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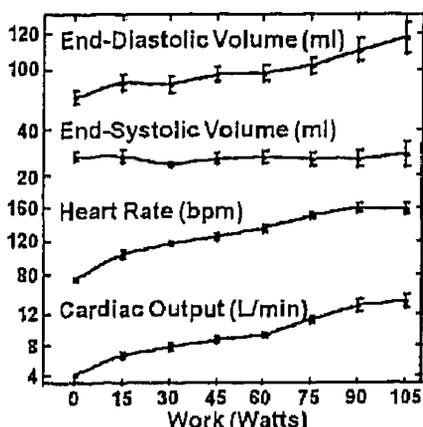
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### 1005-34 The Exercise Echocardiographic Profile of Healthy Post Menopausal Women

Vijay K. Gulati, James M. Hagberg, Steve D. McCole, John Gorcsan III.  
University of Pittsburgh, Pittsburgh, PA

The dynamic cardiac response to upright exercise has not been well characterized in healthy post-menopausal women. Accordingly, 20 such volunteers, aged  $64 \pm 6$  yrs, underwent serial echocardiographic study of LV volumes by modified Simpson's rule at rest and during each stage of upright bicycle exercise. Work rate was increased by 15 W every 3 min until exhaustion. Peak work rate ranged from 45 to 105 W. As expected, progressive increases in cardiac output (CO) occurred with exercise. Seventy-six % of this increase was attributed to increases in heart rate and 24% to increases in stroke volume (SV),  $p < 0.05$ , rest vs. 30 W and 30 vs. 90 W). Augmentation in SV was associated with significant progressive increases in end-diastolic volume ( $p < 0.05$ , rest vs. 45 W and 45 vs. 90 W) as end-systolic volume was unchanged. LV ejection fraction rose slightly from group mean of 67% at rest to 75% at 105 W ( $p < 0.01$ ).



**Conclusions:** The cardiac response to upright exercise in healthy post-menopausal women may be characterized by progressive increases in end-diastolic volume, heart rate, SV, CO, and ejection fraction. These data may be clinically useful to identify an abnormal cardiac exercise response in post-menopausal pts with heart disease.

### 1005-35 Exercise Testing for the Evaluation of Lipid-Lowering Therapy. Functional Assessment Versus Quantitative Coronary Angiography in the Low-Density-Lipoprotein Apheresis Atherosclerosis Regression Study

Wim R. Aengevaeren, Abraham A. Kroon, Tjeerd van der Werf, Gerard J. Uijen, Anton F. Stalenhoef. Departments of Cardiology and General Internal Medicine, University Hospital Nijmegen, The Netherlands

In patients with coronary artery disease (CAD) exercise testing is used for evaluation of PTCA, CABG and anti-anginal drug therapy. Little information is available about the potential of exercise testing for the evaluation of lipid-lowering therapy.

**Method:** We studied 42 patients with familial hypercholesterolemia and extensive CAD who were randomized to diet and simvastatin with or without biweekly LDL-apheresis. LDL-apheresis was performed over dextran sulphate columns. Bicycle exercise testing was performed under standardized conditions at baseline (base), after 1 and 2 years of therapy. The final exercise test was performed 1 month after the last LDL-apheresis to avoid possible short term effects on blood rheology. Mean segment diameter (MSD) and minimal obstruction diameter (MOD) were assessed by QCA.

**Results:** LDL-cholesterol decreased from  $7.72 \pm 1.96$  mmol/l to a time averaged level of  $2.95 \pm 1.13$  (-63%) in the LDL-apheresis (L) group and from  $7.85 \pm 2.34$  mmol/l to  $4.13 \pm 1.58$  mmol/l (-43%) in the medication (M) group, difference in response  $p < 0.01$ .

Exercise testing	LDL-apheresis			Medication		
	base	1 year	2 years	base	1 year	2 years
ST-time (s)	$461 \pm 47$	$548 \pm 51$	$641 \pm 50^*$	$485 \pm 81$	$464 \pm 54$	$442 \pm 60$
ST-max (mm)	$1.4 \pm 0.2$	$0.8 \pm 0.2$	$0.7 \pm 0.2^*$	$1.4 \pm 0.3$	$1.3 \pm 0.4$	$1.4 \pm 0.4$

ST-time, time to 1 mm (= 0.1 mV) ST-depression; ST-max, maximal ST depression; \*difference between L and M group  $p < 0.01$ . QCA revealed no difference in coronary anatomy.

**Conclusions:** Exercise parameters improved only in the LDL-apheresis group along with a pronounced reduction in LDL-cholesterol but without change in coronary anatomy. Exercise testing, a functional test of the coronary circulation, has to be considered as a valuable inexpensive tool for the evaluation of lipid-lowering therapy in patients with myocardial ischemia.

