1145-126   Left Ventricular Assist Device Implantation Induces Neo-Neurogenesis Accompanied by Neo-Angiogenesis in the Nonscarred Myocardium in Patients With Heart Failure

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Background: End stage heart failure (esHF) is associated with reduced blood vessel and nerve density. LVAD implantation reverses ventricular myocyte & fibrous tissue remodeling but it is not clear if it can also optimize neo-angiogenesis and repopulate myocardial nerves.
Hypothesis: LVAD implantation will re-innervate the heart along with neo-angiogenesis while reversing ventricular remodeling.
Methods: Myocardial nerve growth (immunostaining with PGP for total nerves, GAP43 + tyrosine hydroxylase for new sympathetic nerves) and neo-angiogenesis (vWF+Ki-67 staining) was measured in the non-scar myocardium at LVAD implant and at transplantation in 6 patients with esHF (4 ischemic and 2 non-ischemic).
Results: Time between LVAD and transplant 151-681 days. LVAD implantation significantly improved total & new blood vessel density (p<0.05) while inducing reverse remodeling. This was accompanied by increased new sympathetic innervation in the same region. Conclusion: LVAD implantation facilitates neo-angiogenesis. This may help in the process of reverse remodeling seen after LVAD use. LVAD also induces new nerve growth in non-scar myocardium. It significance in terms of arrhythmic potential, especially in patients being considered for LVAD explantation, needs to be determined.
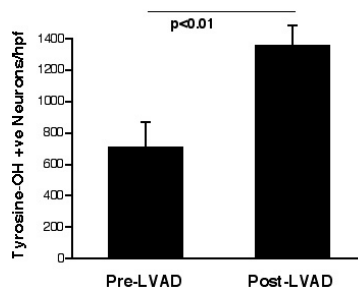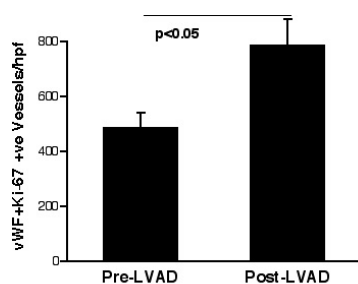
POSTER SESSION

1146   Exercise Testing and Cardiovascular Disease Prognosis

Tuesday, March 09, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1146-105   The Prognostic Significance of Exercise-Induced Atrial Arrhythmias

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Background: Although stress-induced atrial arrhythmias are common during exercise testing, there is a paucity of data regarding the correlation with underlying heart disease and cardiovascular outcomes. Atrial arrhythmias may reflect underlying left atrial enlargement and diastolic dysfunction, which are prognostic of mortality. We hypothesized these stress- induced arrhythmias are associated with long-term adverse cardiac events.
Methods: Exercise echocardiography was performed in 5,375 patients (age 61 ± 12 years) with known or suspected coronary artery disease. An abnormal result was defined as exercise-induced atrial fibrillation/flutter (AF), supraventricular tachycardia (SVT), or atrial ectopy (AE).
Results: Three hundred and eleven patients (5.8%) died (132 (2.5%) cardiac causes) over a period of 3.1 ± 1.7 years. In addition, 193 patients (3.6%) experienced a MI, and 531 (9.9%) required revascularization. During exercise testing, 1272 (24%) developed AE, 185 (3.4%) SVT, and 43 (0.8%) AF. The 5-year cardiac death rate was not statisti-

cally different between groups [none (3.8%), AE (4.3%), SVT (3.7%), AF (0%), p=0.43]. However, the 5-year rate of MI was significantly different between groups [none (5.7%), AE (8.3%), SVT (0%), AF (9.0%), p=0.005]. The 5-year rate of revascularization between groups was not significantly different [none (14.2%), AE (17.0%), SVT (11.8%), AF (14.8%), p=0.50]. A composite of all 5-year adverse endpoints was similar between groups [none (22.7%), AE (27.8%), SVT (17.7%), AF (25.7%), p=0.10]. In stepwise multivariate analysis, AE was not predictive of myocardial infarction when taking into account traditional clinical variables and exercise test results.
Conclusion: In this large cohort of patients, the occurrence of atrial ectopy was predictive of an increased risk of myocardial infarction. However, this association did not persist after adjustment for clinical and exercise variables known to predict adverse long-term cardiovascular outcomes. The rate of long-term cardiac death or revascularization was not influenced by the development of stress-induced atrial arrhythmias.

