vasodilatation (P<0.03) 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, and 16.5±3.9 vs 6.6±2.0 IU/ml, at 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 impair endothelium-dependent vasomotion and augments acute endothelial t-PA release. These findings indicate that TNF-α risks potentially adverse and beneficial effects 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
Taeko Arasazau, 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 intima/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 smoking (1 cigarette/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 smoking increased compared to mice exposed to room air, and was not detected in INOS -/- mice. Intimal thickening in INOS -/- mice exposed to passive smoking 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 aggravation of 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 + Passive smoke</th>
<th>Wild-type + Room air</th>
<th>INOS -/- mice + Passive smoke</th>
<th>INOS -/- mice + Room air</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNA positive nuclei</td>
<td>8.1±2.7</td>
<td>15.7±5.2</td>
<td>ND</td>
<td>4.0±4.0</td>
</tr>
<tr>
<td>NOx level (µM)</td>
<td>22.3±7.3</td>
<td>39.1±12.6</td>
<td>14.3±6.8</td>
<td>12.5±8.6</td>
</tr>
<tr>
<td>Intimal Area (mm² × 10⁶)</td>
<td>9.2±7.5</td>
<td>21.4±4.9</td>
<td>6.6±4.9</td>
<td>2.1±1.6</td>
</tr>
</tbody>
</table>

4p<0.05 vs INOS -/- passive smoke, *p<0.05 vs Wild-type+Room air, **p<0.05 vs Wild-type+Passive smoke

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 Acharya, Michael Broadhead, Mohammad Malaki, James Leiper, Raymond MacAllister, Patrick Vaillancourt, 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 in animals with CHF induced by coronary artery ligation or rapid pacing. Despite these observations the cardiovascular effects of exposure to cigarette smoke. INOS may mediate vaso-occlusive effects of exposure to cigarette smoke.

Table:

<table>
<thead>
<tr>
<th>Groups</th>
<th>1st Quartile</th>
<th>2nd-3rd Quartile</th>
<th>4th Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type+Passive smoke</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
</tr>
<tr>
<td>Wild-type+Room air</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
</tr>
</tbody>
</table>

3:00 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. Kearney, Jr., Joseph A. Vito, 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 linking 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 ±0.6 ml/mol vs. 5.66 ±0.1 ml/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, 1.04 to 15.0; 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.

857-1
Incidence and Characteristics of Ruptured Plaque in Femoro-Popliteal Arteries
Yoichiro Hongo, Ali Hassan, Krishnankutty 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 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 angioplasty 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 calcified plaque <10%, and (4) absence of ulcerations or thrombus.

Results: Plaque rupture was observed in 42 lesions (43%). When lesions with and without plaque rupture were compared, lumen area, degree of calcified plaque, plaque eccentricity index (EI) and remodeling index (RI: lesion/ reference vessel) were measured.

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2:00 p.m.

857-2
Incidence of and Characteristics of Ruptured Plaque in Femoro-Popliteal Arteries
Voichiro Hongo, Ali Hassan, Krishnankutty 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 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 angioplasty 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 calcified plaque <10%, and (4) absence of ulcerations or thrombus.

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