4:15 p.m.

904-2 Inhibition of Platelet Adhesion by Thrombostatin, a PAR1 Activation Inhibitor, in a Model of Arterial Wall Injury Using Balloon Angioplasty

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Background: Thrombus formation after balloon injury has been implicated in the development of vascular complications. We tested the efficacy of a new anti-thrombin agent, thrombostatin in reducing platelet adhesion at balloon angioplasty treated sites. Thrombostatin selectively inhibits the activation of protease activated receptor 1 (PAR1) by thrombin.

Methods: Whole blood (450 ml) was collected from each of 10 dogs prior to sacrifice. Platelet rich plasma (PRP) was obtained by centrifugation of whole blood and 10% of the PRP was labeled with In^{111}. Both carotid arteries (CAs) were removed after sacrifice and mounted side-by-side in a perfusion chamber immersed in oxygenated physiologic buffer solution. Intimal injury to both arteries was induced using 3 inflations (3.0 mm balloon catheter, 60 sec. each). In^{111}-PRP with or without thrombostatin was perfused through arteries for 60 min. separately. Radioactivity was measured with a gamma counter for each arterial segment. A total of 20 CAs were perfused with In^{111}-PRP. 10/20 CAs were perfused with In^{111}-PRP containing 0.5 mM thrombostatin. The other 10/20 CAs were simultaneously perfused with In^{111}-PRP without drug as the control group.

Results: The radioactivity ratio between the control and thrombostatin group was 4.22:1 ($p < 0.05$).

Conclusion: This study shows that thrombostatin significantly decreases platelet adhesion in the dog carotid artery model of balloon injury. These data suggest that a selective thrombin inhibitor, like thrombostatin which prevents thrombin from activating PAR1, maybe an effective anticoagulant.

4:30 p.m.

904-3 Enhanced Shear-Induced von Willebrand Factor Binding and Subsequent Platelet Activation in Acute Myocardial Infarction

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Background: Recent in vitro studies suggested the crucial role of von Willebrand factor (vWF) on platelet thrombus formation occurring under flow. We have tested the effect of plasma obtained from acute myocardial infarction patients on vWF binding to platelet and vWF-mediate platelet activation occurring under various high shear rates.

Methods: Shear-induced vWF binding was measured by quantitative flowcytometry with monoclonal antibody known to bind exclusively to C-terminal domain of vWF (LJ-C3) directly labeled with FITC. FITC-LJ-C3 binding to platelets obtained from normal donors after exposing them to various shear rates in the presence of plasma from either normal donors (control) or fifteen cases of acute myocardial infarction (AMI) was measured. Platelet surface P-selectin molecules were also measured with similar procedure with FITC conjugated anti-P-selectin monoclonal antibody (WGA1). FITC-conjugated anti-thyroglobulin binding was measured as a negative control.

Results: vWF binding as indicated by FITC-LJ-C3 binding increased after exposing platelet to shear rates more than 9,000 s^{-1} in the presence of control plasma. The increased binding indicate increased platelet surface vWF molecules rather than non specific IgG binding since FITC conjugated thyroglobulin binding did not change at all. The number of FITC-LJ-C3 molecules bound after exposing platelet to a relatively high shear rate of 10,800 s^{-1} in the presence of AMI plasma was 6 ± 2% more than that in the presence of control plasma. Moreover, AMI plasma decreased the threshold shear rate to induce vWF binding to 7,200 s^{-1}. Results of platelet surface P-selectin molecules also suggested that the threshold shear rate necessary to induce vWF-mediated platelet activation decreased from 9,000 s^{-1} to 7,200 s^{-1} in the presence of AMI plasma.

Conclusion: vWF binding and vWF mediated platelet activation occurring under shear were enhanced in patients with acute myocardial infarction. This mechanism may be relevant to the onset and recurrence of myocardial infarction.

4:45 p.m.

904-4 Myocardial Platelet Accumulation After Reperfusion Depends on Local Aggregation More Than on Embolization from the Unstable Coronary Lesion, and Is Not Prevented by Aspirin

José A. Barrabés, David Garcia-Dorado, Bernat Soriano, Jaume Figueras, Yolanda Puigfel, Julia Solares, Lourdes Trobo, Jordi Soler-Soler. *Hospital General Universitari Vall d'Hebron, Barcelona, Spain*

Background: Platelet aggregates have been found in small myocardial vessels from patients dying of acute coronary syndromes. We sought to investigate the contribution of "in situ" aggregation and embolization from the active coronary plaque on myocardial platelet accumulation after ischemia and reperfusion, and its modification by aspirin.