### 1005-36 Elevated Intramuscular Diprotonated Pi ( $H_2PO_4^-$ ) During Exercise in Patients With Chronic Heart Failure

Michael Welsch, Heidi Kluess, William Brechue, Ray Ballinger, Katherine Scott, Michael Pollock, Carl J. Pepine. Div. of Cardiovascular Med., Center for Exercise Science, Univ. of Florida and the VAMC, Gainesville, FL

We have shown that metabolic downregulation may depress muscle function in chronic heart failure (HF). This study examined muscle energetics in 10 HF pts (age:  $58 \pm 5$  yrs, EF  $< 40\% \pm 10$ , NYHA II-III) and 10 controls (CON) (age:  $62 \pm 4$  yrs) during low (LO; 25% MVC) and high (HI; 85% MVC) intensity calf flexion exercise (1 contract/4 s). From an RF coil positioned over the medial gastroc head continuous spectra were collected (32 s time resolution). LO was terminated at 10 min and resulted in a decrease in [PCr] (HF:  $38.75 \pm 0.76$  to  $20.46 \pm 1.95$  mM, CON:  $38.01 \pm 0.73$  to  $27.75 \pm 2.74$  mM) and pH (HF:  $7.09 \pm 0.04$  to  $6.91 \pm 0.05$ , CON:  $7.05 \pm 0.05$  to  $7.04 \pm 0.08$ ), and an increase in [Pi] (HF:  $5.51 \pm 0.57$  to  $16.12 \pm 1.47$  mM, CON:  $5.15 \pm 0.46$  to  $13.41 \pm 1.67$  mM). HI was terminated at exhaustion (HF: 4:00, CON: 4:25) resulting in greater changes in [PCr] (HF:  $37.78 \pm 1.04$  to  $12.79 \pm 2.64$  mM, CON:  $38.43 \pm 0.78$  to  $12.89 \pm 1.68$  mM) and pH (HF:  $7.11 \pm 0.10$  to  $6.65 \pm 0.19$ , CON:  $7.09 \pm 0.02$  to  $6.90 \pm 0.08$ ), and an increase in [Pi] (HF:  $4.96 \pm 0.41$  to  $20.42 \pm 1.95$  mM, CON:  $4.99 \pm 0.62$  to  $19.61 \pm 1.06$  mM) compared to LI. [ATP] remained unchanged during both conditions. Exercise was associated with a greater decline in pH (LO&HI) and increase in [Pi] (LO) in HF. This resulted in more  $H_2PO_4^-$  in HF compared to CON (LO:HF:  $275\% \pm 51$ , CON:  $101\% \pm 20$ ; HI:HF:  $740\% \pm 192$ , CON:  $441\% \pm 43$ ) ( $p < 0.05$ ). This increase in  $H_2PO_4^-$  may be associated with reduced contractile function by altering cross-bridge kinetics and may contribute to the marked exercise limitations in HF.

### 1006 Thrombosis, Atherosclerosis, and Regulation of Vascular Biology

Wednesday, March 27, 1996, 9:00 a.m.—11:00 a.m.  
Orange County Convention Center, Hall E  
Presentation Hour: 10:00 a.m.—11:00 a.m.

### 1006-15 Apoptosis of Human Endothelial Cells Is Induced Synergistically by Ox-LDL and $TNF\alpha$ ; Attenuation by $17\beta$ -Estradiol

René J. Alvarez Jr., Arthur T. Hoang, Emily E. Milliken, SanfJrd J. Gips, Chi V. Dang, Pascal J. Goldschmidt-Clermont. Johns Hopkins Hospital, Baltimore, MD

Endothelial cell (EC) dysfunction, increased cell turnover and apoptosis have been implicated in the promotion and progression of atherosclerosis. Estrogen metabolites have been shown to be potent anti-atherogenic agents, although the mechanism of protection has not been completely defined. In other systems,  $TNF\alpha$  and oxidized-LDL (ox-LDL) have been shown to be strong inducers of apoptosis. We have evidence that the estrogen metabolite,  $17\beta$ -estradiol (EST), reduces EC apoptosis induced by ox-LDL and  $TNF\alpha$ . We sought to further characterize the effect of  $17\beta$ -estradiol on EC apoptosis.

Human EC were cultured in the presence or absence of varying concentrations of non-oxidized LDL (LDL) and ox-LDL with or without 50 mg/L of  $TNF\alpha$ . Morphology of the cells was studied by phase microscopy and apoptosis was determined by FACS analysis of digoxigenin-labelled genomic DNA fragments (TUNEL assay).

$TNF\alpha$  (50 mg/L) and ox-LDL (50 mg/L) in combination lead to morphologic changes consistent with apoptosis: retraction of the EC cells, loss of adhesion to the substratum, and membrane blebbing. When cells were analyzed after 72 hrs by TUNEL,  $TNF\alpha$  (50 mg/L) and ox-LDL (50 mg/L) alone lead to apoptosis of EC in 15% and 14% of cells, respectively. However, co-culture of EC with ox-LDL (50 mg/L) and  $TNF\alpha$  (50 mg/L) resulted in apoptosis of 55% of the EC. The apoptosis induced by the combination of 50 mg/L ox-LDL and 50 mg/L  $TNF\alpha$  was attenuated by 39% with pre-treatment of the cells with  $10^{-8}$  M  $17\beta$ -estradiol. LDL did not induce apoptosis of EC in the presence or absence of  $TNF\alpha$ .

Thus, we conclude that  $TNF\alpha$  and ox-LDL seem to act synergistically to induce apoptosis in EC. The process of apoptosis is attenuated by  $17\beta$ -estradiol and may account for some of the anti-atherogenic properties of estrogens.