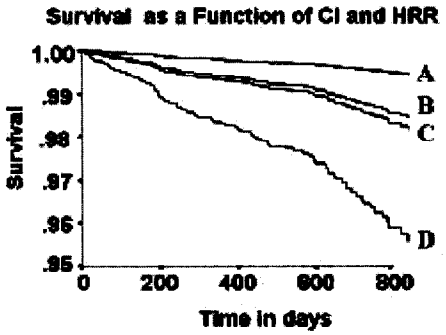
CD (3.3%, p< 0.001).
Conclusion: CI and HRR are independent and incremental predictors of cardiac death.

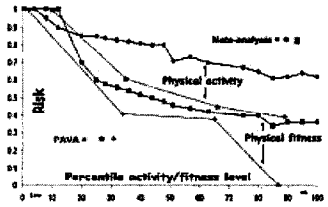


9:00 a.m.

838-3 **Fitness Versus Activity for Predicting Mortality in Men**

Amir Kaykha, Jonathan N. Myers, Sheela George, Joshua Abella, Takuya Yamazaki, Victor F. Froelicher, VA Palo Alto Health Care System, Palo Alto, CA

Background: Both physical fitness and daily physical activity patterns are inversely associated with mortality, but a comparison between the two has not been performed in the same population.
Methods: Physical fitness was determined as METs calculated from speed and grade for 842 males (age 59±12) referred for treadmill testing for clinical reasons. Adulthood recreational activity pattern, expressed in kcal/week, was quantified using a modified Harvard Alumni Questionnaire at the time of exercise testing. Subjects were followed for a mean of 5.5±2.0 years with all-cause mortality as the endpoint.
Results: Recreational energy expenditure showed a graded pattern, with the more active demonstrating a lower mortality (hazard ratio for ≥2000 kcal/week = 0.53, p=0.03). However, adjusting for age, a Cox proportional hazards model showed that peak METs achieved was a stronger predictor of mortality than physical activity pattern (hazard ratio for ≥5 METs=0.30, p<0.001). The Figure shows the reduction in risk for quartiles of fitness and activity we observed relative to the recent meta-analysis of Williams (Med Sci Sports Exerc 2001; 33;754). Both fitness and activity levels in our subjects were similar to the meta-analysis in reducing risk.



Conclusion: Both physical fitness and physical activity patterns were associated with survival, but fitness as estimated in METs from treadmill testing more powerfully predicts survival than activity from a questionnaire.

9:15 a.m.

838-4 **Can a Pre-Exercise Test Score Predict Prognosis in Women With a Low Prevalence of Coronary Disease? The National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study**

Anthony Morise, Marian B. Olson, C. Noel Bairey Merz, Sunil Mankad, William J. Rogers, Carl J. Pepine, Steven E. Reis, Barry L. Sharaf, George Sopko, Gerald M. Pohost, Leslee J. Shaw, West Virginia University School of Medicine, Morgantown, WV

Background: Recent guidelines for exercise testing suggest that a pretest score be used to stratify patients before exercise testing. A Pretest Score derived for use in women without known coronary disease has previously been shown to stratify women according to the prevalence of angiographic coronary disease. However, it has not been tested in a population with a low prevalence of coronary disease. **Methods:** To determine whether this Pretest Score will stratify a separate cohort of women according to prognostic outcomes as well, we evaluated 563 women who underwent coronary angiography for suspected myocardial ischemia with an overall low (26%) prevalence of angiographic coronary disease, defined as >50% stenosis in >1 epicardial vessel. The Pretest Score incorporated age, symptoms, estrogen status, and 6 other coronary risk factors. Using previously defined thresholds, women were placed into low, intermediate, and high probability groups. Women were followed for 2.8 ± 1.5 years for determination of prognostic outcomes. Outcomes considered were death (D), infarction (MI), stroke (SK), other vascular (OV) and revascularization (REV). **Results:** Composite outcome results are shown in table below. Numbers in () are percentages.**Conclusion:** In this cohort of women undergoing coronary angiography with a low prevalence of coronary disease, the Pretest Score stratified women significantly concerning both hard and soft prognostic outcomes.

