most probably due to a high prevalence (66%) of statin therapy. Conclusion: In patients undergoing revascularization, the reinfarction rate associated with a high prevalence of statin therapy is significantly lower than that seen in the control group.

1124-48 Impact of Reocclusion on Six-Year Survival and Reinfarction Following Fibrinolytic Therapy: Long-Term Follow-Up of the APRICOT Trial

Peter C. Kistler, Marc A. Brouwer, Albert Meijer, Gertien Veen, Freerk W. A. Verheugt, University Medical Center Nijmegen, Nijmegen, The Netherlands, Free University Medical Center, Amsterdam, The Netherlands.

Background: Whereas reocclusion within a week after demonstrated patency has been associated with a twofold increased risk of mortality, the prognostic impact of reocclusion after the acute phase remains to be determined.

Methods: In the APRICOT-1 trial 248 patients of 70 years or younger had TIMI 3 flow at coronary angiography, within 48 hours after fibrinolytic therapy. Follow-up angiography and ventriculography was scheduled at three months. Death and reinfarction were recorded using medical charts, telephone contact with the general physician and information from municipal registries.

Results: Reocclusion was observed in 71 patients (29%). Left ventricular ejection fraction increased from 51±10% to 55±11% with sustained patency (p < 0.01); in patients with reocclusion the change in ejection fraction was -1.7±1.6% (p=ns). Mean clinical follow-up was 4.3±1.2 years. At five years, survival was 90% for patients with reocclusion compared to 92% for patients with a patent artery at follow-up angiography (p=ns). Death and reinfarction rates were 34% and 20%, respectively (fig. 1, p < 0.01).

Conclusion: After demonstrated coronary patency following fibrinolysis for acute ST-elevation myocardial infarction, patients who survived the first 48 hours had an excellent 5-year prognosis. Although reocclusion was associated with a higher risk for reinfarction and impaired left ventricular contractile recovery, the potential adverse impact on long-term survival could not be demonstrated.

Survival without reinfarction

100 %

50 %

0 1 2 3 4 5 yr

1124-47 Resting Heart Rate as a Predictive Risk Factor for Sudden Death in the Population


Objective: A relative hyperadrenergic tone related to abnormalities of the autonomic nervous system is suspected in the mechanisms of sudden death. Therefore, we assessed the role of an elevated resting heart rate in the occurrence of sudden death in a long-term cohort study (the Paris Prospective Study I).

Methods: 7749 subjects underwent ECG and physical examination conducted by a physician in standardized conditions, provided blood samples for laboratory tests, and answered questionnaires administrated by trained interviewers. The vital status was obtained from specific in-hand death certificates and by death certificates. Men with known ischemic heart disease were further excluded from analysis which was conducted on the 7079 remaining subjects.

Results: After an average follow-up period of 23 years of the population, there were 2083 deaths, among which 603 cardiovascular deaths including 118 sudden deaths and 192 fatal myocardial infarctions. The crude risk of sudden death increased proportionally with the level of resting heart rate and the relative risk associated with the higher quintile of heart rate was 3.8 fold that associated with the lowest quintile, whereas such a relative risk was approximately 2 for fatal myocardial infarction, cardiovascular and total mortality (all p<0.01). When age, body mass index, systolic blood pressure, tobacco consumption, parental history of myocardial infarction and parental history of sudden death, cholesterol level, diastolic stress, and sport activity were simultaneously entered into the survival model, resting heart rate remained an independent risk factor for sudden death (p<0.03) but not for fatal myocardial infarction.

Conclusion: An elevated heart rate at rest remained an independent risk factor for sudden death in middle-aged men.

ORAL CONTRIBUTIONS

836 Basic Mechanisms of Myocardial Ischemia

Monday, March 18, 2002, 4:00 p.m.-5:30 p.m. Georgia World Congress Center, Room 255W

836-1 Repetitive Brief Myocardial Ischemia and Reperfusion Induces a Cardiomyopathy With Features of Myocardial Hibernation in Mice: A Possible Role for Chemokines

Olie Dewari, Nikolaos G. Frangogiannis, Martin Zoelen, Pascal Kruithof, Thierry T. Pham, George Taffet, Lloyd H. Michael, Mark L. Entman, Section for Cardiovascular Sciences, Department of Medicine, Baylor College of Medicine, Houston, Texas, Winters Center for Heart Failure Research, Baylor College of Medicine, Houston, Texas.

