Results: Among the 119 women (85% white; mean age 58.2 ± 11.5 y), 48 had a history of CAD or extracardiac atherosclerosis (HX+), 71 did not (HX−). At baseline, only 29% HX+ and 17% HX− women were taking LLAs. By index angiography, 40 (83%) HX+ and 42 (59%) HX− women had CAD. Among HX− women not on LLAs at baseline with newly diagnosed CAD and available LDL data, 96% had LDL levels >100 mg/dl, 63% >130 mg/dl, and 25% >160 mg/dl. None were taking LLAs 6 weeks later. Among HX+ women, 73% not on LLAs had LDL levels >100; only 4 were started on LLAs.

Conclusion: Intensification of lipid-lowering therapy was not apparent 6 weeks after angiography in women with newly diagnosed CAD nor among women who had their diagnosis confirmed.

839 Basic Aspects of Acute Myocardial Infarction II

Tuesday, March 31, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Room 257W

10:30

839-1 Impaired Endothelial-dependent Vasodilation in Viable Postischemic Myocardium Results From Reduced Activity of Nitric Oxide Synthase

R.R. Giraldez, B. Sun, J.L. Zweier, L.C. Becker. *Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Endothelium-dependent vasodilation (EDV), mediated by nitric oxide from nitric oxide synthase (NOS), is impaired after myocardial ischemia-reperfusion. To determine whether abnormal EDV is due to loss of NOS enzyme or to a reduction in NOS activity, correlative studies were performed in dog hearts (n = 15) subjected to 90 minutes ischemia followed by 3.5 hr reflow. Microvascular EDV was assessed by radioactive microspheres during intra coronary infusion of 80 μg/min acetylcholine (ACh). NOS activity was measured by the ^{14}C-arginine to ^{14}C-citruline conversion assay. Blood flow and NOS activity were analyzed within infarcted (INF) and non-infarcted (N-INF) portions of the risk region, as defined by postmorten TTC staining. Western-blots (WB) of the endothelial NOS (eNOS) were performed to detect changes in the amounts of enzyme present. Although ACh increased flow by 135% in normal myocardium, there was no significant increase after ischemia-reperfusion in either INF or N-INF zones. NOS activity was mildly reduced in the N-INF zone but a marked 70% decrease was found in the INF zone. No Ca^{2+}-independent activity was evidenced. WB showed similar density of eNOS bands in control and N-INF areas but a major decrease was evident in INF myocardium. Thus, absent ACh response in postischemic myocardium, indicative of impaired EDV, appears to be related to loss of eNOS enzyme in infarcted regions and reduced NOS activity with normal levels of enzyme in viable areas.

	Control	N-INF	INF
NOS activity	100	75 (SD 19)*	30 (SD 8)**
WB density	100	100	30

NOS-% of control; WB-% of control; *p < 0.05, **p < 0.001 vs control

10:45

839-2 Expression of the Inducible Isoform of Nitric Oxide Synthase in Murine Myocardium Following a Myocardial Infarction

F. Sam, F.R. Eberli, S. Ngoy, D.A. Siwik, D.L.F. Chang, C.S. Apstein, W.S. Colucci. *Myocardial Biology Unit Boston University, MA, USA*

Nitric oxide (NO) exerts pleiotropic effects on the growth and phenotype of cardiac myocytes and fibroblasts *in vitro*. Recently, the inducible isoform of NO synthase (NOS2) was detected in myocardium from patients with end-stage heart failure. To address the possibility that myocardial NO expression modulates cardiac remodeling and failure; we determined the time course of NOS2 mRNA expression in murine hearts following a myocardial infarction (MI). MI was induced in 16 adult CD-1 mice by ligation of the left coronary artery. Sham-operated mice served as controls (n = 8). At 3, 7, 14 and 28 days mRNA isolated from the infarct (including the peri-infarct margin) and the remote (i.e., non-infarcted portion of the ventricle) was subjected to northern hybridization with cDNAs for NOS2 and atrial natriuretic factor (ANF). MI size ranged from 27–60% of ventricle (mean, 43 ± 3%). Isovolumic pressure volume loops demonstrated LV dilation and depressed systolic function at 14 and 28 days. In the infarcted area, NOS2 mRNA was detectable at 3 days, peaked at 7 days (approx. 5-fold vs. 3 days), and decreased progressively at 14 and 28 days. In remote myocardium, NOS2 mRNA was not increased at 3 days, but peaked at 7 days, and remained elevated at 14 and 28 days. ANF mRNA was increased at all times in both the infarcted and non-infarcted areas. Thus, in the mouse heart NOS2 mRNA is expressed in both the infarcted and remote areas of the ventricle after a large MI. Myocardial NO production may depress the function of peri-infarct myocytes early post-MI and may modulate the remodeling of the remote myocardium late post-MI.

