1108-01 Exercise Blood Pressure Threshold for Left Ventricular Hypertrophy in Normotensive and Hypertensive Middle-Aged Men

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Background: An abnormal rise in systolic blood pressure (SBP) during exercise is associated with increased risk for hypertension (HTN) and left ventricular hypertrophy (LVH). However, the magnitude of change in exercise SBP associated with LVH is not well defined. Methods: We assessed left ventricular structure (echocardiography) and exercise blood pressure in normotensive and hypertensive middle-aged men (n=121). Men free from heart disease, smoking, and antihypertensive medication, to determine the association between left ventricular structure and exercise SBP.

Results: Multiple regression analysis revealed that SBP at 6 minutes of exercise was the strongest predictor of LVH for normotensive (R²=0.49) and hypertensive (R²=0.51) men, respectively. Further, the magnitude of change in exercise SBP associated with LVH was not well defined. Conclusions: SBP at 6 minutes of exercise is the strongest predictor of LVH for normotensive and hypertensive men. Further, the magnitude of change in exercise SBP associated with LVH is not well defined.

1108-02 Electrocardiographic Markers of Cardiac Hypertrophy Show Greater Heritability Than Echocardiographic Left Ventricular Mass: A Family Study

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Background: Electrocardiographic and echocardiographic measures of cardiac hypertrophy are independent predictors of cardiovascular morbidity and mortality. There is increasing evidence to show that echocardiographic left ventricular mass is genetically determined, but little is known about the magnitude of genetic determination of electrocardiographic measures of cardiac hypertrophy. We set out to assess the heritability of continuous measures of left ventricular hypertrophy determined by electrocardiography and echocardiography.

Methods: We studied 955 members of 225 Causasian extended families, ascertained through a hypertensive proband. Electrocardiographic and echocardiographic measurements were performed manually on normal resting 12-lead electrocardiograms, and echocardiographic parameters were determined on M-mode images. Sex-specific residuals for left ventricular parameters were calculated, adjusted for age, systolic blood pressure, weight, height, waist-hip ratio, and body mass index (BMI). Heritability was assessed from familial correlations with adjustment for spouse resemblance, and using variance component methods with ascertainment correction for proband status.

Results: Heritability estimates (range) were higher for Sokolow-Lyon voltage [39-41%] and RVALL voltage [30-31%] than for echocardiographic left ventricular mass (23-29%). Correlation between Sokolow-Lyon voltage and RVALL voltage was 0.89. Conclusion: The genetic heritability of Sokolow-Lyon voltage and RVALL voltage suggests that electrocardiographic phenotypes may be particularly important for the molecular investigation of the genetic susceptibility to cardiac hypertrophy. Finding genes that influence the electrocardiographic markers could help unravel the pathophysiology of cardiac hypertrophy and lead to improvements in prevention, diagnosis, and treatment of at-risk populations.

1108-03 Is Urinary Albumin Excretion an Independent Predictor of Cardiovascular Mortality in Patients With Electrocardiographic Left Ventricular Hypertrophy? The LIFE Study

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Background: Recently, we found that increased urine albumin/creatinine ratio (UACR) as well as electrocardiographic (ECG) left ventricular hypertrophy (LVH) were related to high blood pressure (BP) in hypertensive patients independent of age, smoking, prevalence of diabetes, and suggesting parallel BP and coronary heart disease (CHD) risk. However, it is not clear whether this predicts an independent effect on mortality.

Methods: ECG and morning spot urine were obtained in 8,165 patients with stage II hypertension and ECG LVH (Cornell voltage-duration or Sokolow-Lyon voltage criteria) after 14 days placebo treatment. Renal glomerular permability was evaluated by UACR and was defined as micro- or macroalbuminuria (~3.5 or 35 mg/mmol, respectively). Results: During 66% [95% CI 67-69] months 902 (6%) deaths occurred. Of these sample (38.0%) were cardiovascular (CV) deaths, which plus non-fatal myocardial infarction and strokes comprised the composite primary CV end-point (p=0.08, 10.8%). Patients with either micro- or macroalbuminuria had on average 1.7 or 3.3-fold higher CV mortality rate, respectively, compared to normoalbuminuric patients. Similar micro- or macroalbuminuria groups had 1.8 or 2.8-fold higher rates of composite anti-end-points compared to normoalbumi- 

nuric groups. CV mortality rate and composite CV end-point rate increased progressively in patients with macroalbuminuria and LVH by both criteria as compared to normoalbuminuric patients without LVH by either criterion (p<0.001). When divided into quartiles a striking increase in CV end-points was seen in the 3rd quartile with UACR-values between 1.2-3.3 gmmol/l. Cox regression analysis showed that UACR predicts CV mortality and composite CV end points independent of LVH, systolic BP, age, sex, diabetes and smoking. Conclusion: UACR is an independent predictor of CV morbidity and mortality, even after taking into account baseline ECG LVH and other CV risk factors. The presence of cardiac end points, damage and albuminuria then predetermines the risk of overall mortality. Furthermore, the threshold limit for macroalbuminuria in patients with hypertension and LVH should be reduced to no more than 1.0 mg/mmol.

