

4:30 p.m.

## ORAL CONTRIBUTIONS

859-3

**Pro B-Natriuretic Peptide (BNP) Measurement for the Emergency Diagnosis of Congestive Heart Failure: The ProBNP Investigation of Dyspnea in the Emergency Department Study (PRIDE)**

James L. Januzzi Jr., Carlos A. Camargo, Saif Anwaruddin, Aaron Baggish, Annabel Chen, Daniel Krauser, Roderick Tung, Toby Nagurney, Claudia Chae, Donald M. Lloyd-Jones, David F. Brown, Patrick M. Sluss, Elizabeth L. Lewandrowski, Kent B. Lewandrowski, Massachusetts General Hospital, Boston, MA

**Introduction:** The role of proB-type natriuretic peptide (proBNP) for the diagnosis of congestive heart failure (CHF) among patients presenting to the Emergency Department (ED) with dyspnea remains undefined. Accordingly, in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, we are systematically assessing the value of proBNP (Elecsys<sup>®</sup> proBNP Immunoassay, Roche Diagnostics Corporation) for the urgent evaluation of dyspneic patients with suspected acute CHF.

**Methods/Results:** Enrollment for the PRIDE study has closed, and clinical follow up is to complete in October, 2003. The PRIDE study is a single-center, prospective, blinded trial of 600 patients, age  $\geq 21$  years, presenting with a complaint of dyspnea to an urban ED. Exclusion criteria include severe renal insufficiency (serum creatinine  $\geq 2.5$  mg/dl), ST segment depression or elevation on ECG, dyspnea following trauma, and  $\geq 2$  hours following urgent administration of intravenous loop diuretic. Following informed consent, information regarding demographics, past medical history, current medications, and presentation of each patient was gathered. A specimen of blood was collected for blinded proBNP measurement. At the end of standard clinical assessment (history, physical exam, ECG, chest x-ray), the treating ED physician provided a clinical estimate of the presence of CHF as the cause of dyspnea. The primary endpoint of the study will be a comparison of the predictive value of proBNP measurement versus clinical judgment for the presence of CHF at the time of clinical evaluation in the ED. Other endpoints will include correlation of proBNP levels with the diagnosis of CHF from presentation to 60 days of follow-up, as well as correlations with hospital length of stay.

**Conclusion:** The PRIDE study is the first large-scale assessment of proBNP for the evaluation of patients with suspected acute CHF in the ED, and will establish a role for this biomarker in the urgent setting.

4:45 p.m.

859-4

**Nonterminal Pro B-Type Natriuretic Peptide in Patients With Chronic Heart Failure: Correlation With B-Type Natriuretic Peptide and Left Ventricular Structure and Function**

Veselin Mitrovic, Inder Anand, Thorsten Dill, Michael Weber, Thomas Notter, Josef Schenk, Thomas F. Luescher, Christian W. Hamm, Kerckhoff Heart Center, Bad Nauheim, Germany

**Background:** Plasma levels of B-type natriuretic peptide (BNP) and non terminal pro BNP (NT-pro BNP) are increased in patients with systolic and diastolic left ventricular (LV) dysfunction and are important prognostic markers of chronic heart failure. The relation between NT-pro BNP, BNP, and LV structure and function in patients with chronic heart failure has not been studied.

**Methods:** 523 patients (434 male, 89 female, mean age  $60.7 \pm 11.4$  years, LV ejection fraction  $25 \pm 10.6\%$ ) in NYHA class II-IV, enrolled in the European part of the EARTH study, and 101 normal control subjects ( $61.5 \pm 7.4$  years, ejection fraction  $59.0 \pm 6.9\%$ ), were studied. LV endsystolic and enddiastolic volumes (ESV, EDV) were measured using magnetic resonance imaging, ejection fraction, stroke volume, cardiac output, and wall stress calculated. Plasma NT-pro BNP was measured using a newly developed sandwich enzyme-linked immunosorbent assay (ELISA) (Elecsys, Roche Diagnostics), and BNP measurement was performed by use of radio immunoassay (RIA).

**Results:** NT-pro BNP [median, (25<sup>th</sup>-75<sup>th</sup> percentile)] was significantly increased as compared to the controls [942 (492-1977) versus 101 (61-163) pg/ml,  $p < 0.0001$ ]. Area under receiver operated curve was 0.96. At a cut-off point of 270 pg/ml, the specificity and sensitivity were 92% and 88% respectively. NT-pro BNP correlated significantly with BNP ( $r = 0.79$ ,  $p < 0.001$ ), LV ejection fraction ( $r = 0.40$ ,  $p < 0.001$ ), EDV (mean  $\pm$  standard deviation =  $256 \pm 94$  ml,  $r = 0.40$ ,  $p < 0.0001$ ), ESV ( $197 \pm 91$  ml,  $r = 0.24$ ,  $p < 0.0001$ ), and wall stress ( $63 \pm 18$ ,  $r = 0.32$ ,  $p < 0.005$ ), but not with stroke volume or cardiac output. NT-pro BNP levels were significantly higher in patients who died (6 months, 21/523 patients), compared to those who survived (median NT-pro BNP, 3148 versus 1741 pg/ml,  $p < 0.0001$ ). NT-pro BNP above the median, and in the 3<sup>rd</sup> and 4<sup>th</sup> quartile were associated with reduced survival ( $p < 0.001$ ).

**Conclusion:** NT-pro BNP correlates well with BNP and LV volumes and is a significant predictor of mortality in patients with chronic heart failure.

**870 Molecular and Cell-Based Studies in Heart Failure**

Wednesday, March 10, 2004, 8:30 a.m.-10:00 a.m.  
Morial Convention Center, Room 222

8:30 a.m.

