associated with higher incidence of cardiovascular events (20% vs. 4%, p=0.004). Previous cardiovascular disease, defined as history of ischemic heart disease and/or peripheral vascular disease, was also associated with higher incidence of cardiovascular events (25% vs. 6%, p=0.003). Urinary 8-iso-PGF2alpha excretion above the median value was associated with cardiovascular events in this high-risk group (43% vs. 5%, p=0.007), but was not in the remaining "low-risk" diabetic patients (9% vs. 4%). In Cox regression analysis adjusting for age, gender, body mass index, glycemic control, and traditional risk factors, urinary 8-iso-PGF2alpha excretion (p=0.01) and previous cardiovascular disease (p=0.04) were independent predictors of cardiac events.
Conclusion: Increased urinary 8-iso-PGF2alpha excretion predicts cardiac events in patients with diabetes, especially in the group with overt cardiovascular disease. These results suggest that the assessment of urinary 8-iso-PGF2alpha excretion has clinical implications as a tool for risk stratification in patients with type 2 diabetes.

1028-173 Association Between Cardiorespiratory Fitness and C-Reactive Protein in Young Adults

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Background: Physical activity is associated with a lower risk of cardiovascular disease but the mechanisms remain uncertain. Inflammatory markers are predictive of cardiovascular risk. We therefore examined the association between cardiorespiratory fitness and C-reactive protein (CRP) in a group of young adults.
Methods: Cardiorespiratory fitness using a bicycle ergometer, blood pressure, smoking history, and anthropometric measurements were determined in 308 women and 399 men aged 26 years. Maximal heart rate during submaximal exercise was used to calculate VO_2 max. (ml/kg/min). Subjects were classified in tertiles of physical fitness according to VO_2 max. level. CRP was measured using an immunoturbidimetric assay.
Results: Geometric mean (95% CI) CRP levels were significantly related to levels of cardiorespiratory fitness in men (p<0.01) and women (p<0.001).

Cardiorespiratory fitness	Males (n=399)	Females (n=308)
Unfit	2.06 (1.69-2.49)	4.31 (3.57-5.17)
Intermediate	1.61 (1.34-1.92)	3.76 (2.97-4.70)
Fit	1.46 (1.18-1.77)	1.94 (1.53-2.42)

There was a significant fitness × sex interaction (p= 0.01) indicating the relationship was stronger for women. When adjusted for body mass index, blood pressure and smoking history the relationship was significant for women only.
Conclusions: CRP level is independently related to cardiorespiratory fitness in young women.

1028-174 Increased Subclinical Atherosclerosis in Young Adults With Metabolic Syndrome: The Bogalusa Heart Study

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Background
Metabolic Syndrome (MetS) is associated with subclinical atherosclerosis and increased cardiovascular risk in older and middle-aged adults, however these associations have not been studied among young adults. Carotid intima-media thickness (CIMT) is a validated measure of atherosclerosis that predicts cardiovascular events. The purpose of this study was to determine if MetS is associated with increased CIMT in young adults.
Methods
Non-diabetic subjects from the Bogalusa Heart Study, a longitudinal study of the natural history of atherosclerosis in young adults and children (20-38 years old), underwent high-resolution B-mode ultrasound imaging of the carotid arteries to determine site-specific and composite CIMT values. Presence of MetS was determined using the NCEP Adult Treatment Panel III definition. Logistic regression analyses were performed to determine if MetS was associated with increased CIMT.
Results
Of 506 subjects (mean age 32 years, 29% black, 39% male), 67 (13%) had MetS. CIMT values were significantly higher among subjects with MetS (table). The prevalence of MetS increased with CIMT (p_{trend} = 0.0028). Odds ratios (95% confidence intervals) for the presence of MetS in subjects with CIMT ≥0.8 mm and ≥1.0 mm were 4.8 (1.7-13.7) and 8.0 (2.0-32.8), respectively.
Conclusions
Even in young adults, MetS is associated with increased carotid atherosclerosis, emphasizing the importance of early screening and treatment in this population.

