Cardioprotection by rosiglitazone against ischemia-reperfusion involves upregulation of AT2 and downregulation of AT1 receptors. P42/44 MAPK is also inhibited by rosiglitazone. Insulin signaling is not involved in cardioprotection by rosiglitazone.

11:45 a.m.

883-6 **Carbon Monoxide Protects Against Cardiac Ischemia-Reperfusion Injury In Vivo Through Mitogen-Activated Protein Kinanse Pathway and Akt-Endothelial Nitric Oxide Synthase Pathway**

Hajime Fujimoto, Seiji Ayabe, Nobukazu Ishizaka, Minoru Ohno, Ryozo Nagai, University of Tokyo, Tokyo, Japan

Background: Heme oxygenase-1 (HO-1) is an endogenous anti-stress enzyme that catabolizes heme to free iron, carbon monoxide (CO), and biliverdin. Recently, CO is postulated to play a protective role against tissue injury induced by several stresses. In this study, we investigated the role of CO in amelioration of cardiac ischemia-reperfusion injury, and the mechanism involved in it. Methods and Results: Rats inhaled CO (250 ppm, 500 ppm, or 1000 ppm, balanced with air) or room air for 24 hr in a chamber. Then the left anterior descending coronary artery was occluded for 30 min, followed by 120 min reperfusion, during which they continued inhaling CO or room air. CO had no effects on body temperature or hemodynamic parameters before ischemia-reperfusion. Pre-treatment with 1000 ppm of CO, but not 250 ppm nor 500 ppm, significantly reduced the ratio of the infarct area to the risk area (I/R ratio; room air 35 ± 4 % vs. 1000 ppm CO 6 ± 2 %, P < 0.001), and suppressed the migration of macrophages and monocytes, and the expression of tumor necrosis factor-a (TNF-a) in the risk areas (P < 0.05, those with 1000 ppm CO vs. without CO). Inhalation of 1000 ppm CO elevated HbCO up to 30% in blood. Thus, tissue hypoxia–induced preconditioning is suspected to be responsible for this phenomenon. However, the simple hypoxia (under 0.5 atom air for 24 hr) did not reduce I/R ratio. CO activated MAPKs (p38, JNK, and ERK), Akt, and eNOS in the heart within 12 hours; although neither 250 ppm nor 500 ppm CO nor exposure to the simple hypoxia activated them. Pre-treatment with SB203580, or wormannin completely blocked the activation of p38, or Akt and eNOS, respectively. They disturbed the cytoprotective effects of CO additively (I/R ratio; 20 ± 3% (SB203580 + CO), 23 ± 2 % (wortmannin + CO), and 39 ± 4 % (SB203580 + wortmannin + CO) vs. those with vehicle + CO; 9 ± 3 %, respectively, P < 0.05). L-NAME (an inhibitor of NO production) also attenuated the tissue protection by CO to almost to the same level as wortmannin (I/R ratio; 22 ± 5 % (L-NAME+CO)). Conclusion: CO protects heart from ischemia-reperfusion injury. P38 pathway and Akt-eNOS pathway are the key pathways in the cytoprotective effect of CO.

ORAL CONTRIBUTIONS

884FO

Featured Oral Session...Biomarkers and Risk Assessment in Acute Coronary Syndromes

Wednesday, March 10, 2004, 10:30 a.m.-Noon
Morial Convention Center, Room 210

10:45 a.m.

884-2 **Cardiac Dysfunction in Non-ST Elevation ACS Is Partly Reversible: Analysis of Serial Measurements of NT-Pro B-Type Natriutetic Peptide**

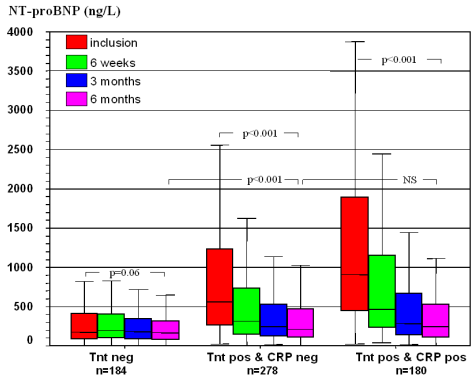
Bertil Lindahl, Nina Johnston, Tomas Jernberg, Matts Stridsberg, Per Venge, Lars Wallentin, The FRISK-II Study Group, University Hospital, Uppsala, Sweden

The inactive form of B-type Natriuretic Peptide, NT-proBNP, is a marker of acute as well of chronic cardiac dysfunction. NT-proBNP is markedly elevated in acute nonSTE-ACS and elevated levels are associated with an increased short- and long-term mortality. However, little is known about the temporal changes of NT-proBNP and their causes after an episode of nonSTE-ACS.