Prognostic Outcomes by Pretest Group

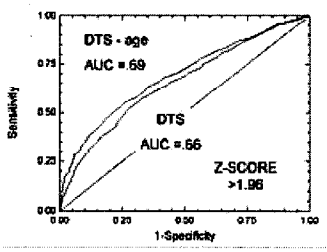
Outcomes	Low	Intermediate	High	p Value
D, MI	4/164 (2.4)	10/245 (4.1)	12/154 (7.8)	0.024
D, MI, SK, OV	8/164 (4.9)	21/245 (8.6)	22/154 (14.3)	0.004
D, MI, SK, OV, REV	15/164 (9.2)	40/245 (16.3)	46/154 (30)	0.001

9:30 a.m.

838-5 **Should Age Be Part of the Duke Treadmill Score?**

Takuya Yamazaki, Amir Kaykha, Jonathan Myers, Victor Froelicher, VA Palo Alto Health Care System, Palo Alto, CA

Background: The Duke Treadmill Score is a validated means of estimating cardiovascular (CV) mortality that has been recommended as part of the routine interpretation of treadmill tests. Age is a predictor of death but not included in the DTS.
Methods: Analyses were performed on the first treadmill test performed on 6,352 consecutive male veterans at the Palo Alto and Long Beach Veterans Affairs Medical Centers since 1987. After removal of all CHF patients, 5,629 patients remained with a mean age of 59±11 years. The main outcome measure was CV mortality; during a mean follow-up of 6.6±4 years, there were 518 CV deaths. The DTS was calculated as METs - (4*[1=angina occurred, 2=reason for stopping])-(5* amount abnormal ST depression).
Results: Using Cox Hazard analysis, the DTS and age were found to have similar coefficients but opposite sign, so a score was made as DTS-age. Using ROC analysis with CV mortality as the outcome, AUCs were calculated for the scores. DTS-age gave a significantly better discrimination than the DTS alone.



Conclusion: The DTS minus age outperformed the DTS for predicting cardiovascular mortality. After validation in other populations, age should be subtracted from the DTS calculation as part of treadmill test interpretation.

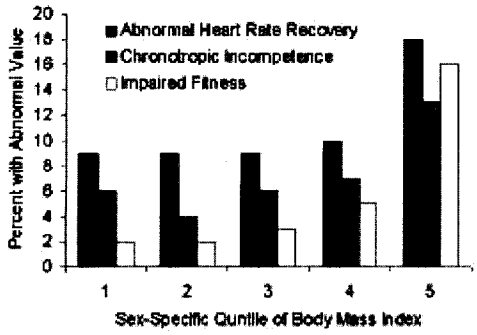
9:45 a.m.

838-6 **Association of Abnormal Heart Rate Recovery and Chronotropic Incompetence With Obesity in a Healthy Cohort**

Michael S. Lauer, David Yu, Claire E. Pothier, Eugene H. Blackstone, Cleveland Clinic Foundation, Cleveland, OH

Background: Obesity is known to be associated with abnormalities of autonomic nervous system balance. We hypothesized that obesity is also associated with exercise heart rate abnormalities, which are reflective of autonomic tone.
Methods: We studied 3,071 adults (mean age 49; 85% men) without a history of cardiac disease or use of cardiovascular medications who referred for symptom-limited exercise stress testing. Exact height and weight were directly measured per routine protocol. Subjects were divided into sex-specific quintiles of body mass index (BMI) (quintile 5 > 30 kg/m^2 in men, > 28 kg/m^2 in women). An abnormal heart rate recovery (HRR) was defined as ≤ 12 beats per minute during the first minute after exercise. Chronotropic incompetence (CRI) was defined as failure to use 80% of heart rate reserve.
Results: There were 333 subjects (11%) who had an abnormal HRR, 222 (7%) who had CRI, and 169 (6%) who had impaired functional capacity for age and gender. Abnormalities of all 3 variables were particularly marked in the highest quintile of BMI (Figure).

After adjusting for age, gender, blood pressure, smoking status, use of aspirin and/or



lipid lowering medication, resting heart rate, and exercise capacity in sequential bootstrapping logistic analyses, obesity (i.e., BMI quintile 5) was independently associated with an abnormal HRR (adjusted odds ratio [OR] 1.68 (1.26 - 2.34) and with CRI (adjusted OR 2.23 (1.56 - 3.17).

Conclusion: Obesity is independently associated with abnormal HRR and with CRI.