1146-106   Does Abatement of Ventricular Ectopy With Exercise Mean a Better Prognosis?

Obadah Alchekakie, Michael S. Lauer, Mina K. Chung, Cleveland Clinic Foundation, Cleveland, OH

Background: Among patients with frequent ventricular ectopy at rest, it is believed that an abatement of ventricular ectopy during exercise testing predicts a lower risk of death.
Methods: We followed 920 consecutive patients (age=62±11, 78% male) with frequent ventricular ectopy at rest just before undergoing exercise testing and who had no history of heart failure, valve disease, pacemakers, or atrial fibrillation.Frequent ventricular ectopy before, during, and after exercise was defined as more than 7 ventricular premature depolarizations per minute, frequent couplets, any triplets, bigeminy, trigeminy, nonsustained or sustained ventricular tachycardia, or ventricular fibrillation. Abatement was considered present if there was there was no frequent ventricular ectopy during exercise.
Results: There were 214 patients (23%) who had an abatement of ventricular ectopy during exercise. During 7 years of follow-up there were 142 deaths. Patients with abatement of ventricular ectopy were more likely to be women (33% vs. 19%, P<0.0001) and less likely to have a history of coronary bypass grafting (18% vs. 27%, P=0.005), but there were no marked differences in age (61 vs. 62), diagnosis of coronary disease (46% vs. 44%), or reduced physical fitness (29% vs. 27%). Seven-year death rates tended to be slightly lower among patients with abatement compared to those without (14.3% vs. 17.3%, P=0.87). After accounting for age, gender, standard risk factors, medications, resting electrocardiographic findings, functional capacity, and heart rate recovery, abatement did not predict a lower risk of death (adjusted hazard ratio 1.03, 95% confidence interval 0.70-1.54, P=0.87).Conclusion: Among patients with frequent ventricular ectopy at rest, abatement of ectopy during exercise does not predict a lower risk of death.

1146-107   Severe Frequent Ventricular Ectopy After Exercise as a Predictor of Death in Patients With Advanced Systolic Heart Failure

James O. O'Neill, James B. Young, Claire E. Pothier, Michael S. Lauer, Cleveland Clinic Foundation, Cleveland, OH

Background: Although ventricular ectopy during recovery after exercise predicts death in patients without heart failure, its prognostic importance in patients with advanced heart failure is unknown.
Methods: Systematic electrocardiographic data during rest, exercise and recovery were gathered on 2123 consecutive Cleveland Clinic Foundation patients with left ventricular systolic ejection fraction ≤ 35% who were referred for symptom limited metabolic treadmill exercise testing.Severe ventricular ectopy was defined as the presence of ventricular triplets, sustained or non-sustained ventricular tachycardia, ventricular flutter, polymorphic ventricular tachycardia or ventricular fibrillation. The primary end point was all cause mortality, with censoring for interval cardiac transplantation.
Results: Of 2,123 patients, 140 (7%) had severe ventricular ectopy in recovery. There were 561 deaths during follow-up (median among survivors 2.9 years). Severe ventricular ectopy during recovery was associated with an increased risk of death compared to patients without severe ectopy (3-year death rates 37% vs. 22%, hazard ratio 1.76, 95% CI 1.32 - 2.34, P<0.0001). After adjustment for ventricular ectopy at rest and during exercise, peak oxygen uptake, and other potential confounders, severe ventricular ectopy in recovery remained predictive of death (adjusted hazard ratio 1.48; 95% confidence interval 1.10-1.97; p=0.0089), whereas ventricular ectopy during exercise was not predictive.
Conclusion: Severe ventricular ectopy during recovery after exercise is predictive of increased mortality in patients with severe heart failure.

