1211 Endogenous Factors Contributing to Ischemic Injury

Wednesday, April 1, 1998, 3:00 p.m.–5:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 4:00 p.m.–5:00 p.m.

1211-131 Expression of Plasma Soluble Fas, an Apoptosis Inhibitor, and Plasma Soluble Fas Ligand, an Inducer of Apoptosis, in Patients With Acute Myocardial Infarction

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Background: It has been reported that apoptotic myocytes are seen in acute myocardial infarction (AMI). The Fas receptor (Fas) - Fas ligand (Fas-L) system is representative system of apoptosis. Fas on the cell membrane induces apoptosis when it binds Fas-L or soluble Fas ligand (sFas-L) expressed mainly from activated T cell. However, soluble Fas (sFas) blocks apoptosis by inhibiting their bindings on the cell membrane. We previously reported that plasma sFas, but not plasma sFas-L levels, in patients with chronic heart failure (CHF) were increased with the severity of CHF. However, plasma levels of sFas-L and sFas in patients with AMI are unknown.

Methods: In 22 patients (average age: 63 ± 2 yrs, mean ± SEM) with initial AMI (proximal LAD infarction, TIMI 0 or I, reperfused by direct PTCA within 6 hrs), 62 age- and gender-matched normal subjects, and 8 patients performed elective PTCA to stable angina, plasma sFas and sFas-L were serially assessed by sandwich ELISA using monoclonal anti-human antibodies.

Results: Plasma sFas level was not increased 3 or 6 hrs after the onset of AMI (sFas (ng/mL): 3 hrs: 1.73 ± 0.14, 6 hrs: 2.19 ± 0.32), but was significantly elevated 24 hrs (3.47 ± 0.17*, $p < 0.05$ vs. Normal: 2.10 ± 0.12). Then, the level decreased 48 hrs (2.40 ± 0.22), and normalized at 240 hrs (2.07 ± 0.29).

However, plasma sFas-L was within the normal range in all samples during AMI. Plasma sFas levels 24 hrs after the onset of AMI correlated well with peak CPK levels ($r = 0.75$, $p < 0.05$) and infarcted size of AMI.

Conclusion: We found that plasma sFas level was increased in AMI, and correlated well with infarcted size of AMI. It may play an important role in the pathophysiology of AMI.

1211-132 Pacing-induced Ischemia Results in Transcardiac Activation of Leukocyte to Produce Tumor Necrosis Factor-α in Patients With Angina Pectoris

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Background: Transcardiac leukocyte activation during a brief myocardial ischemia has not been clarified.

Methods: We examined the effects of myocardial ischemia on cytokine production by lipopolysaccharide (LPS)-stimulated whole blood in patients with stable angina. The transcardiac activation of leukocyte to produce cytokines before and during rapid atrial pacing was assessed in 10 patients with stable exertional angina and the left anterior descending coronary artery disease (Group A) and in 10 control patients with chest pain but normal coronary artery (Group B). Heparinized blood was collected in the great cardiac vein (GCV) and aortic root simultaneously, diluted in RPMI, stimulated with LPS, and incubated for 24 hours. Tumor necrosis factor-α (TNF-α), interleukin (IL)-1 β, and IL-6 were measured by an enzyme-linked immunosorbent assay.

Results: The GCV-arterial differences of TNF-α increased significantly during pacing-induced ischemia in Group A (10 ± 260 to 115 ± 113 pg/ml, $p < 0.01$)(mean ± SD), but remained unchanged in Group B (15 ± 85 to −20 ± 90 pg/ml) in comparison with those before pacing. There were no such significant changes in GCV-arterial differences of IL-1 β (Group A: −52 ± 215 to −45 ± 139, Group B: −84 ± 210 to 88 ± 160 pg/ml) and IL-6 (Group A: −270 ± 1210 to 197 ± 280, Group B: 60 ± 320 to −220 ± 920 pg/ml).

Conclusion: These results suggest that a brief myocardial ischemia activates the potential of leukocytes to produce tumor necrosis factor-α in patients with ischemic heart disease.