870-1

**Chronic Beta<sub>3</sub>-Adrenergic Receptor Blockade Causes Regression of Cardiac Dysfunction in a Rat Model of Progressive Heart Failure**

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**Background.** The negative inotrope and upregulation of  $\beta_3$ -adrenergic receptors (AR) in failing human and animal hearts suggest a direct and contributing role of cardiac  $\beta_3$ -AR activation on heart failure (HF) progression. Therefore, we tested the hypothesis that chronic  $\beta_3$ -AR blockade may limit or prevent the progression of HF.

**Methods.** Left ventricular (LV) and myocyte functional response and  $\beta_1$ - and  $\beta_3$ -AR expression were compared in 3 groups of rats (6 each) for a period of 4 months: 1) Iso-proterenol (ISO)-treated, 4 months after receiving ISO (340 mg/kg, sq, for 2 days); 2) ISO/ $\beta_3$ -ANT, one month after receiving ISO, L-748,337, a selective  $\beta_3$ -AR antagonist ( $\beta_3$ -ANT) ( $10^{-7}$  M/kg/day by implanted osmotic mini pump) was initiated after the onset of HF and was given for 2 months; and 3) sham controls.

**Results.** Compared with controls, ISO-treated rats had HF onset at one month after ISO and progressed to severe CHF at 4 months. Plasma norepinephrine (NE, 1482 vs 247 pg/ml) increased 6 fold. Both stroke volume (SV) and ejection fraction (EF, 34 vs 62%) decreased more than 45%, and LV end-diastolic pressure ( $P_{ED}$ , 16.3 vs 6.4 mmHg) doubled, parallel with 49% reductions in cell contraction ( $dL/dt_{max}$ , 95 vs 189  $\mu$ m/s) and relaxation ( $dR/dt_{max}$ , 75 vs 158  $\mu$ m/s) and a much less increase in  $dL/dt_{max}$  (32 vs 74%) in response to superfusion of ISO ( $10^{-8}$  M). These changes were associated with significantly decreased  $\beta_1$ -AR mRNA (52%, 0.30 vs 0.62), but increased  $\beta_3$ -AR mRNA (119%, 1.25 vs 0.57) expression. Treatment with  $\beta_3$ -ANT significantly decreased  $P_{ED}$  and plasma NE (197 pg/ml). Both SV and EF (59%) increased to more than 75% from ISO-treated values. The signal ratios of  $\beta_1$ -AR mRNA (0.59) and  $\beta_3$ -AR mRNA (0.66) remained close to control levels. ISO-induced increase in  $dL/dt_{max}$  (75%) was also significantly augmented.

**Conclusion.** Chronic  $\beta_3$ -ANT causes normalization of  $\beta_1$ - and  $\beta_3$ -AR gene expression, restores normal responsiveness of myocyte to  $\beta$ -AR stimulation, and leads to regression of LV and myocyte dysfunction in a rat model of progressive CHF. Thus,  $\beta_3$ -AR blocker may provide a new therapeutic strategy for the treatment of CHF.

8:45 a.m.

870-2

**In Vivo Evidence of Isolated Impaired Myocardial Relaxation in Mice Overexpressing the Transcription Factor RTEF-1**

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RTEF-1 mediates transcriptional responses to  $\alpha_1$ -adrenergic signaling in cardiac myocytes. Mice with cardiac-specific overexpression of RTEF-1 develop atrial dilation and atrial arrhythmias. To assess whether mechanical abnormalities contribute to these observations, we performed transthoracic echocardiography and pressure-volume conductance catheterization (closed chest via right carotid artery) in RTEF-1 and wild type (WT) mice (Avertin anesthesia). Conductance catheter data (mean  $\pm$  SD) are summarized in the table. Acute IV volume loading (200  $\mu$ l NS) revealed no difference between groups in the slopes of the end-diastolic pressure-volume relation (0.54 vs. 0.68 mmHg/ $\mu$ l;  $p = NS$ ), indicating normal passive compliance. This is in keeping with the absence of myocardial fibrosis seen on pathology. Echocardiography revealed no difference in LV mass (confirmed by *ex vivo* heart weights) or dimensions. Doppler interrogation of LV filling revealed an increase in the E/A ratio in RTEF-1 mice ( $1.59 \pm 0.15$  vs.  $1.26 \pm 0.23$ ;  $p < 0.05$ ), mediated by trends toward an increase in the E wave velocity ( $60 \pm 18$  vs.  $55 \pm 8$  cm/s;  $p = NS$ ) and a decrease in the A wave velocity ( $38 \pm 10$  vs.  $44 \pm 7$  cm/s;  $p = NS$ ). **Conclusions:** Mice overexpressing RTEF-1 exhibit preserved LV systolic function with impaired relaxation, resulting in elevated filling pressures. While the mechanisms by which RTEF-1 overexpression impairs LV relaxation are unknown, this may serve as a useful model of diastolic dysfunction in the absence of LV hypertrophy.

Group	HR (bpm)	LVEDP (mmHg)	LVEDV ( $\mu$ l)	EF (%)	+dP/dt (mmHg/sec)	-dP/dt (mmHg/sec)	tau (ms)
RTEF-1 (n=9)	437 $\pm$ 53	12.6 $\pm$ 4.0	16.1 $\pm$ 4.3	61.3 $\pm$ 9.1	5883 $\pm$ 1997	-3745 $\pm$ 1475	13.3 $\pm$ 4.8
WT (n=10)	440 $\pm$ 49	4.9 $\pm$ 1.1	17.2 $\pm$ 5.7	62.3 $\pm$ 8.5	6515 $\pm$ 1726	-5274 $\pm$ 1036	7.7 $\pm$ 1.6
P	NS	<0.001	NS	NS	NS	<0.01	<0.001