1146-108   Association of Triglyceride to High-Density Lipoprotein Cholesterol Ratio With Heart Rate Recovery in Healthy Adults

Mehdi H. Shishebor, Byron J. Hoogwerf, Michael S. Lauer, Cleveland Clinic Foundation, Cleveland, OH

Background: Insulin resistance is associated with altered autonomic function. An attenuated decrease in heart rate immediately after exercise (or heart rate recovery) predicts all-cause mortality and is believed to reflect decreased parasympathetic activity. Utilizing TG/HDL-C concentration as a marker of insulin resistance we sought to assess the association between insulin resistance and heart rate recovery.
Methods: Our study population included 4963 healthy adults who participated in the Lipid Research Clinics' Prevalence Study and who underwent exercise testing. Heart rate recovery was considered abnormal if ≤ 42 beats per minute two minutes into recovery. Fasting blood specimens were drawn for lipid profiles and blood glucose.
Results: Individuals in the highest quartile of TG/HDL-C had significantly higher prevalence of abnormal heart rate recovery (HRR) (40% vs. 30%; multivariable adjusted prevalence ratio, 1.18; 95% CI 1.01-1.39; P = 0.04). When considered as a continuous

variable, an increase in one standard deviation (0.37) of TG/HDL-C ratio was associated with a greater likelihood of an abnormal HRR, even after adjusting for over 20 covariates (adjusted odds ratio, 1.16; 95% CI, 1.07-1.25; P < 0.001). During 12 years of follow-up, there were 284 deaths. In age and sex-adjusted analysis, participants with an abnormal HRR and high TG/HDL-C ratio had significantly higher mortality than those with a normal HRR and high TG/HDL-C ratio (hazard ratio = 1.49; 95% CI 1.08-2.04; P = 0.015).

Conclusions: Heart rate recovery is associated with TG/HDL-C ratio and identifies patients with insulin resistance who are at increased risk of death.

1146-109 The Effect of Leisure-Time Physical Activity on Inflammation Markers: The ATTICA Study

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BACKGROUND: Physical activity is associated with a reduced risk for coronary heart disease (CHD), although the exact mechanisms remain unknown.As CHD is increasingly seen as an inflammatory process, it is reasonable to hypothesize that physical activity reduces CHD risk by modifying inflammatory processes. METHODS: The ATTICA study is a population -based cohort that has randomly enrolled 2282 cardiovascular disease free individuals, stratified by age group, from the greater area of Athens, during 2001-2002. Of them, 1128 were men (48 ± 14 years old, range: 18 – 86) and 1154 women (47 ± 14 years old, range: 18 - 88). We assessed the relationship between self reported physical activity status and inflammation, thrombogenic markers as indicated by C-reactive protein, amyloid-A, fibrinogen and white blood cell counts, after taking into account the effect of several demographic, clinical and biochemical characteristics of the participants. RESULTS: Compared with persons that reported sedentary life, those who defined as highly physical active had 33%, lower concentrations of C-reactive protein (1.5 ± 1.4 vs. 0.9 ± 1.3 mg/dl, p = 0.020), 10% of white blood cells (6.9 ± 1.9 vs. 6.2 ± 1.7 counts, p = 0.012), 17% of amyloid-A (5.1 ± 5.4 vs. 4.2 ± 5.3, p = 0.059), and 3% of fibrinogen (328 ± 145 vs. 318 ± 74 mg/dl, p = 0.445), after controlling for several potential confounders. CONCLUSIONS: Physical activity is associated with lower concentrations of C-reactive protein, white blood cells and other inflammation and thrombogenic markers. These findings suggest that the inflammation process and consequently atherosclerotic disease can be attenuated by increased physical activity.