11:00

839-3 Disease Specific Patterns of Cytokine Production by T-Lymphocytes in Coronary Atherosclerosis: Evidence for a Role of Infectious Agents in the Pathogenesis of Unstable Angina?

G. Liuzzo, S.L. Kopecky, J.J. Goronzy, K. Cornwell, A. Maseri, R.L. Frye, C.M. Weyand. *Mayo Clinic Rochester, MN and Catholic University, Rome, Italy*

Background: Recent studies have demonstrated the presence of activated T-lymphocytes in coronary plaques and peripheral blood of patients with unstable angina (UA). However, the mechanisms responsible for lymphocyte activation in UA are still unknown. The pattern of cytokine production by different subsets of T-lymphocytes may provide information on the nature of the antigenic stimuli to which the cells have been exposed. Therefore, we assessed the intracellular cytokine production of CD4+ and CD8+ T-lymphocytes using three-color flow cytometry in 15 pts with UA, 16 pts with chronic stable angina (SA), and 10 healthy subjects (C).

Methods: After separation by Ficoll gradient, peripheral blood mononuclear cells were stimulated for 4 hours with phorbol myristate acetate and ionomycin; Brefeldin A was added to inhibit cytokine secretion. Cells were stained with either anti-CD4 FITC/anti-CD3 PerCP or anti-CD8 PerCP/anti-CD3 FITC and, after membrane permeabilization, with PE labeled antibodies specific for interleukin-2 (IL-2), interferon-γ (IFN-γ) and interleukin-4 (IL-4).

Results: Frequencies (%) of IL-2, IFN-γ, and IL-4 producing cells (mean ± SE) are shown in the table.

	UA		SA		C	
	CD4+	CD8+	CD4+	CD8+	CD4+	CD8+
IL-2	15 ± 7.4	4.2 ± 1	28.6 ± 5.8†	6.2 ± 3.3	15 ± 5	4.6 ± 2.2
IFN-γ	26.6 ± 15*	59.7 ± 7*	15 ± 10	41.2 ± 11.6	10.7 ± 6	32.3 ± 5
IL-4	1.4 ± 0.9	0.9 ± 0.2	2.5 ± 1.2†	1.2 ± 0.5	0.6 ± 0.2	0.5 ± 0.3

*P < 0.01 UA vs SA and C, †P < 0.01 SA vs UA and C

Conclusions: Patients with UA and SA expressed disease specific T-cell cytokine patterns. SA was characterized by a high proportion of CD4+ cells producing IL-2 and IL-4. UA was associated with a high proportion of CD4+ and CD8+ cells producing IFN-γ. The high rate of T-cells able to secrete IFN-γ in UA would be consistent with an infectious pathogenesis.

11:15

839-4 Tissue Factor Antigen and Activity in Unstable Coronary Plaques

P.A. Merlini, E. Bramucci, L. Angoli, R. Coppola, R. Ariens, P.M. Mannucci. *Division of Cardiology, Ospedale Niguarda Milan, IRCCS, Policlinico S. Matteo, Pavia; Hemophilia and Thrombosis Center, Milan, Italy*

Rupture or fissuring of a coronary atherosclerotic plaque with subsequent thrombosis is considered the key event in the pathogenesis of unstable angina or acute myocardial infarction. Recent studies have shown that tissue factor (TF), the primary initiator of blood coagulation, is involved in platelet deposition and thrombus formation on disrupted human atherosclerotic lesions in vitro, but whether the content of tissue factor is related to the clinical expression of coronary syndromes is unknown. The present study correlates the amount of tissue factor antigen and activity in human coronary atherosclerotic lesion extracted during atherectomy with the clinical and angiographic presentation of the different coronary syndromes. TF antigen was quantitated through an ELISA (ng/mg plaque weight), and TF activity was measured, by a novel technique, through a factor Xa generation assay (mU/mg plaque weight) in 50 patients (19 stable angina, 24 unstable angina and 7 myocardial infarction). In the whole population there was a close correlation between the amount of tissue-factor antigen and activity (r = 0.87, p < 0.0001). Tissue factor antigen and activity were significantly higher in plaques extracted from the 31 patients with unstable angina or myocardial infarction (antigen: median 66.1 pg/mg; interquartile range: 43.8–82.5 pg/mg, activity: median 0.22 mU/mg; interquartile range 0.172–0.41 mU/mg) than in 19 patients with stable angina (antigen: median 32.4 pg/mg, interquartile range: 9.8–43.4 pg/mg;p = 0.0001; activity: median 0.131 mU/mg; interquartile range 0.05–0.164 mU/mg; p = 0.0004). Complex coronary lesions with thrombosis at angiography, observed in 23 patients, contained higher levels of tissue factor antigen and activity (antigen: median 73.2 pg/mg, interquartile range: 47.5–92.3 pg/mg; activity: median 0.27 mU/mg; interquartile range 0.159–0.41 mU/mg) than uncomplicated lesions (antigen: median 32.8, interquartile range: 12.5–48.9; p = 0.0001; activity: median 0.159 mU/mg;

