*Conclusions:* There were no significant national gender differences in in-hospital complications, management or outcome. Despite recurrent ischaemia in up to 40%, only up to 16% were investigated invasively during admission which demonstrates a national potential for improvement in the management of acute coronary disease.

## 901 Biochemical Markers and Treatment of Myocardial Ischemia

**Wednesday, April 1, 1998, 2:00 p.m.–3:30 p.m.**
**Georgia World Congress Center, Room 264W**

2:00

### 901-1 Daily Life Ischaemia in Chronic Stable Angina is Related to Platelet Activation Induced by Increased Cytokine Plasma Levels

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*Backround:* Circulating macrophage colony stimulating factor (MCSF) causes macrophage/monocyte activation at atherosclerotic lesions and thus release of vasoactive substances, interleukins 1b (IL1b) and 6 (IL6), platelet chemoattractants and tissue factor. Our aim was to assess the relation of cytokines to a) platelet activation and thrombin generation in vivo and b) to the presence of transient myocardial ischaemia in stable angina (SA).

*Methods:* We measured prothrombin fragments (PF1+2, nmole/l) MCSF, IL1b, IL6 (pg/ml) plasma levels and 24 h urine excretion of 11-dehydrothromboxane B2 (DHTXB2, ng/mg creatinine) in 60 patients with SA and in 21 healthy contols by ELISA. Blood samples and urine collections were obtained at the end of a 48 h Holter monitoring (HM). Patients were off aspirin for 3 weeks before blood and urine sampling, had angiographically documented disease and positive exercise test.

*Results:* PF1+2, MCSF, and IL6 were increased in patients with SA compared to controls (PF1+2: 2.26 ± 1.8 vs 0.93 ± 0.5, MCSF: 1076 ± 613 vs 479 ± 287 IL6: 4.2 ± 1.3 vs 2 ± 0.9, $p < 0.01$). Only patients with 3 vessel disease had higher IL1b than controls (0.41 ± 0.3 vs 0.25 ± 0.2, $p < 0.05$). Analysis of variance showed that MCSF and IL1b increased according to the number of diseased (1-2-3) vessels ($p < 0.05$). Patients with ischaemia on HM (40/60) had higher MCSF and DHTXB2 levels compared to those without (MCSF: 1124 ± 651 vs 528 ± 417, DHTXB2: 4.2 ± 3.2 vs 2.3 ± 1.9, $p < 0.05$). Higher MCSF levels were related to higher IL1b and DHTXB2 levels ($r = 0.47$ and $r = 0.40$, $p < 0.01$).

*Conclusion:* Elevated cytokine and PF1+2 plasma levels in SA are suggestive of enhanced inflammatory activity and increased thrombin generation. We found for the first time in vivo, that transient ischaemia during daily life in patients with SA is related to enhanced cytokine and platelet activity and not to increased thrombin generation.

2:15

### 901-2 Local Perivascular Basic Fibroblast Growth Factor (bFGF) Treatment in Patients With Ischemic Heart Disease

R.J. Laham, F.W. Sellke, E.R. Edelman, J.D. Pearlman, M. Simons. *Harvard Medical School, BIDMC, Boston, MA, USA*

*Background:* The completeness of revascularization in ischemic heart disease is a major determinant of long-term outcome. We have previously demonstrated that perivascular bFGF delivery results in functionally significant angiogenesis in an animal model of chronic myocardial ischemia. The purpose of this study is to determine the safety and efficacy of local perivascular bFGF delivery in patients (pts) undergoing CABG who have an underperfused but ungraftable territory.

*Methods:* 8 pts (5 men, 3 women, age 66 ± 6, EF 47 ± 14%) undergoing CABG with an ischemic myocardial area supplied by a non-graftable vessel had implantation of bFGF-heparin alginate microcapsules in the epicardial fat surrounding that vessel (5 RCA, 3 LCX). 4 pts received a total dose of 10 μg and 4 pts received 100 μg of bFGF. Hemodynamic monitoring was performed for 5 days after treatment. Laboratory parameters, nuclear perfusion scans, cardiac MRI, and echocardiograms were performed before and 3 months after treatment.

*Results:* bFGF was well tolerated. Implantation added 2.8 ± 1.1. min to operative time. There were no hemodynamic effects (baseline MAP 91 ± 13 mmHg, 5 day MAP 93 ± 8 mmHg) or significant changes in hematologic or chemistry profiles during follow-up. Plasma bFGF levels did not increase above baseline (17.4 ± 3.3 pg/ml at baseline, 15.9 ± 1.8 pg/ml at 3 days, and 16.0 ± 1.8 pg/ml at 5 days). Clinical follow-up was available on all pts. Two pts had superficial wound infections. No other adverse events were noted. All pts were free from angina. 4 pts had enhanced perfusion in the unrevascularized myocardium by nuclear scans and MRI.