1146-110 Chronotropic Incompetence as a Predictor of Death Among Patients Taking Beta-Blockers

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Background: Chronotropic incompetence, or an inability to increase heart rate during exercise, independently predicts death. Whether it predicts death in patients taking beta-blockers is not known.

Methods: We followed for a mean of 5.2 years 7456 patients (age 60±11, 70% men) who were taking either metoprolol or atenolol and were referred for symptom-limited exercise treadmill testing between 1990 and 2002. Chronotropic response was defined as the percent of heart rate reserve used, that is (peak heart rate – resting heart rate)/(maximum predicted heart rate – resting heart rate). A value of $\leq$ 59%, corresponding to the lowest quartile, was defined as abnormal.

Results: There were 3868 patients (52%) taking atenolol and 3588 (49%) taking metoprolol. There were 644 deaths. Patients with chronotropic incompetence had a higher mortality risk (6-year death rates 14% vs. 7%, hazard ratio 2.1, 95% CI 1.8 – 2.5, P<0.0001). After adjusting for age, gender, resting heart rate, standard risk factors, other medications, exercise capacity, and heart rate recovery, chronotropic incompetence predicted death (adjusted hazard ratio 1.4, 95% CI 1.1-1.6, P=0.0005). The association of chronotropic incompetence with death was present irrespective of which drug was taken or the number of half-lives elapsed since the last dose. Even among patients in the lowest quartile of half-lives elapsed ($\leq$ 0.9), chronotropic incompetence predicted death (10% vs. 6%, hazard ratio 2.0, 95% CI 1.4 – 2.9, P<0.0001).

Conclusion: Among patients taking beta-blockers, chronotropic incompetence is predictive of death.

1146-111 Exercise Cardiopulmonary Predictors of Major Clinical Events in Advanced Heart Failure

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Background: Numerous studies indicate that exercise cardiopulmonary tests (CPX) predict prognosis of chronic systolic heart failure (HF). We investigated the interactions of various clinical and CPX variables in assessing prognosis in patients with advanced HF. Methods: CPX was performed in 98 consecutive advanced HF patients (NYHA class III-IV, mean EF 20%) followed for 18 ± 12 months for major clinical events (cardiovascular death or urgent transplantation). We examined CPX variables associated with clinical events by conducting univariate and multivariate analyses and assessed several standard variables to predict prognosis.
Results: Compared with 20 patients with major clinical events, the 78 patients without events had significantly higher percent of predicted peak VO2 (63.7 ± 19.8% vs. 54.2 ±13.0%, p < 0.02), peak VO2 corrected for lean body weight (20.0 ± 6.6 vs. 16.7 ± 4.5 cc/kg/min lean, p < 0.02), O2–pulse (10.9 ± 4.5 vs. 9.0 ± 2.5 cc/beat, p < 0.02), body fat adjusted O2–pulse (15.0 ± 5.9 vs. 11.8 ± 3.6 cc/beat, p < 0.01), and lower VE/VCO2 (34.7 ± 7.9 vs. 41.5 ± 7.2, p < 0.01). Peak VO2 (14.5 ± 5.1 vs. 12.9 ± 3.9 cc/kg/min, p = 0.12), peak heart rate and peak systolic blood pressure were statistically similar in both groups. In multivariate analysis, a non-ischemic cardiomyopathy was the strongest independent predictor of event-free survival (chi-square 8.3, p < 0.01), followed by body fat adjusted O2-pulse (chi-square 7.1, p < 0.01) and peak VO2 lean (chi-square 3.8, p = 0.05). The "Mancini" cut-off for peak VO2 (14 ml/kg/min) was particularly poor for prog-

nostic stratification (16% vs 25% events; p=NS); this was improved considerably by using O2–pulse (cut-off 10 ml/beat;13% vs 28% events, p=0.05), peak VO2 lean (cut-off 19 ml/kg/min; 9% vs 30% events; p<0.01) and especially by O2 pulse lean (cut-off 14 ml/beat;9% vs 31% events, p<0.01).
Conclusions: This investigation suggests that while unadjusted peak VO2 is unreliable in segregating risk in advanced HF, a combination of clinical and exercise cardiopulmonary variables, particularly body fat adjusted O2-pulse and peak VO2, more robustly predict clinical outcome in this clinical syndrome.