1211-133 The Association Between a Polymorphism of the Endothelial Nitric Oxide Synthase Gene and the Risk of Acute Myocardial Infarction in the Young Population

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Smoking is the most prominent risk factor for acute myocardial infarction (AMI) in young patients. Genetic predisposition might also be important in the development of AMI in this group. Endothelium-derived nitric oxide (NO) has been shown to be involved in the smoking effects on the endothelium. We investigated the distribution of the endothelial nitric oxide synthase (*ecNOS*) gene a/b polymorphism in 72 AMI patients and 153 control subjects in relation to smoking status and age. The aa, ab, and bb genotypes were found in 5, 17, and 50 cases among AMI patients and 0, 34, and 119 cases among the control subjects. There was a significant correlation between the ecNOS polymorphism and AMI ($p = 0.00487$). The presence of the ecNOSa allele was also significantly related to the development of AMI ($p = 0.038$). When the correlation was analyzed by age, the significance only remained in the group below age 50 ($p = 0.013$). Smoking status and the ecNOS polymorphism had a synergistic effect in the risk of AMI. Young persons who are smoking and have the ecNOSa allele, especially aa homozygotes, may have an increased risk of developing AMI.

1211-134 Hemodynamic and Inotropic Effects of Endothelin Antagonists

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The potent vasoconstrictor endothelin-1 (ET-1) is involved in the development of several diseases and therapy with endothelin receptor antagonists may be of importance in future. Previous in vivo studies with a selective endothelin$_B$ (ET_B) receptor antagonist showed that the positive inotropy of ET-1 is mainly mediated by ET_B receptors while its vasoconstrictive effect is mainly mediated by endothelin$_A$ (ET_A) receptors. This study examined the effects of selective ET_A and ET_B receptor blockade on hemodynamics and myocardial contractility.

In open-chest rats the i.v. effects of the ET_A antagonist BQ 610 (0.15 μmol/kg) and the ET_B antagonist BQ 788 (0.5 μmol/kg) were compared with NaCl-controls. Additionally to measurements in the intact circulation isovolumic measurements (isovol. LVSP, isovol. dp/dt_{max}) were performed to determine myocardial contractility.

	CO	TPR	isovol. LVSP	isovol. dp/dt_{max}
BQ 610	126 ± 3†	86 ± 2*	100 ± 1*	106 ± 2*
BQ 788	117 ± 4	89 ± 3	94 ± 2	94 ± 2*
NaCl	111 ± 1	94 ± 1	96 ± 1	100 ± 1

Means ± SEM in % of preinfusion values. * $p < 0.05$, † $p < 0.01$

While selective ET_A receptor blockade by BQ 610 causes vasodilatation with a consecutive increase of the cardiac output selective ET_B blockade with BQ 788 has no favourable effects on hemodynamics. The isovolumic measurements indicate a positive inotropic effect of BQ 610 and a cardiodepressive effect of BQ 788.

Conclusions: Selective ET_A blockade can unmask the positive inotropic effect of endogenous ET-1 via ET_B receptors. Thus ET_A blockade may be an advantage over unselective ET_A/ET_B blockade.

1212 New Discoveries in Unstable Angina

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1212-125 Coronary Stenting Versus Balloon Angioplasty for Unstable Angina

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While unstable angina (UA) has been associated with increased complications and restenosis after conventional balloon angioplasty (PTCA), the efficacy of coronary stenting in acute ischemic syndromes remains unknown.

