in exercise (P < 0.05). DDAHs metabolise ADMA to citrulline and dimethylamine (DMA).

CONCLUSIONS: This study defines the cardiovascular effects of a systemic increase in ADMA in humans. These are similar to changes seen in diseases associated with ADMA.

35.3 ± 10.6% during exercise, representing a significant reduction in the cardiac response increase in ADMA metabolised by DDAHs. Urinary DMA:Cr ratios significantly increased from 1.26 ± 0.32 to 2.73 ± 0.59 following Handgrip exercise. Increased cardiac output in control subjects by a maximum of 9.2 ± 1.4% from 58.9 ± 2.0 beats per min (P < 0.001), and reduced cardiac output in ADMA-exposed patients by a maximum of 23.7 ± 2.1% from 163.9 ± 91.6 dynes.s.cm⁻⁵ (P < 0.001). In contrast, those subjects given ADMA increased their cardiac output by a maximum of 6.0 ± 1.2% from 66.3 ± 3.4 mm Hg (P < 0.001). These findings suggest that ADMA could directly contribute to their pathogenesis. Finally, our data also indicate that ADMA is metabolised by DDAHs extensively in humans in vivo.

2:45 p.m.

**856-4**

**INOS is a Mediator of Increased Arterial Intimal Thickening Induced by Passive Cigarette Smoke Exposure in Mice**

Takero Arasaka, Paul C. Dlimayuga, Hongyan Li, Previn de Silva, Juliana Yano, Kuang-Yuh Chyu, Prediman K. Shah, Bojan Cercek, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Active and passive smoking was associated with increased intimal/media thickening in the Atherosclerosis Risk in Communities study, but molecular mechanisms contributing to this risk are incompletely understood. We evaluated the effect of passive smoking on arterial response to injury, and the potential role of iNOS gene in smoking induced effects on the arterial wall using iNOS−/− mice.

Methods: Vascular injury was induced by placing a cuff around the right carotid artery. Wild type mice and INOS−/− mice of the same background were exposed to passive smoke (1 cigarette/day) or filtered room air. Expression of INOC and PCNA in the arterial wall 3 days after injury was determined by immunostaining. Nitrate and nitrite (NOx) levels 3 days after injury were measured by Griess reaction. Intimal thickness was measured 21 days after injury.

Results: INOS expression in wild type mice exposed to passive smoke increased compared to mice exposed to room air, and was not detected in INOS−/− mice. Intimal thickening in INOS−/− mice exposed to passive smoke was profoundly reduced compared to wild type mice exposed to passive smoke (Table). Medial areas were similar in all groups of mice.

Conclusion: Our results suggest that INOS expression is a key mediator in the augmented response to injury in mice exposed to cigarette smoke. INOS may mediate vasoocclusive effects of exposure to cigarette smoke.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Wild-type + Room air</th>
<th>Wild-type + Passive smoke</th>
<th>INOS−/− mice + Room air</th>
<th>INOS−/− mice + Passive smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNA positive</td>
<td>8.1 ± 2.7</td>
<td>15.7 ± 5.2</td>
<td>4.0 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>nuclei (n=5)</td>
<td></td>
<td>(n=5)</td>
<td>(n=3)</td>
<td></td>
</tr>
<tr>
<td>NOx level (µM)</td>
<td>39.1 ± 12.6</td>
<td>143.6 ± 6.8</td>
<td>12.5 ± 8.6</td>
<td></td>
</tr>
<tr>
<td>(n=6)</td>
<td></td>
<td>(n=6)</td>
<td>(n=6)</td>
<td></td>
</tr>
<tr>
<td>Intimal Area (mm² ± 10⁻⁶)</td>
<td>9.2 ± 7.5</td>
<td>6.4 ± 7.9</td>
<td>2.1 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>(n=5)</td>
<td></td>
<td>(n=5)</td>
<td>(n=5)</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.05 vs INOS−/− Passive smoke, †P < 0.05 vs Wild-type + Room air, ‡P < 0.05 vs Wild-type + Passive air, ANOVA

3:00 p.m.

**856-5**

**Cardiovascular Effects of the Endogenous Nitric Oxide Synthase Inhibitor Asymmetric Dimethylarginine (ADMA) and Evidence for ADMA Metabolism in Humans In Vivo**

Vinod Achan, Michael Broadhead, Mohammed Malski, James Leiper, Raymond MacAlister, Patrick Valantine, University College London, London, United Kingdom

Background: Plasma levels of an endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA), are elevated in chronic renal failure, hypertension, and atherosclerosis. ADMA levels are also significantly raised in patients with chronic heart failure (CHF) and those with CHF induced by coronary artery ligation or rapid pacing. Despite these observations the cardiovascular effects of a systemic increase in ADMA have not been shown in humans. In a randomised, double-blind, placebo-controlled study using healthy male volunteers, we compared the effects of intravenous low dose ADMA and placebo on heart rate, blood pressure, cardiac output and systemic vascular resistance (SVR) at rest and during exercise. We also tested the hypothesis that ADMA could be metabolised extensively in humans in vivo by a family of dimethylarginine dimethylamine (DDAH).

Results: Plaque rupture was observed in 42 lesions (43%). When lesions with and without plaque rupture were compared, the lesion area, degree of calcification, plaque eccentricity index (EI) and remodeling index (RI: lesion / proximal reference vessel area) were measured. Vessel area and RI were significantly higher in lesion with plaque rupture (30.1 ± 8.0 vs 26.0 ± 9.9 mm², P = 0.001). The distribution of remodelling

3:15 p.m.