1146-112 Systolic Blood Pressure During Recovery Is Related to the Risk of Acute Myocardial Infarction in Middle-Aged Men

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Background: We assessed the association of systolic blood pressure (SBP) after exercise with the risk of an acute myocardial infarction in middle-aged men with no prior history of coronary heart disease. Limited information currently exists on the association of the SBP during recovery and the risk of acute myocardial infarction.
Methods: SBP was measured every two minutes during and 2 minutes after a progressive cycle ergometer exercise test in a representative population-based sample of 1789 Finnish men (age 42-61 years), 243 of whom were using antihypertensive medications. During an average follow-up period of 12.7 years, 191 acute myocardial infarctions occurred.
Results: An incremental rise of 10 mmHg per minute in SBP after exercise (relative risk=1.12, 95 % CI 1.04 to 1.20, p=0.001) was associated with the risk of acute myocardial infarction among men not on antihypertensive medications, after adjustment for age, alcohol consumption, smoking, serum lipids, diabetes mellitus, body mass index, physical fitness, heart rate and ischemic ECG findings and resting SBP. Men with elevated SBP of over 198 mmHg after exercise had a 2.10-fold (95 % CI 1.26 to 3.41, p=0.004) risk for an acute myocardial infarction as compared to those with SBP less than 165 mmHg, after adjustment for age, other risk factors and resting SBP. High SBP after exercise relative to maximal SBP was also related to the risk of AMI.
Conclusions: Systolic blood pressure during recovery period was risk predictor for acute myocardial infarction among middle-aged men not receiving antihypertensive medications. This measure can provide incremental predictive value for an acute myocardial infarction to elevated resting SBP.

1146-113 A Pretest Score Used in Patients With Suspected Coronary Disease Referred for Pharmacologic Stress Testing Stratifies Well According to Cardiac Death but Not All-Cause Mortality

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Background: Patients with suspected coronary disease referred for pharmacologic stress testing (Pharm) have a higher all-cause mortality (ACM) than those referred for exercise testing. In exercise test patients, a pretest score has been shown to stratify well according to ACM. **Methods:** To determine how well the pretest score stratified patients referred for Pharm, we analyzed 3999 consecutive ambulatory patients with symptoms of suspected coronary disease who presented for their initial stress evaluation between 1995 and 2001. Mean follow-up time was 4.4±1.7 years. Endpoints were cardiac death (CD) and ACM. Variables considered in the pretest score were age, sex, symptoms, and risk factors. Analysis was performed using the Kaplan-Meier method and contingency table analysis. **Results:** There were 259 deaths (6.5%; 1.5%/year) of which 37% were CDs (2.3%; 0.5%/year). Within the 1036 Pharm patients, there were 165 deaths (16%; 3.6%/year) of which 38% were CDs (6.1%; 1.4%/year). Within the 2963 exercise patients, there were 94 deaths (3.2%; 0.7%/year) of which 34% were CDs (1.0%; 0.2%/year). Patients were stratified by the pretest score into either low or intermediate-high groups (see table). ** = p<0.0001, * = p<0.01 by Kaplan-Meier.**Conclusion:** Patients who underwent Pharm were stratified by the pretest score according to both ACM and CD. However, low risk Pharm patients were at low risk for CD, but not ACM.

	Exercise		Pharm	
	ACM	CD	ACM	CD
Low	12/1294	5/1294	10/213	1/213
Percent	0.9	0.4	4.7	0.5
Annualized %	0.2	0.1	1.1	0.1
Intermediate-High	82/1669	27/1669	155/823	62/823
Percent	4.9**	1.6*	18.8**	7.5**
Annualized %	1.1	0.4	4.3	1.7