1108-04 Increased Expression of Type-2A and Type-2B Protein Phosphatases During the Development of Left Ventricular Hypertrophy

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Background: Type-2B protein phosphatase (PP2B) is implicated in the development of LV hypertrophy (LVH). The role of type-2A protein phosphatase (PP2A) in LVH, however, is not known. We tested the hypothesis that both PP2A and PP2B are involved in the LVH process.

Methods: Expression of the catalytic subunit of PP2A (PP2Ac) and PP2B (PP2Bc) was examined by Western blot in SDS-extract of LV myocardium obtained from Lewis rats (n=16) in which LVH was produced using one kidney-one clip (1K1C) and in sham-operated rats (n=16). Rats from each group were sacrificed at 1, 4, and 8 weeks thereafter. LV weight to body weight (LW/BW) ratio was used to index of LVH. Western blots were quantified in densitometric units and the data expressed as percent change from sham values.

Results: 1K1C rats developed LVH as early as week 1 post-operatively and the extent of LVH increased progressively thereafter. In LVH rats, PP2Ac but not PP2B expression increased at week 1. Expression of both PP2Ac and PP2Bc, however, increased significantly at 4 weeks and 8 weeks compared to sham. Both PP2Ac and PP2Bc were lower at week 8 compared to week 4 (data in table).

Conclusions: The results suggest that increased expression of PP2Ac is associated with initiation and progression of LVH. Increased expression of PP2Ac follows at a later stage of LVH and may play a role in its progression. These temporal differences in the expression of PP2Ac and PP2Bc represented therapeutic opportunities to interfere with the LVH process at different stages of its evolution.

1108-05 Older Women With Mild Hypertension Have Higher Left Ventricular Mass Than Men After Adjustment For Lean Body Mass

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Background: Left ventricular mass (LVM) is indexed by measures of body size, such as body surface area (BSA) and height, gender difference persist with men having a higher LVM index. Recent studies suggest that LVM indexed by lean body mass (LBM) may elimi

nate the gender difference seen in general populations. With the novel techniques for...
Aging and cardiovascular risk factors: The LIFE Study


Background: Arterial stiffness can be assessed by the ratio pulse pressure (PP) over echocardiographic stroke volume (SV). We evaluated relations of arterial stiffness to left ventricular (LV) geometry and function in hypertensive patients with electrocardiographic (ECG) LV hypertrophy (H).

Methods: Of participants in the echo-substudy of the Losartan Intervention For Endpoint Reduction (LIFE) reduction in hypertension study, selected to have ECG-LVH by Cornell voltage-duration product or Sokolow-Lyon voltage criteria, no heart failure or severe aortic stenosis, we identified 655 subjects (88%, 65±y) with PP/SV assessed. The sample study was divided in tertiles of PP/SV (uppermost 0.88±1.11 mm Hg/mm). Minmore and Doppler SV were averaged.

Results: With higher PP/SV, age, proportion of women and diabetics, and systolic blood pressure were higher (all <p<0.01); diastolic BP, body weight and height, and LV mass and LV internal diameter were lower while relative wall thickness (RWT=LV+LBM/2)/LBM was higher with higher PP/SV (all <p<0.01). Injection test was similar across tertiles (p=0.35) while stress-corrected midwall shortening (sLOVMS) was lower with higher PP/SV (p<0.01). After adjustment for age and gender, LV filling parameters and heart rate were similar in tertiles of PP/SV (all <p>0.1). In multivariate models, independent correlates of PP/SV were older age, lower body weight, femoral-gender and diabetes (R=0.48, <p<0.001); higher RWT was related to higher PP/SV independent of age, gender, and mean BP (R=0.30, <p<0.01); higher LV mass was independently predicted by higher SV, male-gender, higher body weight, older age and higher mean BP; but not by RWT (R=0.04). LV Ejection Fraction (LVEF) was not related to PP/SV independent of RWT.

Conclusions: In elderly hypertensives with ECG-LVH, higher arterial stiffness is related to concentric LV geometry, which may offset afterload and preserve LV chamber function, but is associated with impaired myocardial function.