**856-6**

**Levels of Nitrotyrosine, an Inflammatory Marker Generated by Nitric Oxide-Derived Oxidants, Is Associated With Risk of Coronary Artery Disease**

Mehdi H. Shishehbor, Ronnier J. Aviles, Marie-Luise Brennan, Xiaoming Fu, Marc S. Penn, Dennis L. Sprecher, Noyan Gokce, John F. Keaney, Jr., Joseph A. Vita, Stanley L. Hazen. The Cleveland Clinic Foundation. Cleveland, OH. Boston University School of Medicine, Boston, MA

Background: Formation of nitric oxide (-NO)-derived oxidants may serve as a mechanism facilitating development of atherosclerosis. Nitrotyrosine, a specific marker for protein modification by NO-derived oxidants, is enriched in human atherosclerotic lesions and LDL recovered from human atheroma. Whether systemic levels of nitrotyrosine predict coronary artery disease (CAD) is not known.

Methods: Serum nitrotyrosine levels in 262 consecutive patients at a major metropolitan medical center were determined by mass spectrometry and correlated with the prevalence of CAD.

Results: The median nitrotyrosine content of plasma proteins was significantly higher in the CAD group (9.13 µmol/L vs. 5.66 µmol/L, P = 0.001). Subjects in the upper quartile of nitrotyrosine levels had higher risk of CAD (unadjusted odds ratio, 4.06; 95% confidence interval, 1.28 to 7.07, P < 0.001). Conclusion: Elevated levels of nitrotyrosine, a specific protein modification produced by NO-derived oxidants and which is linked to CAD pathogenesis, serves as a significant and independent predictor of CAD risk. These results support a potential role for -NO-derived oxidants as an inflammatory mediator in CAD and may have important implications for atherosclerosis diagnosis and risk assessment.

**ORAL CONTRIBUTIONS**

**857**

**Vascular Diseases: Clinical Insights and Clinical Trials**

Tuesday, April 01, 2003, 2:00 p.m.-3:30 p.m.

**Mc Cormick Place, Room S405**

2:00 p.m.

**857-1**

**Incidence and Characteristics of Ruptured Plaque in Femoro-Popliteal Arteries**

Voichiro Hongo, Ali Hassan, Krishnamurtty Sudhir, Daniel Adelman, Yasuhiro Honda, Paul G. Yock, Peter J. Fitzgerald, Stanford University, Stanford, CA, Pharmaceuticals Inc., Sunnyvale, CA

Background: Numerous studies have reported the characteristics of atherosclerotic lesions with plaque rupture in coronary arteries. However, incidence and characteristics of plaque rupture in the peripheral circulation have not been well studied.

Methods: Ninety-seven lesions in 40 patients scheduled for elective angloplasty in either the femoral or popliteal arteries were enrolled. IVUS was performed before intervention. Lesion inclusion criteria were: (1) segmental, (2) proximal reference % plaque area < 50%, (3) degree of calcification (< 5), (4) non-calcified plaque, (5) plaque eccentricity index (EI) and remodeling index (RI: lesion / proximal reference vessel area) were measured.

Results: Plaque rupture was observed in 42 lesions (43%). When lesions with and without plaque rupture were compared, the lesion area, degree of calcification and EI were identical (9.9 ± 3.7 vs 8.9 ± 5.2 mm², 22.25 ± 25.31, P = 0.74 ± 0.18 vs 0.73 ± 0.18, NS). However, vessel area and RI were significantly higher in lesion with plaque rupture (30.1 ± 8.0 vs 26.0 ± 9.9 mm², P = 0.001). The distribution of remodelling...
The Effects of Exercise on Lower Extremity Functioning in Peripheral Arterial Disease Patients Without Intermittent Claudication: A Randomized Controlled Clinical Trial

Mary M. McDermott, Susan D. Tuktukho, Ty Gluckman, Shaw Unterriner, William H. Pearce, Michael H. Cough, Kiang Liu, Jack M. Guralnik, Philip Greenland, Northwestern University Feinberg School of Medicine, Chicago, IL

BACKGROUND: Most patients with lower extremity arteriosclerotic arterial disease (PAD) do not have classical symptoms of intermittent claudication (IC). We hypothesized that supervised exercise training would improve leg functioning in patients with PAD who do not have IC. METHODS: PAD subjects were identified from a non-invasive vascular laboratory at an academic medical center. Those without IC were included. Subjects were randomly assigned to a supervised treadmill exercise intervention vs. usual care. Exercise occurred 3 times weekly for 12 weeks for up to 60 minutes each session. The six-minute walk test was our primary outcome. The 6-minute walk distance was measured using a treadmill, and the total distance walked was recorded. The secondary outcomes included changes in walking endurance, quality of life, and other measures of mobility.

RESULTS: A total of 19 paired patients (1.9% vs. 2.1% respectively; P = 0.02) were included in the study. The mean age of the patients was 66 years (range: 48-81). The mean body mass index was 28.5 kg/m² (range: 18.9-39.2). The mean walking distance at baseline was 600 m (range: 100-900). After 12 weeks of exercise training, the mean walking distance increased to 700 m (range: 200-900). The change in walking distance was statistically significant (P = 0.001).

CONCLUSION: Supervised exercise training improves walking endurance in patients with PAD without IC. Further studies are needed to determine the long-term effects of exercise training on walking endurance and other measures of mobility.