1145-104  Green Tea Inhibits Stat1 Activation and Reduces Apoptosis in Cardiac Myocytes Exposed to Ischemia/Reperfusion Injury

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Background: We have previously reported that the transcription factor Stat-1 is activated following IR and is also a modulator of apoptotic cell death in cardiac myocytes. Recently green tea (GT) has been shown to have antioxidant properties and also to reduce the expression of Stat-1 in non-cardiac cells. In the present study, we have assessed the role of GT as a cardioprotective agent in cultured cardiac myocytes exposed to simulated IR.

Methods: Primary rat neonatal cardiac myocytes were pretreated with GT (50µg/ml) and either left under normoxic condition or exposed to simulated IR by an ischemic chamber for 4 hours followed by 16 hrs of reoxygenation to simulate reperfusion. Western blotting and immunofluorescence studies were performed with specific phospho-antibodies against STAT1 Tyr701 and STAT1 Ser727. Results: Cardiac myocytes pre-treated with GT reduced the level of apoptotic cell death following simulated IR injury from 37% (IR) to 17% (GT plus IR). Western blot analysis demonstrated that GT also reduced the level of phosphorylated STAT1-Tyr701 and STAT1-Ser727 in cardiac myocytes exposed to simulated IR. Finally, treatment with GT also reduced the expression of FAS-l and FAS receptor in cardiac myocytes.

Conclusion: Our data demonstrates that GT is able to protect cardiac myocytes from apoptosis following simulated IR injury, which may in part be acting by preventing the activation and nuclear translocation of Stat-1. Hence, GT may have a therapeutic role in modulating pro-apoptotic Stat-1-target genes.

1145-105  Bag-1 Relocates Within Cardiac Myocytes Following Ischemia/Reperfusion and Prevents Myocyte Apoptosis by Interaction With Hsc70

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Background: Bag-1 is a family of proteins, which promotes cell survival and modulates chaperone activity by interacting with a wide range of cellular targets. Here we examined the level of protein expression and the subcellular distribution of Bag-1 both in cultured myocytes and the isolated rat heart, as well as its potential cardioprotective role during ischemia/reperfusion (IR) injury.

Methods and Results: By immunocytochemistry, in tissue sections from control hearts, Bag-1 positive staining was seen in the nuclei of the majority of myocytes (63±6%). In only 2±4% of control myocytes cytoplasmic staining was observed. Conversely, in rat hearts exposed to 35 mins I and 120 mins R, nuclear staining for Bag-1 was reduced (10±2.3%) with a corresponding increase in cytoplasmic staining. In rat hearts exposed to I/R, Bag-1 positive staining was observed. Moreover, in rat hearts exposed to 35 mins I/R, Bag-1 positive staining was seen in the nuclei of the majority of myocytes (57±6%). In only 2±4% of myocytes cytoplasmic staining was observed. Conversely, in rat hearts exposed to 35 mins I/R, Bag-1 positive staining was observed. Moreover, in rat hearts exposed to I/R, Bag-1 positive staining was seen in the nuclei of the majority of myocytes (57±6%). In only 2±4% of myocytes cytoplasmic staining was observed. Furthermore, protection is dependent upon association with Hsc70.

Discussion: Since western blot analysis of rat hearts exposed to IR did not detect any Bag-1 induction, the above finding suggests that Bag-1 can actively relocate from the nucleus to the cytoplasm upon IR. Similar results were observed by western blotting analysis of subcellular fractions from cultured myocytes and the intact heart. Overexpression of human Bag-1 in primary cultures of neonatal cardiac myocytes, exposed to 4 hours of simulated I followed by 16 hours of R, significantly reduced the percentage of TUNEL positive myocytes from 37±5% to 2±4.3% (p<0.001). Moreover, in both cultured myocytes and the intact heart following IR, Bag-1 co-immunoprecipitated with Hsc70. Finally, overexpression of a Bag-1 dominant negative, lacking the C-terminal Bag domain, which is critical for the interaction with the 70 kDa heat shock proteins HSC70 and HSP70, failed to ameliorate myocyte apoptosis induced by simulated IR. Conclusions: We conclude, therefore, that Bag-1 is a cardioprotective protein and that IR induces Bag-1 intracellular relocation. Furthermore, protection is dependent upon association with Hsc70.