Background: Repetitive brief myocardial ischemia, in the absence of myocardial infarction and permanent necrosis has been implicated in the pathogenesis of the ventricular dysfunction associated with myocardial hibernation. We have previously demonstrated in a murine model that a single brief episode of myocardial ischemia followed by reperfusion (I/R) is associated with increased contractile function and the induction of chemokines. In this study we examine the effects of repetitive I/R in the murine heart.

Methods: C57BL/6 mice underwent daily 15 minute left anterior descending coronary occlusions followed by reperfusion. After 7, 14, 21 and 28 days, echocardiography studies were performed, and hearts of I/R and sham operated animals were processed for RNA and histological studies.

Results: Echocardiographic studies showed a decreased fractional shortening in the left ventricle from day 7 to day 14 as well as day 28. Histological and RNA expression studies showed no ischemia area in the murine myocardium. Repetitive brief episodes of myocardial ischemia followed by reperfusion of the murine heart induces a cardiomyopathy. Histological analysis showed no necrosis area in the ischemic region. RT-PCR analysis showed increased expression of CCL2, also known as MIP-1c, MIP-1β, MIP-2 and MCP-1 at 7 days I/R, and was reduced at 28 days. Conclusion: Repetitive brief I/R in the murine heart induces fibrotic remodeling and systolic dysfunction of the left ventricle, in the absence of myocardial infarction and repetitive brief episodes of myocardial ischemia followed by reperfusion.
neurogenesis leading to a cardiomyopathy with a feature of hypertrophy. Early chemokine induc- tion and interstitial fibrosis due to frequent sublethal ischemic episodes may have a role in mediating left ventricular dysfunction in ischemic cardiomyopathy.

4:15 p.m.

836-2

Serum Levels of Unbound Free Fatty Acids Reveal High Sensitivity for Early Detection of Acute Myocardial Infarction in Patient Samples From the TIMI II Trial

Alan M. Kleinfield, Kevin J. Kleinfield, Jesse Adams, III, Torrey Pines Institute for Molecular Studies, San Diego, California, Jewish Hospital, Louisville, Kentucky.

Background: Levels of unbound free fatty acids (FFAu) have been found to increase with myocardial cellular ischemia in patients undergoing balloon angioplasty (Kleinfield et al, Am J Cardiol 1996;78:1305). To assess whether FFAu are an effective marker of ischemia in acute myocardial infarction (AMI), levels of FFAu were determined in serum samples from patients enrolled in the TIMI II trial (TIMI Study Group, Engl J Med 1993;320:618). Methods: Patients in this trial were treated with tissue plasminogen activator (t-PA) for AMI. Blood samples were drawn upon presentation, and then 50 minutes, 5 hours, and 22 hours after t-PA. All samples have been generated at 70°C by the National Heart Lung Blood Institute. FFAu measurements and partial data analysis has been completed on 458 patients (75 F, 383 M). Measurements were done at 22°C using the ADIFABP (Richen et al, J Biol Chem 1996;271:11259) fluorescent probe of FFAu (hepatic controls ±0.6 ±0.6 mmol/L). Results: FFAu values for the TIMI patients ranged from 2 to 5000 nmol/L. Average values and standard deviations for each of the 4 blood draws from time of admission to 8 hours were: 13 ±7, 22 ±5, 11 ±3, and 10 ±1 (nmol/L). These results indicate, relative to the control population, an approximately 4 fold increase upon admission, a further 2 fold increase following t-PA with a gradual decrease within 5 hours of t-PA. Using a 5 nmol/L cutoff, the predicted sensitivity for detection of AMI was 91% using samples at time of admission and 98% using time of admission and the 50 minute sample. Only 19% of patients had elevated levels of cardiac creatine kinase on admission. Specificity was estimated as 93% by comparison with a distribution that includes healthy individuals plus patients with non cardiovascular diseases. FFAu values for samples drawn at presentation were found to be highly (p<0.025) correlated with mortality; an increase of 4 fold in mortality rate is predicted from lowest to highest FFAu levels. Conclusions: These data indicate that levels of FFAu are: 1) a sensitive indicator of ischemia in AMI, 2) elevated well before markers of cardiac necrosis, 3) an indicator of reperfusion therapy, and 4) a predictor of mortality in these patients.

4:30 p.m.

836-3

A Cardioprotective Agent, JTV519, Inhibits Apoptotic Cell Death of Postischemic Reperfused Myocardium Through a PKC-Mediated ERK Activation

Hiroyuki TakamagD, Yasuki Kihara, Koichi Inagaki, Takeshi Yoneda, Department of Cardiovascular Medicine, Kyoto University, Kyoto, Japan.