POSTER SESSION

1158 Cardiac Function: Peptides and Receptors

Tuesday, April 01, 2003, 9:00 a.m.-11:00 a.m.
McCormick Place, Hall A
Presentation Hour: 10:00 a.m.-11:00 a.m.

1158-68 Chronic Subcutaneous Administration of the Cardiac Peptide BNP in Experimental Heart Failure Does Not Result in the Development of Tolerance to Exogenous BNP

Horng H. Chen, John A. Schirger, Alessandro Cataliotti, Gail Harty, John C. Burnett, Jr., Mayo Clinic and Foundation, Rochester, MN

BACKGROUND: Brain natriuretic peptide (BNP) is a cardiac peptide with vasodilating, lusitropic, natriuretic and renin-angiotensin-aldosterone (RAAS) inhibiting properties which are mediated by the second messenger cGMP. BNP is FDA approved for the management acute congestive heart failure (CHF). We have previously shown that chronic subcutaneous (SQ) administration of BNP in experimental CHF improves hemodynamics, however, it is unknown if chronic BNP administration leads to the development of tolerance to exogenous BNP. **METHODS:** We compared the cardiorenal effects of acute administration of SQ BNP (5μg/Kg) in a group of dogs (n=5) with pacing induced CHF (180 bpm for 10 days) to a separate group of CHF dogs (n=6), who received chronic SQ BNP (5μg/Kg) three times a day during10 days of pacing. **RESULTS:** Chronic SQ BNP therapy for 10 days improved cardiac output (3.6± 0.4 vs 2.5± 0.1 L/min) with decreased pulmonary capillary wedge pressure (PCWP) (9± 2 vs 16± 3 mmHg) and systemic vascular resistance (35± 5 vs 45± 4 RU) as compared to the untreated group (p<0.05). Importantly, acute administration of SQ BNP on day 11, resulted in similar increases in plasma cGMP (35± 5 vs 29± 2 pmol/ml) and urinary cGMP excretion (UcGMPV) (6000± 1000 vs 4000± 600 pmol/min) in both the chronic SQ BNP treated and the untreated groups (p>0.05). These were associated with decreased cardiac filling pressures and increased in urine flow, which were also similar in both the chronic SQ BNP treated and the untreated groups (p>0.05). **CONCLUSION:** In this model of experimental CHF, chronic SQ BNP administration did not result in the development of tolerance as demonstrated by similar increases in plasma cGMP and UcGMPV in the chronic BNP treated and the untreated groups with acute administration of SQ BNP. Furthermore, acute administration of SQ BNP resulted in similar decreases in cardiac filling pressures and increases in urine flow. This may have important clinical implications, suggesting that chronic SQ BNP administration does not lead to the development of tolerance to acute BNP administration and supporting this strategy as efficacious for chronic protein-based therapy for CHF.

1158-69 Chronic Oral Endothelin-A Receptor Antagonism Activates the Renin-Angiotensin-System With Persisting Sodium Retention in Experimental Heart Failure

John A. Schirger, Horng H. Chen, John C. Burnett, Jr., Mayo Clinic and Foundation, Rochester, MN

Background: Although acute endothelin (ET) receptor antagonism improves systemic hemodynamics in congestive heart failure (CHF), clinical trials with chronic ET receptor antagonism report exacerbation of CHF symptoms. The mechanisms for this remain unclear. **Methods:** We first defined the temporal activation of the ET and renin-angiotensin-systems (RAS) at the onset of sodium retention in a canine model of pacing induced CHF. Next, we evaluated the effect of chronic oral ET-A receptor antagonism (LU135252: started day 3 of pacing) on sodium excretion, glomerular filtration rate and neurohumoral activity in canine CHF. **Results:** Plasma endothelin-1 but not plasma renin activity (PRA) increased with the onset of sodium retention in CHF (n=5) compared to normal dogs (n=5) (17.0±2.0 vs 7.0± 2.0 pg/mL, p<0.05). Northern blot analysis demonstrated myocardial endothelin-1 mRNA activation at the onset of sodium retention (n=5) compared to normal dogs (n=5). Myocardial angiotensin II was not activated at this point in either group. After 7 days of treatment (n=7) with LU135252 there was no difference in sodium retention (7±3 vs 4±2 uEq/min) or glomerular filtration rate vs. untreated CHF dogs (n=6). PRA (7±2 vs 16±4 ng/mL/hr, p<0.05) and plasma endothelin-1 increased with treatment. After 18 days of treatment (n=9), despite maintaining glomerular filtration rate at normal values, LU135252 did not increase sodium excretion vs. untreated CHF dogs (n=8), and PRA tended to further increase with treatment. **Conclusion:** Activation of the ET system precedes activation of the RAS in CHF. ET-A receptor antagonism in CHF does not increase sodium excretion but may further activate the RAS. These findings suggest a mechanism for the exacerbation of CHF symptoms observed in clinical trials with chronic ET receptor antagonism and support a possible strategy for combining antagonism of the ET system and RAS in CHF.