Methods: NT-proBNP was measured at inclusion in the study, after 6 weeks, 3 and 6 months together with Troponin T and C-Reactive Protein at inclusion in 642 patients included in the FRISC-II invasive trial. The association between changes of NT-proBNP over time and a number of clinical and laboratory parameters was evaluated by multiple linear regression analysis.

Results: The NT-proBNP level decreased in median 172 ng/L (25^{th}-75^{th} perc.; 2-671) from inclusion to 6 months. There was no significant statistically change in patients without any myocardial damage (tnT <0.01 μg/L). In patients with myocardial damage (tnT ≥0.01 μg/L) higher levels of tnT and CRP were associated with a larger decrease in NT-proBNP, whereas higher weight, a history of diabetes, smoking and chronic heart failure, respectively, were associated with increasing NT-proBNP levels.

Conclusion: Cardiac dysfunction, as measured by NT-proBNP, is to a large extent reversible in nonSTE-ACS patients. Reversible dysfunction is associated with tnT and CRP elevation. Irreversible dysfunction is associated with diabetes, chronic heart failure, smoking and weight.



11:00 a.m.

884-3 **Clinical Implications of Discordant Creatine Kinase-MB and Troponin Results in Patients With Acute Coronary Syndromes**

L. Kristin Newby, Eric D. Peterson, Anita Chen, Robert A. Harrington, Charles V. Pollack, Jr., James W. Hoekstra, Robert H. Christenson, Robert L. Jesse, W. Brian Gibler, E. Magnus Ohman, Matthew T. Roe, Duke Clinical Research Institute, Durham, NC, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Creatine kinase-MB (CKMB) and cardiac troponins (Tn) are often measured concurrently in patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS). The significance of discordant CK-MB and Tn results remains controversial and their effect on ACS care delivery is unknown.

Methods: Among 29,357 NSTE ACS patients in the CRUSADE Initiative who had both CKMB and Tn measured during the first 36 hours, we examined relationships of 4 combinations of marker results (CKMB-/Tn-, CKMB+/Tn-, CKMB-/Tn+, CKMB+/Tn+) with clinical outcomes and use of ACC/AHA guidelines-recommended acute management strategies. (Markers considered + if above upper limit of normal.)

Results: 28% had discordant CKMB and Tn results (10% CKMB+/Tn-; 18% CKMB-/Tn+). Results are shown in the Table. Patterns were similar after excluding patients with renal insufficiency.

Conclusions: Mortality in Tn+ patients is increased regardless of CKMB status, but CKMB elevation in the absence of elevated Tn does not predict increased mortality. Paradoxically, use of GPIIb-IIIa and early invasive strategies among Tn+ patients appears biased by CKMB results despite this risk pattern and that the bulk of evidence for use is based on Tn+ status. Recognition of these risk differences may contribute to more appropriate early use of antiplatelet therapy and early invasive management strategies for all Tn+ patients.

Use of guideline-recommended acute treatment strategies (medications given within 24 hours) and clinical outcome by marker category

	CKMB-/Tn- (n=3,502)	CKMB+/Tn- (n=2,988)	CKMB-/Tn+ (n=5,349)	CKMB+/Tn+ (n=17,518)
Aspirin (%)	89	91	91	92
B-blocker (%)	70	70	76	79
Heparin (%)	71	72	76	87
GP IIb-IIIa (%)	18	24	23	38
Cath <48 hrs (%)	39	36	35	45
PCI (%)	31	31	29	36
In-hospital death (%)	2.71	2.95	4.45	5.87

11:15 a.m.

884-4 **Higher Levels of Thrombus Precursor Protein Are Associated With Increased Death and Ischemic Complications in Patients With Acute Coronary Syndromes**

Jessica L. Mega, Marc S. Sabatine, David A. Morrow, James A. de Lemos, Sabina A. Murphy, Carolyn H. McCabe, Christopher P. Cannon, Eugene Braunwald, TIMI Study Group, Brigham and Women's Hospital, Boston, MA

Background: Thrombus Precursor Protein (TpP), which measures soluble fibrin, is a marker of active thrombosis. We evaluated the relationship between TpP and clinical outcomes in patients with acute coronary syndromes (ACS).

Methods: Baseline TpP levels were measured in 2349 patients with ACS enrolled in OPUS-TIMI 16. Death, nonfatal MI, recurrent ischemia requiring urgent revascularization (Urg Revasc), and severe ischemia leading to rehospitalization (Sev Isch) were evaluated