POSTER SESSION

1146  In-Hospital Complications of Acute Coronary Syndromes

Tuesday, April 01, 2003, 9:00 a.m.-11:00 a.m.
McCormick Place, Hall A
Presentation Hour: 9:00 a.m.-10:00 a.m.

1146-105  Management and Outcomes of Patients with Acute Coronary Syndromes and Gastrointestinal Bleeding

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Background: Potentially lethal antithrombotic agents along with early revascularization are increasingly used in patients hospitalized with acute coronary syndromes (ACS). An important adverse event associated with these therapies is gastrointestinal bleeding (GIB); yet, the optimal management and outcomes related to GIB in ACS patients are poorly studied.

Purpose/Methods: We retrospectively analyzed the diagnostic studies, pathological/clinical findings and survival associated with GIB in patients hospitalized with ACS at a tertiary center between 1996-2001.

Results: Three percent (88/3,043) of patients with ACS developed or had concurrent clinically significant GIB. In-hospital mortality was significantly higher in patients with versus without GIB (38% vs. 7%, p<0.001). Thirty percent underwent endoscopy during the index hospitalization with no associated complications of death, arrhythmia, urgent ischemia, or hemodynamic deterioration. Definitive GI diagnosis from endoscopy are shown in the table below.

Endoscopy N (%) 30 (38.5%)
Gastritis N (%) 7 (9%)
Pectic ulcer disease N (%) 7 (9%)
Polyps N (%) 6 (7.7%)
Neoplasm N (%) 6 (7.7%)
Diverticulosis N (%) 4 (5.1%)
AVM N (%) 1 (1.3%)
Malory Weiss Tear N (%) 1 (1.3%)
Esophagitis N (%) 1 (1.3%)

Conclusion: GIB is a rare complication following ACS associated with increased inhospital mortality. Endoscopy may be safely performed during the ACS hospitalization and confrms diagnosis of GI malignancy in 7.7% of patients.

1146-106  Major Bleeding Incidence After Coronary Artery Bypass Grafting in Patients With Unstable Angina/Non-ST Elevation Myocardial Infarction-Based on Coronary Artery Bypass Graft Timing in TACTICS-TIMI 18

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Background: Observational studies report an association between major bleeding rates after coronary artery bypass grafting (CABG) and timing of antithrombotic therapy post-CABG. In 1 non-randomized study, pts having CABG <5d of the last dose of clopidogrel had a 2-10 fold higher major bleeding rate compared to pts not receiving it. In contrast, a comparison of similar pts in the GUSTO trial found higher transfusion rate and no difference in TIMI major bleeding post-CABG. We hypothesized that the difference in bleeding seen in observational studies (and attributed to only 1 factor, clopidogrel ) might be explained by other factors such as pt characteristics, CABG timing, and other treatments.

Methods: In TACTICS-TIMI 18, 2220 pts with unstable angina/non-ST MI (UANISTEMI) were treated with aspirin, heparin and fibrinol for 48 hours (clopidogrel reserved for post-establ in all but 5 patients). We evaluated associations of major bleeding and stroke in relation to CABG timing. Results: Factors related to increased bleeding in addition to those below, were: history of diabetes, MI, aspirin, PCI, CABG, stable angina, PVD, and current tienilic acid. TIMI definition and study.

Characteristics

CABG <5d    CABG >5d during preop

N=222     N=128

Age

64±11       62±8.5

Male

74%          73%

3 vessel disease

66%          64%

Left main

29%          16%

ASA stopped ≤5 days preop

0%          32%

IABP

7.7%         9.9%

Death

3.6%         3.1%

Stroke

2.3%         0.8%

MI

5.4%         6.2%

Major bleeding

21%          5.5%

30-day post-CABG death, MI, or stroke rates did not differ among groups, but there was a significantly higher rate of major bleeding in pts sent for CABG ≤5d (P<0.001). By multivariate analysis, major bleed risk in CABG ≤5d remained higher after correcting for baseline differences(OR=4.4, 95% CI 1.6-12.1, P<0.004).

Conclusion: 1) in UANISTEMI, CABG performed ≤5d has a 4 fold major bleeding rate compared to CABG performed >5d. 2) Major bleeding is also dependent on disease severity, antithrombotic therapy, other procedures. 3)Caution is required in interpreting observational studies that attribute associations (eg higher bleeding) to any 1 factor.