Mean Carotid IMT Values (mm, standard deviation)

	MetS Present	MetS Absent	$P_{unadjusted}$	P adjusted for age, sex, race, and smoking
Composite	0.780 ± 0.130	0.728 ± 0.097	0.0005	0.0016
Common Carotid	0.699 ± 0.108	0.659 ± 0.084	0.0008	0.0012
Bulb	0.922 ± 0.211	0.852 ± 0.174	0.0037	0.0222
Internal Carotid	0.721± 0.206	0.676 ± 0.121	0.0202	0.0384

POSTER SESSION

1029

Molecular Mechanisms for Hypertrophy and Failure

Sunday, March 07, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1029-175 Anti-ErbB2 Modulation of Bcl-x_L/Bcl-x_S Causes Mitochondrial Dysfunction and Apoptosis

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Background
ErbB2 is a co-receptor and important signal integrator for the EGF family of receptor tyrosine kinases.Over expression of erbB2 occurs in many cancers. A monoclonal antibody inhibiting erbB2 is a potent chemotherapeutic agent but is associated with cardiac toxicity. Here we investigate the effects of anti-erbB2 antibody on cardiomyocyte survival and mitochondrial function.
Methods and Results
Primary cultures of neonatal were exposed to anti-erbB2 antibody (anti-erbB2 Ab 5-7.5 μg/ml) for up to 24 hours. Cell viability, mitochondrial function, and apoptosis were measured using multiple complementary techniques. Selected studies were confirmed in primary cultures of adult rat cardiomyocytes.
ErbB2 inhibition was associated with a dramatic increase in expression of the pro-apoptotic Bcl-2 family protein, Bcl-x_S, and decreased levels of pro-survival Bcl-x. There was a time dependent increase in mitochondrial translocation and oligomerization of the mitochondrial pore former, BAX, as indicated by BMH crosslinking. Bax oligomerization was associated with release of cytochrome c and activation of caspase 9.
This alteration of Bcl-2 family signaling induced mitochondrial dysfunction evident as a loss of mitochondrial membrane potential (delta psi) as measured by JC-1 red fluorescence on fluorescent plate reader (5242 ± 191 vs 4606 ± 87 p<.05 N=6) and by fluorescent flow cytometry of mitotracker stained NRVM (76.85 ± 2.4 vs 51.7 ± .072 p<.05 N=4). There was also a 35% decline in ATP level (p<.05) as measured by luciferin-luciferase bioluminescence and a loss of redox capacity as measured by MTT (.7224 ± .036 vs .6421 ± .017 p<.01).
Restoration of Bcl-x_L levels through TAT-mediated transduction prevented the decline in delta psi;, MTT activity and cytosolic ATP.
Anti-erbB2 Ab treatment resulted in a modest increase in apoptosis as measured by TUNEL (6.5± 0.7 vs 3.1 ± 0.4%. p<.05) and propidium iodide flow cytometry(8.3±0.9 vs 4.5±0.6 % p<.01)
Conclusion
Anti-erbB2 activates the mitochondrial apoptosis pathway through direct modulation of bcl-x_L and bcl-x_S and causes impairment of mitochondrial function, integrity, cellular energetics and low level apoptosis.

1029-176 Rescue of Internalization-Impaired Angiotensin II AT1 Mutants by β-Arrestin Overexpression

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The pathophysiological effects of Angiotensin II (Ang II) are mostly mediated by the G-protein coupled type 1 receptor (AT1), which internalizes upon Ang II binding. Recently, β-arrestin was shown to play a role in AT1 endocytosis by binding the cytoplasmic, C-terminus region T332-S338, the major site of Ang II-induced phosphorylation. The process responsible for recruiting β-arrestin to the activated receptor has not been defined. Using CHO-K1 and HEK 293 cells to express wild type or mutant AT1, we investigated whether T332-S338 phosphorylation is a prerequisite for β-arrestin-dependent AT1 internalization. We first established that phosphorylation of this region is important for AT1 internalization in our cells. Substitution of T332, S335, T336 and S338 with alanine to preclude phosphorylation, markedly attenuated AT1 internalization, while replacement of these sites with acidic residues glutamate (E) and aspartate (D) to mimic phosphorylation, partially rescued internalization. We next assessed the ability of β-arrestin overexpression to rescue agonist-induced internalization of phosphorylation-impaired receptors. β-arrestin 1 or 2 overexpression enhanced internalization of the TSTS/A mutant, with β-arrestin 2 having the more pronounced effect. β-arrestin 2, alone or with β-arrestin 1, increased the rate of TSTS/A internalization towards that of wild-type AT1. The TSTS/ED mutant was also responsive to β-arrestin 1 or 2 expression. These findings indicate that a signal besides C-terminus phosphorylation is responsible for recruiting β-arrestin to AT1. However, ligand-induced phosphorylation of AT1 likely facilitates receptor internalization by enhancing β-arrestin binding.