*Conclusion:* This preliminary study shows that local perivascular bFGF-heparin alginate (10–100 μg) treatment is feasible and well tolerated, with no short-term adverse events and no detectable increase in circulating bFGF levels. Further studies examining the safety, efficacy and long-term outcome are ongoing.

2:30

### 901-3 Reperfusion Prevents Apoptosis in Hibernating Myocardium

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Prior studies from our laboratory have shown that ongoing myocyte death through apoptosis occurs in hibernating myocardium (HM). This study was designed to assess whether reperfusion after 7 days of severe coronary stenosis affects apoptosis in HM.

*Methods:* Three groups of pigs were studied. In group 1 (n = 6) a fixed LAD stenosis was created, reducing LAD flow from 0.94 ± 0.11 to 0.56 ± 0.11 ml/min/g of myocardium ($p < 0.01$). Regional wall thickening decreased from 39 ± 4% to 10 ± 7% ($p < 0.01$). After maintaining stenosis for 7 days, the animals were sacrificed and the LVs were examined. In group 2 (n = 5), identical LAD stenoses were placed, reducing flow to 0.54 0.08 ml/min/g and wall thickening to 8 ± 5% (both $p < 0.01$). The stenoses were released at 7 days to reperfuse the HM, and the pigs were kept alive for 4 weeks. In group 3 (n = 4) a sham operation was done without stenosis. In situ TdT-dUT-biotin nick end-labeling was applied to detect DNA fragmentation, indicating myocyte apoptosis and "DNA laddering" on agarose gel electrophoresis was used to confirm the DNA fragmentation. Severity of apoptosis was expressed as percent of myocyte nuclei that were apoptotic.

*Results:* Apoptotic myocytes were detected by in situ end-labeling in the hibernating region in all 6 pigs without reperfusion and in 2 of 5 pigs with reperfusion. Severity of apoptosis was 2.47 ± 0.66% in the permanent stenosis group and 0.23 ± 0.36% in the group with 4 weeks of reperfusion ($p < 0.01$. Apoptotic myocytes were not found in sham pigs or in other non-LAD territories in groups with stenoses.

*Conclusions:* Severe coronary stenosis with resting hypoperfusion induces apoptosis in dysfunctional HM. The induced apoptosis can be prevented almost entirely by rephrasing the HM.

2:45

### 901-4 Preconditioning of Human Myocardium With Bradykinin During PTCA

M. Leesar, R. Matharu, N. Xenopoulos, J. Pruitt, M. Stoddard, R. Bolli. *Univ. of Louisville, Louisville, KY, USA*

Brief ischemia renders the myocardium more resistant to subsequent ischemia (ischemic preconditioning). Animal studies have shown that bradykinin (BK) receptors play a critical role as mediators of this cardioprotective effect and that pretreatment with BK preconditions the heart in a manner similar to ischemic preconditioning. However, nothing is known regarding the role of BK in preconditioning human myocardium. Thus, 30 patients were randomized to receive a 10-min intracoronary (IC) infusion of saline (controls [C], n = 15) or BK (n = 15). Ten-min after the end of infusion, pts underwent PTCA (three 2-min balloon inflations, each separated by 5-min). The ST segment shifts on the IC-ECG and surface 12-lead ECG (S-ECG) were measured at the end of each inflation:

| | IC-ECG (mm) | | S-ECG (mm) | | Chest Pain Score | |
|---|---|---|---|---|---|---|
| | C | BK | C | BK | C | BK |
| Inflation 1 | 23 ± 3 | 12 ± 2* | 16 ± 3 | 7 ± 1* | 68 ± 5 | 39 ± 5* |
| Inflation 2 | 14 ± 2 | 11 ± 2 | 10 ± 2 | 7 ± 1 | 54 ± 7 | 37 ± 5 |
| Inflation 3 | 13 ± 2 | 11 ± 2 | 9 ± 1 | 7 ± 1 | 41 ± 6 | 36 ± 5 |

X ± SEM; *P < 0.05 vs. controls

In the control group, the ST shift decreased during the second and third inflation compared with the first, indicating ischemic preconditioning. In the BK group, the ST segment shift was significantly reduced during the first inflation compared with controls (−48% on IC-ECG), indicating attenuation of ischemic injury by BK. Furthermore, there were no appreciable differences in ST shifts between the first, second, and third inflation, indicating that BK induced a preconditioning effect during the first inflation comparable to that induced by ischemic preconditioning during the second and third inflation. The severity of chest pain was also markedly decreased by BK during the first inflation.

*Conclusions:* Pretreatment with BK preconditions human myocardium against ischemia *in vivo*, suggesting a pathophysiologic role of BK receptors