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Mortality in End Stage Heart Failure Is Associated with Paradoxically Low NT-Pro BNP and BNP Levels: "Natriuretic Peptide Exhaustion"?

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Background: In heart failure patients elevated levels of natriuretic peptides usually indicate worse heart failure and poorer outcomes; lower levels a more stable compensated state. It has been suggested that some patients with advanced heart failure have low levels because their neurohormonal systems can no longer respond with ventricular synthesis and release of natriuretic peptides. In order to assess this hypothesis of "natriuretic peptide exhaustion" we analyzed whether the values of NT-pro BNP and BNP pre- and post-nesiritide therapy were related to mortality in a severely ill cohort of patients. **Methods:** A non-consecutive cohort of patients (n = 40) was studied during the period of June 2002 to January 2004. These patients were hospitalized for management of severely decompensated chronic heart failure. Blood samples for NT-pro BNP (Elecsys™ NT-pro BNP, Roche Diagnostics, Indianapolis, IN) and BNP (Shinogi) were drawn prior to, at 6 and 24 hours during, and 6 hours post-nesiritide infusion. Post-hospital survival was evaluated with follow-up of 22 months. **Results:** Forty patients (27 males, mean age 68 ± 2 years; LVEF 25 ± 1% were enrolled. All patients clinically responded with diuresis, weight loss, reduced symptoms and were discharged "improved." Cardiovascular related death during post-hospital follow-up was 40% (16/40); time to death was 5.4 ± 1 months. Pre-infusion NT-pro BNP and BNP levels (pg/ml) were significantly lower in patients who died (NT-pro BNP: 9507 ± 1178 vs. 17611 ± 4337, $p < 0.05$; BNP: 487 ± 60 vs. 836 ± 99, $p < 0.05$). There were no differences in the response of NT-pro BNP or BNP during nesiritide infusion between survivors and non-survivors. However, post-infusion NT-pro BNP and BNP values were still markedly lower by 38% and 42%, respectively, in those who did not survive (NT-pro BNP 8012 ± 1392 vs. 12858 ± 3274, $p < 0.05$; BNP: 402 ± 54 vs. 697 ± 107, $p < 0.05$). **Conclusions:** With both analytes used to evaluate the natriuretic peptide system these data support a hypothesis that patients with chronic end-stage heart failure who are at high risk to succumb have lower natriuretic peptide levels both prior to and after nesiritide therapy. These findings are compatible with an "exhausted" neurohormonal system when endogenous mechanisms can no longer contribute adequately to neurohormonal compensation. Paradoxically low natriuretic peptide levels are adverse prognostic markers in end stage heart failure.

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Modulation of B-type Natriuretic Peptide with Epoprostenol in Pulmonary Arterial Hypertension

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Background: B-type natriuretic peptide (BNP) levels are elevated in pulmonary arterial hypertension (PAH), in response to right ventricular wall stress. To overcome limitations of invasive testing for evaluation of therapeutic responsiveness, we examined the utility of early modulation of BNP levels as a surrogate marker for predicting efficacy of response to epoprostenol therapy. **Methods:** In 20 PAH patients eligible for epoprostenol therapy, we measured serial BNP levels (pretreatment and at 3 months post initiation of therapy). The primary endpoint of this prospective study was to evaluate the relationship between early change (0-3 months) in BNP (absolute and relative reduction) and PAH related clinical events (hospitalizations and deaths). Additionally, the predictive power of this biomarker was also assessed in the context of clinical indices (functional class, 6 minute walk test), structural parameters (echocardiographic variables) and invasive hemodynamics by catheterization. **Results:** Twenty patients (50 ± 14 years, 60% primary PAH, 80% female, 50% Caucasian) were enrolled. The baseline BNP level in this cohort was 828 ± 217 pg/ml. A total of 25 hospitalizations and 1 death occurred in nine patients during follow-up period of 10.3 ± 2.8 months. BNP levels between the event-free group (Group A) demonstrated significantly greater absolute and relative decreases from baseline compared with patients with clinical events (Group B). A decrease in BNP level of ≥50% was strongly associated with event-free survival on epoprostenol ($p = 0.0003$). BNP modulation was the only independent predictor of response to epoprostenol in the context of clinical, echocardiographic and invasive hemodynamic variables analyzed.

	Baseline BNP	BNP at 3 Months	Change in BNP	% Change in BNP
Group A (n = 11)	1090 ± 372	288 ± 92	− 801 ± 301	− 70
Group B (n = 9)	510 ± 135	610 ± 121	+ 101 ± 137	+ 11
p Value	0.07	0.04	0.02	0.005

BNP in pg/ml

Conclusions: This investigation establishes the utility of a biomarker strategy using BNP for predicting response to epoprostenol therapy in PAH. A failure to demonstrate a rapid early decrease in BNP levels is a poor prognostic indicator and warrants reassessment for more aggressive therapeutic strategies.