interquartile range 0.09–0.21 mU/mg; p = 0.0019). Thus, in plaques of patients with unstable coronary syndromes, the higher content of tissue factor may be related to the thrombotic response to rupture.

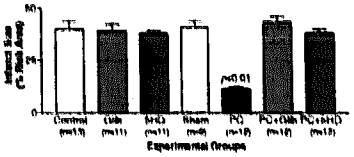
11:30

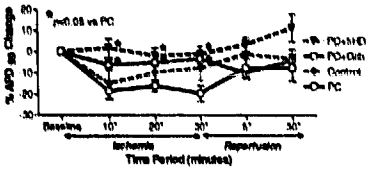
839-5 ATP-sensitive Potassium (K_{ATP}) Channel Blockers Suppress Monophasic Action Potential Shortening and Abolish the 'Second Window of Protection' Induced by Ischemic Preconditioning in Rabbit Hearts

N.L. Bernardo, M. D'Angelo, A.B. Jao, M.A. Wood, R.C. Kukreja. *Division of Cardiology, VCU-Medical College of Virginia, Richmond VA, USA*

Background: Ischemic preconditioning (PC) brings about a delayed phase of myocardial protection 24 hours later. We hypothesized that this 'second window of protection' (SWOP) involves the opening of K_{ATP} channels.

Methods: Seven groups of rabbits were studied using the *in vivo* model of myocardial infarction. *1.* Control. *2.* Glibenclamide (G) 0.3 mg/kg IP 30 min before ischemia/reperfusion (I/R). *3.* 5-hydroxydecanoate (5HD) 5 mg/kg IV 15 min before I/R. *4.* Sham operated 24 hrs prior to I/R. *5.* PC - preconditioned with four 5-min coronary occlusions, each separated by 10 min of reperfusion, 24 hrs before I/R. *6.* PC + G. *7.* PC + 5HD. All rabbits underwent 30 min of coronary occlusion followed by 3 hrs of reperfusion. Risk area was delineated by Evan's blue dye and infarct size was determined by tetrazolium staining. Monophasic action potential duration (APD) was measured by an epicardial electrode.





Results: A significant reduction in infarct size was observed in PC which was blocked by G and 5HD. These specific K_{ATP} channel blockers significantly suppressed APD shortening in PC hearts.

Conclusion: The 'SWOP' afforded by PC is mediated via the opening of K_{ATP} channels.

840 Optimizing Heart Failure Therapy: Latest Strategies

Tuesday, March 31, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Lecture Hall 1

10:30

840-1 Irbesartan Combined With Conventional Therapy, Including Angiotensin Converting Enzyme Inhibitors, in Heart Failure

M. Tonkon, N. Awan, I. Niazi, P. Hanley, L. Baruch, C.-S. Lin, D. Costagliola, G. Cucinotta, R.A. Wolf, A.J. Block for the Irbesartan Heart Failure Group. *Anaheim Heart & Research Institute, Anaheim, CA, USA*

Irbesartan (IRBE; BMS/Sanofi) efficacy and tolerability, combined with conventional therapy including angiotensin converting enzyme inhibitors (ACE-Is), was evaluated in a double-blind, placebo-controlled (PBO), pilot study of patients (pts) with mild-to-moderate heart failure (HF; NYHA Class II or III) and left ventricular ejection fraction (LVEF) ≤40%, on diuretic (≥2 wks) and ACE-I (≥6 wks) therapy. Pts with 2 consistent Modified Naughton exercise tolerance tests (ETTs) were randomized to IRBE (n = 57) [starting doses: 12.5 mg, 37.5 mg, or 75 mg; titrated to 150 mg as tolerated] or PBO (n = 52) QD. ACE-I therapy continued. Angiotensin II (AII) and plasma renin activity (PRA) were studied in 20 pts. Pts were mainly NYHA Class II (79%), male (76%), white (82%), with ages equally ≥ and <65.