FEATURED ORAL PRESENTATION
825F0-2 Addition of Statin Attenuates the Increase in C-Reactive Protein During Estrogen Replacement Therapy in Postmenopausal Women


Background: Randomized clinical trials have shown that HMG-CoA reductase inhibitors (statins) therapy reduces cardiovascular risk, the mechanism of which may include diminishment arterial inflammation as evidenced by reduction in levels of C-reactive protein (CRP) in serum. Because estrogen replacement therapy increases CRP in postmenopausal women, which could lead to proinflammatory consequences and compromise any benefit to cardiovascular risk, we determined whether the addition of statin might modify the estrogenic effect on CRP. Methods: In a double-blind, 3-period crossover study, we randomly assigned 28 healthy postmenopausal women to conjugated equine estrogens (CEE) 0.625 mg, simvastatin 10 mg, and their combination daily for 6 weeks, with each treatment period separated by 6 weeks off drugs. CRP was measured by high sensitivity immunometric assay (sensitivity 0.01mg/dL) before and after 6 weeks of each treatment. Results: CEE increased CRP by 0.07 ± 0.06 mg/dL (p<0.04). CEE plus simvastatin reduced CRP from 0.85 ± 0.13 mg/dL, which is statistically similar to the CEE group, and CRP values were significantly lower with higher PP/SV (p<0.01). The effect of combination therapy on CRP did not correlate with baseline CRP, or with baseline or treatment-induced changes in levels of LDL cholesterol, HDL cholesterol, inter-leukin-6, or brachial artery flow-mediated dilation as a measure of nitric oxide bioavailability (all <p>0.32). Conclusion: The combination of statin with estrogen therapy may attenuate the potential proinflammatory effect of estrogen administration to postmenopausal women, and maximize any benefit of hormone replacement therapy to cardiovascular risk.

2:30 p.m.

825F0-3 The Differential Effects of Hormone Replacement Therapy and Selective Estrogen Receptor Modulator on Endothelial Function Seem Related to an Effect on Plasma Asymmetric Dimethylarginine, an Inhibitor of Nitric Oxide Synthase

Giuseppe Mercurio, Massalmo Fini, Cristina Vitale, Osvaldo Gobara, Sandra Zorcu, Mauricio Weigandzen, Antonio Silvestri, Paolo Rossini, Jose Antonio F. Flamini, Giuseppe M. Rosano, San Raffaele Hospital, Rome, Italy, University of Cagliari. Cagliari, Italy.

Background: Hormone replacement therapy (HRT) improves endothelial function in postmenopausal women. Although in vitro animal studies suggest that the selective estrogen receptor modulator (SERM) raloxifene (R) improves endothelial function, its effect in women has yielded conflicting results. One mechanism by which R may reverse endothelial dysfunction and increase NO bioavailability is by lowering asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO) synthase. The aim of this study was to evaluate the effects of SERM and placebo on endothelial function and plasma ADMA. Methods: Brachial artery diameter, endothelium-dependent flow-mediated vasodilation (FMD) of the brachial artery, and plasma levels of nitrite, nitrate, endotheon-1 and ADMA were measured in 20 postmenopausal women with increased cardiovascular risk, treated with either HRT (0.625 conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate) or R (40 mg) for weeks, in a double-blind, single-cross-over study. Results: Baseline brachial artery diameters remained unchanged after each treatment phase. FMD significantly improved with HRT but not with R. ADMA significantly increased with HRT while a trend towards increased plasma ADMA levels was noted with R. Conclusions: HRT improves endothelial function in postmenopausal women at risk of cardiovascular disease, which may be due, at least in part, to a reduction in ADMA. In contrast, R seems to increase plasma ADMA, which may negatively affect endothelial function.

10:30 a.m.

825F0-4 Hormone Replacement Therapy and Risk of Myocardial Infarction in Women With Diabetes

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Background: The effect of hormone replacement therapy (HRT) on coronary heart disease (CHD) in postmenopausal women is controversial. Women with diabetes are at markedly increased risk of CHD, yet data on HRT in this population is scarce. The purpose of this study is to describe the effect of HRT on risk of MI in postmenopausal women with diabetes.

Methods: We conducted a case-control study in which case subjects (n = 99) were consecutively enrolled and compared to control subjects (n = 197) matched on age, gender, and admission year, postmenopausal women with diabetes admitted with principal diagnosis other than MI. Medical records were reviewed for demographics, medical history including diabetes complications, CHD risk factors, laboratory data, and current medications. Differences between case and control groups were assessed by the two-sample T-test for continuous variables and the chi-square test for dichotomous variables. The odds ratio, adjusted for group differences by logistic regression models, was used to estimate the relative risk of incident MI for HRT users.

1:15 p.m.

2:25 p.m.