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Renal Resistance to BNP in Severe Experimental Heart Failure is Overcome with High Dose Nesirtide

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Background: Previous human studies report improved cardiac filling pressures and clinical status in acute decompensated congestive heart failure (CHF) using human brain natriuretic peptide (BNP)/Nesiritide. Severe CHF however may be associated with reduced sensitivity to BNP due to receptor down-regulation, enhanced degradation or reduced renal perfusion pressure. We studied the effects of clinical dose IV Nesiritide on systemic hemodynamics and renal function in normal and severe CHF dogs. We hypothesized severe CHF is characterized by renal resistance to these effects of BNP and that supraclinical doses of BNP overcome this resistance. **Methods:** IV Nesiritide was infused in 4 normal dogs at doses approximating clinical trials (see below). Clearances were obtained as described for CHF below. CHF, characterized by decreased cardiac output, increased cardiac filling pressures, sodium retention and neurohumoral activation was induced (n = 7) by rapid ventricular pacing (240 bpm, 10 days). After a baseline clearance IV Nesiritide was infused with a lead in (15 min) followed by 30 minute clearances at doses of 100 (approximating doses in clinical trials) and 1000 ng/kg/min (10 fold greater than clinical trials). **Results:** Clinical dosing of IV Nesiritide markedly increased UnaV (469 ± 94 vs 50 ± 29 μEq/min, $p < 0.05$) and increased plasma cGMP (44 ± 3 vs 11 ± 1pmol/mL, p,0.05) vs baseline in normals with no change in MAP or PCWP. In CHF, clinical dosing did not increase UnaV (7 ± 4 vs 2 ± 1μEq/min, p = NS), GFR (41 ± 10 vs 26 ± 15mL/min, p = NS) or plasma cGMP (39 ± 5 vs 27 ± 8pmol/mL, p = NS) vs baseline consistent with renal resistance to BNP. MAP and PCWP decreased vs baseline. High dose in CHF increased UNaV (12 ± 6 vs 2 ± 0.4 μEq/min, $p < 0.05$) vs baseline without further decreasing MAP. GFR tended to increase compared to baseline (26 ± 5 mL/min) with high (48 ± 15 mL/min, p = NS) dose of IV Nesiritide in severe CHF in association with increased urinary cGMP excretion (data not shown). PCWP decreased further compared to clinical dose. **Conclusion:** These studies support the concept of renal resistance to BNP in severe experimental CHF. They also suggest the possibility of overcoming this resistance using high dose IV Nesiritide to promote natriuresis and diuresis, resulting in further decreases PCWP compared to standard dosing. These effects occurred without any deleterious systemic or renal hemodynamic effects. Therefore, carefully designed clinical studies utilizing higher doses of BNP in severe CHF are warranted.

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Elevated Depressive Symptoms and Inflammation Among Heart Failure Patients

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Many studies have linked psychological depression to heart failure, both an antecedent to heart failure and as a risk factor for poor outcomes among patients with existing heart failure. Elevated levels of proinflammatory cytokines have been proposed as a possible physiological link between depression and morbidity and mortality associated with heart disease. There is an extensive body of literature linking major depression, and, independently, heart failure to elevated levels proinflammatory cytokines. The objective of this study was to compare heart failure patients with and without elevated symptoms of depression with respect to the proinflammatory cytokines IL-6, IL-1β, and TNFα. Thirty-two heart failure patients were recruited from an outpatient heart failure clinic. Depressive symptoms were measured with the Beck Depression Inventory (BDI) and a patient was classified as having elevated symptoms of depression if he/she had a score of 10 or higher. In the multiple linear regression models controlling for age, gender, smoking, and anti-depressant medication use, there was no relation between elevated symptoms of depression and IL-6 ($p = 0.7612$) or IL-1β ($p = 0.8261$). However, there was a statistically significant positive relation between elevated symptoms of depression and TNFα ($p = 0.0374$). The cognitive-affective subscale scores of the BDI were also examined. The BDI scores among patients with heart failure could be inflated due to the overlap in depressive symptoms and the physical symptoms associated with heart failure, such as fatigability, weight loss, and sleep disturbance. Evaluation of the cognitive-affective subscale score facilitates examination of the influence of depressed mood and depressed thinking on cardiovascular function. In the multivariable regression model, there was a significant relation between an elevated cognitive-affective score and TNFα ($p = 0.0322$), but no association with IL-6 ($p = 0.8593$) or IL-1β ($p = 0.3737$). The association between TNFα and the cognitive-affective subscale, which eliminates the physical signs and symptoms that are shared by depression and heart failure, demonstrates a depression-specific activation of proinflammatory cytokines that may promote disease progression and mortality in patients with heart failure.