting reductions in endogenous vasoconstrictors. It remains to be seen whether those with the steepest early drops in BNP levels are at highest risk for adverse events, particularly aggravated renal dysfunction (45).

Limitations. The severity of illness of the patients studied, as indicated by the resting hemodynamics, prevents generalization of these study results to patients with a milder degree of hemodynamic compromise. Beta-blocking agents were not used in severe HF at the time of this study. Neurohormonal measurements were not obtained in untreated patients to serve as controls. The third time point occurred after re-initiation of the ACE inhibitor, typically at a higher dose than before therapy. Although this may have some effect on the neurohormonal milieu, most changes observed occurred before ACE inhibitor treatment was restarted, and time point C reflects changes shortly after the ACE inhibitor was re-introduced. Lastly, the study was designed to utilize hemodynamic information to better understand the changes during therapy, but it was not designed to assess the utility of therapy guided by hemodynamic measurement.

Implications. This study demonstrates that neurohormonal activation, as reflected in plasma levels of endothelin, ANP and BNP, rapidly decreases after intensive therapy tailored to improve loading conditions, while norepinephrine levels also decline, but may respond over a slightly longer time course. The rapid decline of neurohormonal occurred without the need for intravenous inotropic therapy, despite the severe hemodynamic compromise.

This study defines the extent to which these neurohormones may change during vasodilator and diuretic therapy for resting hemodynamic decompensation. Moreover, these data support the use of natriuretic peptide levels as markers...
of circulatory decompensation. The differing time course of the vasodilator hormones, BNP and ANP, and the vasoconstrictor hormone, norepinephrine, could create a transient period of endogenous vasoconstrictor dominance potentially compromising re-establishment of optimal volume status, particularly while influencing intrarenal hemodynamics. When resting hemodynamics are severely compromised, therapy specifically designed to improve loading conditions may serve as an important adjunct to neurohormonal antagonists and may facilitate subsequent titration of such medications after stabilization.

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REFERENCES