PRA and AII increases were consistent with AII receptor blockade. IRBE was well tolerated; serious adverse events were rare in both groups; no deaths occurred. More PBO pts required supplemental diuretics than did IRBE pts (21% vs 12%).

	ETT (sec) median change	LVEF (units) mean change	AII (pg/mL)	PRA (ng/ml-hr)
IRBE	63.5, 21–109*	5.2 (3.2–7.3)	pre: 3.5, post: 6.9	pre: 9.4, post: 21.3
PBO	47.0, −6–131*	2.4 (−0.4–5.1)	pre: 0.8, post: 2.0	pre: 7.0, post: 14.1

*25th–75th quantiles; values in () represent 95% confidence limits.

Conclusion: IRBE, combined with conventional therapy including ACE-I, produced favorable trends in ETT and LVEF and was well tolerated in pts with mild-to-moderate HF.

10:45

840-2 Angiotensin II Receptor Blockade Combined to ACE-Inhibition Improves Left Ventricular Dilation and Exercise Ejection Fraction in Congestive Heart Failure

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Angiotensin II type 1 receptor antagonist losartan (LOS) has recently emerged as a valuable alternative to ACE-inhibitors (ACEI) in the management of congestive heart failure (CHF). Aim of this study was to determine if the association of LOS and ACEI in pts with CHF may enhance the well-recognized beneficial effects of ACEI alone on left ventricular (LV) dimensions and function as assessed by 2D echocardiography at rest and during submaximal supine bicycle exercise (SBE). Seventy-three pts (74% male, age 64 ± 6 yrs) with impaired systolic LV function (EF 28 ± 9%) and stable mild to moderate CHF (NYHA class 2.1 ± 0.4) were randomized in a double blind fashion to receive LOS 50 mg/d (n = 42) or placebo (P, n = 31) in addition to ACEI (enalapril, mean dose 29 mg/d or captopril, mean dose 86 mg/d) for 3 months. All pts were on digoxin and diuretics. The two groups were comparable in age, gender, EF, LV end-diastolic (EDVI) and end-systolic (ESVI) volume index at rest and during SBE. After three months, both groups showed improved EF and LV volumes with respect to values at randomization ($p < 0.01$). However, treatment with LOS resulted in significantly greater improvement of LV dimensions and function with respect to P, as shown in the Table.

	ACEI + LOS		ACEI + P	
At 3 months	Rest	SBE	Rest	SBE
EF (%)	31 ± 10*	36 ± 12†	28 ± 12	32 ± 9
EDVI (ml/m²)	79 ± 13*	71 ± 10†	87 ± 14	76 ± 11
ESVI (ml/m²)	69 ± 10*	58 ± 8†	72 ± 10	66 ± 9

Mean ± SD. *p < 0.05 vs ACEI + P Rest; †p < 0.05 vs ACE + P SBE

In conclusion, these results indicate that LOS combined to ACEI may confer incremental functional benefit as compared to ACEI alone in pts with CHF.

11:00

840-3 Clinical Benefits of Long-term Angiotensin II Receptor Blockade in Patients With Severe Symptoms of Congestive Heart Failure Despite Full Angiotensin Converting Enzyme Inhibition

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After initial improvement, symptoms tend to recur in patients with congestive heart failure (CHF) despite angiotensin converting enzyme (ACE) inhibition at maximally recommended or tolerated dose, digoxin and loop diuretics. The present study was undertaken to determine if the addition of AII type 1 (AT1) receptor blockade to full ACE inhibition would improve functional class (FC, NYHA) and maximal exercise capacity (peak VO2, ml/kg/min) in patients with severe CHF, i.e. peak VO2 <16 and FC III–IV at baseline (BL). Thirty-two patients (mean age 61 yrs, ejection fraction 26%) were randomized to placebo (P) or losartan (L) 50 mg daily. They were evaluated at 3 and 6 mos. Results were as follows:

	BL		3 mos		6 mos	
	L	P	L	P	L	P
FC	3.2	3.0	2.9	3.0	2.5*	3.0
Peak VO2	13.1	14.5	14.7	14.7	15.1*	14.2

* = p < 0.05 L vs P; L (n = 15); P (n = 14)

L at a daily dose of 50 mg was well tolerated by all patients. Three patients were lost to follow up. In conclusion, long-term AT1 receptor blockade improves symptoms and exercise capacity in patients with CHF who are severely symptomatic despite full ACE inhibition, digitalis and diuretics.