1158-70 Role of Kinins and Angiotensin II Type 2 Receptors in the Cardioprotective Effect of Angiotensin II Type 1 Receptor Antagonists in Brown Norway Kininogen-Deficient Rats

Yun-He Liu, Xiao-Ping Yang, Ai-Li Yu, Edward G. Shesely, Oscar A. Carretero, Henry Ford Hospital, Detroit, MI

Background: Previously we reported that lack of kinins influence neither cardiac function nor development of HF post-MI; however, kinins play an important role in the cardioprotective effect of ACEi. Here, we studied the role of kinins and AT_2 receptors in the protective effect of AT_1-ant in rats with HF.

Methods: Brown Norway Katholiek (BNK) rats, which are genetically deficient in kinins due to a mutation in the kininogen gene, and their wild-type control (BN) underwent either sham or coronary artery ligation. 2 months later, they were treated for 2 months with a) vehicle, b) AT_1-ant (L158809, 1.5 mg/kg/day), c) AT_1-ant + AT_2-ant (PD-123319, 10 mg/kg/day), or d) AT_1-ant + kinin B_2 receptor antagonist (icatibant, 100 μg/kg/day, in BN). We measured left ventricular end-diastolic volume (LVEDV), end-systolic volume (ESV) and ejection fraction (EF) by ventriculography, and (interstitial collagen fraction-ICF), myocyte cross-sectional area (MCSA), assessed histologically and heart weight (HW).

Results: In BNK, the protective effect of AT_1-ant was diminished, blockade of AT_2 receptors did not influence the effect of AT_1-ant on cardiac function and fibrosis; however, it blocked the effect of AT_1-ant on hypertrophy, and in BN rats, effect of AT_1-ant was blocked by AT_2-ant, and partially blocked by icatibant.

Conclusion: 1) AT_2 receptors acting via kinins play an important role in the cardioprotective effect of AT_1-ant. 2) the antihypertrophic effect of AT_1-ant is mediated by a factor other than kinins.

Effect of AT1-ant on cardiac function and remodeling in BN and BNK

	BN				BNK			
	Sham	HF-Vehicle	HF-AT1ant	HF-AT1ant + AT2ant	Sham	HF-Vehicle	HF-AT1ant	HF-AT1ant + AT2ant
LVEF (%)	64 ± 1	25 ± 3(1)	42 ± 2(2)	24 ± 2(3)	68 ± 1	28 ± 1(4)	33 ± 2	34 ± 3
LVEDV (μl)	358 ± 29	846 ± 64(1)	582 ± 28(2)	856 ± 110(3)	417 ± 20	869 ± 49(4)	743 ± 37	761 ± 52
HW (mg/100 g BW)	254 ± 7	324 ± 12(1)	264 ± 6(2)	314 ± 14(3)	261 ± 7	306 ± 10(4)	283 ± 7(5)	323 ± 17(6)
ICF (%)	4.9 ± 0.3	10.4 ± 0.5(1)	8.1 ± 0.7(2)	12.6 ± 1.1(3)	4.9 ± 0.1	12.4 ± 1(4)	11± 0.9	10 ± 0.9

Mean SE; (1) : p < 0.01 versus BN-sham; (2): p < 0.01 versus BN-HF-Vehicle; (3): p < 0.001 versus BN-HF-AT1-ant; (4): p < 0.001 versus BNK-sham; (5): p < 0.05 versus BNK-HF-AT1-ant; (6): p < 0.05 versus BNK-HF-AT1-ant.