Methods: Twenty-six open-chest pigs, in which platelets had been labelled with ^{99m}Tc, were submitted to catheter-induced intimal injury of the LAD followed by no intervention (n = 6) or by 25-min (n = 6) or 48-min (n = 14) coronary occlusion (CO). Eight of the pigs submitted to 48-min CO received 250 mg ev ASA 90 min before CO. After reflow, 24 animals had 12 ± 1 cyclic reductions in LAD flow (CFVs, transit time flowmeter) reflecting extensive thrombosis. After 2 h, the heart was excised, the aortic root perfused for 5 min with 0.5% albumin in Ringer solution, and platelet content ($\times 10^6$/g) in samples from LAD-dependent and control myocardium was determined.

Results: In the control region, platelet content was similar among groups (12.0 ± 2.7, 12.6 ± 2.6, and 13.6 ± 1.7, respectively). In LAD territory, platelet accumulation was modest in the absence (17.1 ± 5.6) or after brief ischemia (22.9 ± 3.1), but much larger after 48-min CO (51.1 ± 13.4, $p < 0.05$), and was not correlated with platelet deposition on the LAD or with the number of CFVs. In the 48-min CO group, platelet content in LAD territory was similar in animals treated or not with aspirin (59.4 ± 21.3 vs 38.0 ± 7.5, NS), despite less CFVs in aspirin-treated animals (7 ± 2 vs 14 ± 2, p = 0.04).

Conclusion: Local aggregation and not embolization from the coronary plaque is the main cause of platelet accumulation in reperfused myocardium, despite an active coronary thrombosis, and is not prevented by aspirin.

ORAL

905 Late Outcomes After Cardiac Arrest

Wednesday, March 10, 1999, 4:00 p.m.–5:00 p.m.
Morial Convention Center, Room 262

4:00 p.m.

905-1 Prediction of Pre-Discharge Cognitive Deficits in Cardiac Arrest Survivors using Serum Protein S-100 and Neuron Specific Enolase

Neil R. Grubb, Catriona Simpson, Ronan O'Carroll[1], Ian Deary, Roy Sherwood[2], Hagosa Abraha[2], Keith A. Fox. *Edinburgh University; [1]MRC Brain Metabolism Unit, Edinburgh; [2]Kings College, London, UK*

Background: Over 30% of out-of-hospital cardiac arrest (OHCA) survivors suffer moderate or severe chronic memory deficits. These are mediated by hypoxic brain injury during cardiac arrest. Brain enzyme assays can be used to predict survival after stroke but have not been evaluated as potential predictors of functional deficits in OHCA survivors. This study evaluates serum protein S100 and neuron specific enolase (NSE) as markers of brain injury after OHCA.

Methods: Of 43 early OHCA survivors admitted during the study period, 21 survived to discharge. 19 agreed to assessment with the Rivermead Behavioural Memory Test (RBMT), a test of episodic long term memory which allocates a score out of 24 points. Serum had been obtained from all OHCA survivors on admission and at 24 and 72 hours. NSE and S100 were measured using radioimmunoassay. We compared enzyme levels at each time point in those with severe memory impairment (Group A, RBMT < 16) and without (Group B, RBMT > = 16). We calculated correlation coefficients for enzyme levels versus RBMT scores.

Results: S100 level at 24 hours was the best predictor of memory impairment at discharge, mean (95% CI) Group A: 0.29 (0.18–0.4). Group B: 0.08 (0.04–0.12), **p = 0.004.** Admission and 72 hour S100, and all NSE estimates, were poorer predictors. Correlation values are shown below:

Correlations vs RBMT	r	r squared	p value
S100 24 hours (μg/l)	0.57	0.33	*0.009*
NSE 24 hours (ng/ml)	0.45	0.21	*0.048*

Conclusions: Serum measurement of NSE and S 100 24 hours after resuscitation predicts memory function after OHCA. A 24 hour S100 value