The goal of this STRESS substudy was to compare PTCA and stenting in patients with UA. Of 598 patients enrolled in the STRESS I–II trial, 330 patients (55%) had UA (with angina at rest in 66%). Baseline characteristics were similar in the two treatment groups. Procedural success (residual stenosis <50% and no major complication) was achieved in 80% of PTCA patients and 88% of stent patients (p = 0.055). Reclosure within 30 days occurred in 1.3% after PTCA and 2.3% after stenting (p = ns). QCA results (in mm) were:

Treatment Group	Vessel Diameter	Lesion Length	Pre MLD	Post MLD	6 mo MLD
Angioplasty	2.97	8.6	0.76	1.97	1.48
Stent	2.95	8.9	0.74	2.42	1.68
p	NS	NS	NS	<0.001	0.01

Compared to PTCA, stenting was associated with significantly greater acute gain (1.21 vs 1.69 mm, p < 0.001), late loss (0.52 vs 0.76 mm, p < 0.01), and net gain (0.72 vs 0.93 mm, p = 0.01). Restenosis was 47% (55/117) after PTCA and 35% (50/145) after stenting (p < 0.04). Target lesion revascularization was performed in 26% of PTCA and 20% of stent patients (p = 0.19). This retrospective analysis from the STRESS trial suggests that stent placement provides superior angiographic results to balloon angioplasty in patients with UA. Further prospective trials of stenting in the treatment of acute ischemic syndromes are warranted.

1212-126 Transient Decrease of Thrombin Generation During Hirudin Treatment in Patients With Acute Coronary Syndromes

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In the acute phase of acute coronary syndromes (ACS) heparin (H) is able to suppress increased thrombin activity, as quantified by fibrinopeptide A plasma levels (FPA) but not thrombin generation, as indicated by prothrombin fragment 1 + 2 (F_{1+2}). At drug termination there is a rebound increase in both markers. The effect of hirudin (D on FPA and F1 + 2 has been less investigated. We measured plasma levels of F1 + 2 (RIA) and FPA (ELISA) in 78 patients with ACS receiving heparin or hirudin in the GUSTO IIb study. None of the patients received thrombolytic therapy. Coagulation activation markers were measured at baseline (BL), after 3–5 days of drug administration immediately before drug termination (T), 3, 6 and 24 hours after drug termination, and after 1 month. Data are expressed as medians (interquartile ranges):

FPA	B	T	3 h	6 h	24 h	1 mo.
D	2.0	0.9*	1.1*	1.8	1.6	1.0*
	(0.7–3.5)	(0.7–1.1)	(0.9–1.6)	(1.05–3.4)	(1.3–2.3)	(0.9–1.3)
H	2.1	1.1*	2.2	2.1	2.0	1.0*
	(1.12–4.2)	(0.8–1.9)	(1.1–8.6)	(1.1–4.9)	(0.9–3.7)	(0.8–1.2)
F1 + 2						
D	1.1	0.95*	1.04	1.01	1.07	1.3*
	(0.93–1.4)	(0.76–1.1)	(0.78–1.2)	(0.85–1.2)	(0.85–1.4)	(1.12–1.8)
H	1.07	1.13	1.45*	1.46*	1.37*	1.26*
	(0.85–1.4)	(0.90–1.4)	(1.12–2.0)	(1.06–2.0)	(1.12–1.7)	(0.94–1.7)

*p < 0.05 vs baseline

Thus, D induced significant decrease both in thrombin generation and activity during treatment. After T there was a increase in thrombin generation and activity to baseline values in both D and H patients. After 1 month both groups showed a persistent elevated thrombin generation. The early clinical benefit shown by D during treatment in the GUSTO IIb may be linked to more effective inhibition of thrombin generation. The loss of the favourable effect after T may be due to the persistently increased thrombin generation.

1212-127 Different Thrombotic and Inflammatory Patterns Between Unstable Angina and Peripheral Vascular Disease

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Background: Although Peripheral Vascular Disease (PVD) and acute coronary syndromes have a common atherosclerotic background, their clinical presentation and evolution are very different, raising the question whether they have similar or distinct pathogenetic mechanism.

Methods: To this aim we studied C-Reactive Protein (CRP; an acute phase reactant), Myeloperoxidase Intracellular Index (MPXI; whose reduction is a marker of neutrophil activation; expressed in arbitrary units, AU) and D-Dimers (DD; hemostatic system activation marker) in 20 patients (pts) with PVD symptomatic for intermittent claudication or rest pain but without cutaneous ulcerations (Stage Leriche-Fontaine II–III) with angiografically proven severe obstructions and thrombosis and 20 pts with unstable angina (UA) and single vessel disease and no clinical evidence of PVD.

