vasodilatation (P<0.05) and resulted in higher plasma t-PA antigen and activity concentrations during bradykinin infusion (11.3±0.8 vs 6.8±0.5 ng/mL, 16.5±3.9 vs 6.6±2.0 fU/mL, peak bradykinin dose: P<0.002) and a doubling of estimated net t-PA release (P<0.05). Conclusion: Intra-arterial TNF-α causes an acute local vascular inflammation associated with a substantial and sustained increase in local t-PA and IL-6 release, TNF-α also impairs endotheliump-dependent vasomotion and augments acute endothelial t-PA release. These findings indicate that TNF-α in humans potently adversely and beneficially affects on endothelial and vascular function.

2:45 p.m.

856-4 INOS is a Mediator of Increased Arterial Intimal Thickening Induced by Passive Cigarette Smoke Exposure in Mice Takeo Arasaka, Paul C. Dlimiayuga, Hongyan Li, Previn de Silva, Juliana Yano, Kuang-Yuh Chyu, Predman K. Shah, Bojan Coreck, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Active and passive smoking was associated with increased intimal/medial thickening in the Atherosclerosis Risk In Communities study, but molecular mechanisms contributing to this risk are incompletely understood. We evaluated the effect of passive smoke on arterial response to injury, and the potential role of INOS gene in smoke 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 cigarettes/day) or filtered room air. Expression of INO and PCNA in the arterial wall 3 days after injury was determined by immunostaining. Nitrate and nitrite (NOx) levels 3 days after injury was measured by Griess reaction. Intimal thickening 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+/+ exposed to passive smoke was profoundly reduced compared to wild type mice exposed to passive smoke (Table).

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 vaso-occlusive effects of exposure to cigarette smoke.

Table:

<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 nuclei</td>
<td>8.1 ± 2.7 (n=5)</td>
<td>15.7 ± 5.2 (n=5)</td>
<td>ND</td>
<td>4.0 ± 4.0 (n=3)</td>
</tr>
<tr>
<td>NOx level (μM)</td>
<td>22.3 ± 7.3 (n=6)</td>
<td>39.1 ± 12.6 (n=6)</td>
<td>14.3 ± 6.8 (n=6)</td>
<td>12.5 ± 8.6 (n=6)</td>
</tr>
<tr>
<td>Intimal Area (mm² x 10⁶)</td>
<td>9.2 ± 7.5 (n=5)</td>
<td>22.3 ± 7.2 (n=5)</td>
<td>6.4 ± 4.7 (n=5)</td>
<td>2.1 ± 1.6 (n=5)</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 smoke, **ANOVA

3:30 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 MacAllister, Patrick Valentine, 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, and associated with a substantial increase in local t-PA and IL-6 release, TNF-α also impairs endotheliump-dependent vasomotion and augments acute endothelial t-PA release. These findings indicate that TNF-α in humans potently adversely and beneficially affects on endothelial and vascular function.

2:15 p.m.

856-6 Levels of Nitrotyrosine, an Inflammatory Marker Generated by Nitric Oxide Derived Oxidants, Is Associated With Risk of Coronary Artery Disease Mehrz H. Shaielbeh, Ronnier J. Aviles, Marie-Luise Brennan, Xiaoming Fu, Marc S. Penn, Dennis L. Sprecher, Noyan Gokce, John F. Keeaney, 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 for inflammation 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 umol/mol vs. 5.66 umol/mol, P<0.001). Subjects in the upper quartile of nitrotyrosine levels had higher risk of CAD (unadjusted odds ratio, 4.06; 95% confidence interval, 1.94 to 8.50; P<0.001). After adjusting for Framingham risk factors and high sensitive C-reactive protein, upper quartiles of nitrotyrosine remained predictive for CAD risk (odds ratio, 3.01; 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.

3:15 p.m.

857 Vascular Diseases: Clinical Insights and Clinical Trials Tuesday, April 01, 2003, 2:00 p.m.-3:30 p.m. McCormick Place, Room S405

2:00 p.m.


Background: Numerous studies have reported the characteristics of atherosclerotic lesions with plaque rupture in coronary arteries. However the 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 angionplasty 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 < 50% characterized by near circumferential or circular smooth muscle wall, (4) subintimal blood pool. After adjusting for Framingham risk factors and COX, COX2, NOX2, and NOS2 expression, we used Cox proportional hazards analysis to estimate the hazard ratio for plaque rupture.

Results: Plaque rupture was observed in 42 lesions (43%). When lesions with and without plaque rupture were compared, lumen area, degree of calcification and COX were identified (8.9±3.7 vs 8.9±2.5mm², 22.25 vs 25.3±1.0, 7.4±.8 vs 0.7±3.0x1.8, NS). However, vessel area and RI were significantly higher in lesion with plaque rupture (50.1±8.0 vs 26.0±9.9mm², P=0.001, 0.9±0.9 vs 0.9±0.8, P=0.008). The distribution of remod-