Objective: JTV519, a 1,4-benzothiazepine derivative, confers cardioprotective effects on the post-ischemic, reperfused myocardium through a specific activation of the 5-isozyme of protein kinase C (PKC) (Inagaki et al., Circulation, 2000). In this study, we further tested the hypothesis whether the downstream of JTV519 activation may link to its inhibitory effects on the apoptotic cell death. Methods: Hearts were isolated from male SD rats (n=7, for each group), and were coronary-berfused in a Langendodf setup at a constant coronary flow for 5 min, and then subjected to a 30-min global ischemia and the subsequent 60-min reperfusion period. Both the heart and cell preparations were subjected to TUNEL staining, to assess the effects on the apoptotic cell death. Results: Methods: Heart rates of the STAT 6 knockout (KO) mice were lower compared to wild-type (WT) mice at baseline and at 15 min of reperfusion (15R). Knockout mouse hearts displayed significantly better (p<0.05) post-ischemic ventricular recovery as evidence by higher left ventricular pressure (LVP), peak left ventricular end diastolic pressure (LVEDP) and left ventricular end systolic pressure (LVESP) in WT compared to KO mice at 15R (15R: 75.2±1.4 (WT) vs. 82.2±2.2 (KO); 30R: 71.8±1.4 (WT) vs. 77.8±2.1 (KO); higher dp/ dtmax (mm Hg/sec): BL: 4515±87 (WT) vs. 5085±120; 15R:3807±130 (WT) vs. 4282±134 (KO); 30R: 392±131 (WT) vs. 426±133 (KO). Infarct size determined by TTC staining was lower in STAT 6 KO mouse hearts (41±1.6%) compared to those for the WT mice (48±6.2%). Conclusion: The results of this study demonstrate that hearts of STAT 6 knockout mice are resistant to ischemia/reperfusion injury suggesting a role of STAT 6 gene in the mediation of cardiac injury.

5:00 p.m.

836-4

Glucagon-Like Peptide-1 (GLP-1) Limits Myocardial Stenosis Following Acute Coronary Occlusion and Reperfusion in Conscious Canines

Laarrca A. Nikiforakis, Teresa Hentosa, Aaron Doversap, Rhonda Huebin, Lee Zoureas, Carol Stolarci, Darilsh Elahi, Richard P. Shannon, Allegheny General Hospital, Pittsburgh, Pennsylvania, Massachusetts General Hospital, Boston, Massachusetts.

Background: Myocardial ischemia is associated with increased glucose utilization. Glucose insulin K+ infusion has been shown to improve outcomes. We hypothesized that the insulin-sensitizing peptide GLP-1 facilitates recovery of post-ischemic contractile dysfunction (stunning). Methods: We studied 13 conscious dogs, instrumented with LV pressure gauges, aortic and coronary flow (CFB) probes, piezoelectric crystals to measure regional systolic wall thickening (WT) and a hydraulic coronary artery occluder. All dogs underwent a 10 min coronary occlusion (CAO) followed by reperfusion (CAR). Five dogs received a 24-hr infusion of GLP-1 (1.5 pmol/kg/min) initiated 1 min prior to CAR; 8 dogs received placebo. We obtained serial recordings for the first 3 hrs and at 24-hr post-CAR. Results: Hemodynamic responses and global LV function during CAO and CAR were similar in the two groups. Baseline regional WTs (2.6±0.3mm; and initial hyperemic responses were similar. Despite comparable changes in CFB, GLP-1 treated dogs demonstrated significantly (p<0.01) less post-ischemic contractile dysfunction. The salutary effects of GLP-1 were sustained for 24 hrs.

5:15 p.m.

836-5

Cardiac Serum Marker Release After Percutaneous Transluminal Septal Myocardial Ablation: A Human Model


Background: Multiple cardiac serum markers are available for determining myocardial cell death, but the comparative kinetics of these markers in humans have not yet been fully described due to the inability to precisely correlate symptom onset with vessel closure. Percutaneous transluminal septal myocardial ablation (PTMSA) for hypertrophic obstructive cardiomyopathy permits a unique opportunity to identify the time of vessel closure in a series of patients experiencing a MI and compare the course of cardiac serum marker elevation. Methods: We obtained blood samples every 2 hrs for 48 hrs from 11 pts after PTMSA and measured the serum levels of the following: troponin-I (0.0-2.0 ng/ml), high sensitive troponin-I (0.0-0.4 ng/ml), myoglobin (0-30 mg/L), cardiac troponin-T (0.0-0.1 ng/ml). Results: Mean marker values are displayed in the figure below. In all patients studied, all markers were elevated above normal by 2 hrs after vessel closure. Mean peak measure-