Results: (median and range): PVD pts presented a greater activation of the hemostatic system than UA pts (DD: 22 microgr/L, 9.1 to 140, in PVD pts and 8.8 microgr/L, 2.2 to 149, in UA pts; p = 0.006). However, CRP levels was similar in both groups (4.2 mg/L, 0.8 to 24 in PVD pts and 6 mg/L, 1.40 to 28 in UA pts; p = NS). In contrast, MPXI was significantly reduced in UA than in PVD pts (−4 AU, −10 to 2.4, in UA pts and 1.0 AU, −12.5 to 6, in PVD pts; p = 0.02).

Conclusions: In spite of a much smaller atherosclerotic and thrombotic burden, UA pts exhibit an acute phase response similar to PVD pts and a significantly greater nautrophil activation. These findings indicate that inflammatory response in UA is largely unrelated to severity of atherosclerotic and thrombotic burden.

1212-128 Comparison Between a Very Low Molecular Weight Heparin and Unfractionated Heparin in Patients With Unstable Angina. A Pilot Study

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Background: Aim of the study was to compare the efficacy of very low molecular weight heparin (VLMWH) combined with aspirin and standard heparin (SH) plus aspinn, during the acute phase of unstable angina.

Methods: One hundred and twenty patients (pts) with unstable angina were randomized to receive SH (dosage: bolus of 5.000 U.I. followed by APTT control dose) plus aspirin 100 mg/die (Group 1; 60 pts, mean age 69.12 ± 9.56) or VLMWH at the dosage of 150 mg for the first administration and than 150 mg/die plus aspirin 100 mg/die (Group 2; 60 pts, mean age 64.62 ± 11.06). Pts were followed for 6 days. The major end-points determined were: Death; Acute myocardial infarction (AMI); Recurrent angina (RA) and Urgent revascularization (UR). Minor end-point was silent ischemia (SI). Event rates were evaluated using χ^2 analysis. Platelets were periodically checked during the in-hospital period.

Results: are shown in the table I.

	n°	Events	death	AMI	RA	UR	SI
SH	60	26	0	2	20	3	1
VLMWH	60	14	0	0	10	4	0

p < 0.005 p < 0.05

Events were significantly less frequent in pts treated with vlmwh (p < 0.005). During treatment the mean value of platelets count decreased in patients treated with SH (p < 0.05), no differences were observed in VLMWH patients.

1212-129 Angiographic Disease Progression in Patients With Angina Pectoris and Normal Coronary Angiograms who Are Restudied due to Unstable Symptoms

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Patients with chest pain and normal coronary angiograms have a favorable long-term prognosis but may be readmitted to hospital with symptoms and electrocardiographic changes suggestive of unstable angina. The factors which may be associated with angiographic disease progression in such patients are not fully understood. We investigated 139 consecutive patients with chest pain and "normal" coronary angiograms. 101 patients had completely normal angiograms and 38 patients had minimal lumenal irregularities (<20% stenosis). During a five year study period, 24 patients developed primary unstable angina and underwent repeat angiography. This group consisted of 19 women and 5 men with a median age 56 years old (range 42 to 74 years). 16 patients also had objective evidence of reversible ischaemia. The median interval separating the angiograms was 58 months (range 8 to 130 months). At repeat angiography, none of 21 restudied patients with completely normal baseline angiograms had developed significant stenoses. In contrast, 2 of the 3 restudied patients with minimal irregularities at baseline had developed significant lesions (>50%). Both patients with progression also had left bundle branch block and more than one risk factor for coronary disease. However, the positive predictive accuracy of left bundle branch block (50%) was greater than that for multiple risk factors (10%) in regard to angiographic disease progression. We conclude that angiographic progression in patients with chest pain and previously normal coronary arteriograms is unusual even