TARGET: Do Tirofiban And ReoPro Give Similar Efficacy Trial?

There is considerable debate about the choice of intravenous platelet glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention, after a meta-analysis of 7 trials and 16,771 patients has shown a 38% reduction in death or non-fatal MI 30 days after the index procedure. At 149 hospitals in 18 countries throughout North America, Europe and Australia, 4810 patients were randomized between 12/30/99 and 8/25/00 and treated with either tirofiban or abciximab on a double-blind, double dummy basis. Clopidogrel and aspirin were administered pre-procedurally, along with a 70 U/kg intravenous heparin bolus. The dose of tirofiban was 10 mcg/kg/min infusion for 18–24 hr; for abciximab it was 0.25 mcg/kg bolus and 125 mcg/kg/min infusion. Patients qualified by history and anatomy for “intent-to-stent” lesions addressed by percutaneous revascularization, and were not with evolving ST-elevation MI or with serum creatinine >2.5 mg/dl. The primary endpoint is 30 day or non-fatal MI and the trial has 90% power to determine non-inferiority for tirofiban with an expected event rate in the control (abciximab) group of 5.3% based on the primary endpoint data will be presented along with the key subgroups such as diabetic. Follow-up data for the trial to 1 year will also be performed.

Late Breaking Science: Linking Genes to Function in the Heart and Vasculature

BASIC ABSTRACTS

Exogenous Hematopoietic Stem Cells Can Regenerate Infarcted Myocardium

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To determine whether hematopoietic stem cells (HSC) can transform into cardiomyocytes with the potential to repair dead myocardium after infarction, Lin~+c-kit~+ HSC were harvested from transgenic mice expressing green fluorescent protein (GFP) and injected in the region bordering the infarct, 3–5 hours after coronary artery occlusion in mice. A band of completely packed cells was identified at 17 days and at 60 days in nearly 50% of hearts. Between the endocardial and epicardial surface of the infarcted ventricle. This band occupied 50% of the damaged portion of the wall. c-kit/GFP positive HSC were found in the infarcted area shortly after coronary ligation and were still detectable at 7 days, c-kit stained HSC were not labeled by marker antibodies to myogenic, ~sarcocin actin and myosin, endothelial cells, factor VIII, and smooth muscle cells, smooth muscle actin. The band of tissue included in the infarcted zone was constituted 75% by GFP, ~sarcrocin actin, myosin and ~actin positive cardiac muscle cells. Other GFP-positive cell populations were endothelial cells and smooth muscle cells, organized in nascent capillary structures and arterioles. Preexisting myocytes were partially aligned myofibrils and resembled late fetal-neonatal cells. GFP-positive replicating myocytes, endothelial cells and smooth muscle cells were c-kit negative. Infarcted mice were injected with BrdU, once a day for 4 days, to establish the % of cell proliferation in the regenerating myocardium. 28% myocytes, 17% endothelial cells and 12% smooth muscle cells were BrdU positive. These three levels of BrdU labeling were statistically different. Additionally, the percentages of positive cells to BrdU were measured to evaluate the fraction of cycling cells at this stage of repair: 18% myocytes, 10% endothelial cells and 8% smooth muscle cells were in G1-,G2-M. In conclusion, HSC, when injected in the heart, rapidly differentiate into myocytes resulting in significant recovery of muscle mass after infarction.

Mutations in the β1α Regulatory Subunit of Protein Kinase A Cause Familial Cardiac Myxomas

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Cardiac myxomas arise from primitive pluripotent mesenchymal cells within the subendocardium. In autosomal dominant Carney complex, intracardiac myxomas develop in the setting of familial cardiac myxomas and Carney complex. Here we report the screening of β1α-sarcoglycan causing an amino acid change from a polar (serine) to nonpolar amino acid (alanine) altering the protein secondary structure. In 2 of the 50 sporadic cases, a 3bp deletion in exon 9, which deletes lysine at position 236, occurred. Neither the missense mutation nor deletion mutation was seen in 200 control patients. Immunohistochemistry demonstrated significant reduction of β-sarcoglycan. Conclusion: Mutation of the β-sarcoglycan gene causes autosomal dominant FDCM. As mutations of this gene are also known to cause the Syrian hamster cardiac myxoma as well as human germ line muscular dystrophy, it appears that mutations in this gene place patients at risk for a spectrum of clinical features ranging from cardiomyopathy to skeletal myopathy. This is similar to other DAPC members and dystrophin itself, supporting our current pathology hypothesis which suggests that DCM results from disruption of the cytoskeleton/sarcosome, not sole cardiac myxoma.

Dual Modulation of Cell Survival and Cell Death by β2-Adrenergic Gi and Gs Signaling in Adult Mouse Cardiomyocytes

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Cardiac β2-AR activates both Gi and Gs proteins whereas β1-AR couples only to Gi. The goal of this study is to determine whether β1-AR and β2-AR differ in regulating cardiomyocyte survival and apoptosis, if so, to explore underlying mechanisms. To avoid complicated crosstalks between β-AR subtypes, we express β1-AR or β2-AR individually in the null background. We find that β1-AR and β2-AR differ in regulating cardiomyocyte survival and apoptosis. Using adult mouse myocyte culture and adenovirus gene transfer techniques. Stimulation of β2-AR when β2-AR-coupled Gi, Gi with pertussis toxin, scavenging Gb from β2-AR signaling from survival to apoptotic. Thus, β2-AR, markedly induces myocyte apoptosis, as indicated by increased TUNEL or Hoechst staining positive cells and DNA fragmentation. Inhibition Gi signaling with pertussis toxin converts β2-AR to β1-AR in terms of its apoptotic effect, suggesting that Gi is essential for β2-AR-mediated survival effects. To explore the downstream signaling events of β2-AR-coupled Gi, we first examined the possible involvement of p38 MAPK, since recent studies propose that p38 MAPK underlies Gi-dependent anti-apoptotic effects. We found that although stimulation of either β1-AR subtype increases p38 MAPK activity, this effect is insensitive to PTX, excluding a role of p38 MAPK in β2-AR-mediated cell-survival. In contrast, β2-AR (but not β1-AR) elevates the activity of Akt, a powerful survival signal, this effect is fully abolished by inhibiting Gi with pertussis toxin, scavenging Gs with sARL1, or blocking β2-AR with LY294002, indicating that β2-AR activates Akt via Gi2/3-Pi3K pathway. Most importantly, inhibition of the Gi2/3-Pi3K-Akt pathway converts β2-AR signaling from survival to apoptotic. Thus, β2-AR, unlike β1-AR, activates concurrent apoptotic and survival signals in cardiomyocytes, and the survival effect is mediated by the Gi2/3-Pi3K-Akt pathway. The strikingly different effects of β-AR subtypes on cardiac cell survival and apoptosis may have important pathophysiological and therapeutic implications in chronic heart failure.

Functional Proteomic Analysis of Protein Kinase C ε Signaling Complexes in Preconditioning.

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Studies from our laboratory and others have shown that transgenic (Tg) mice expressing low levels of active protein kinase C ε (PKCε) exhibit resistance to ischemic injury, a cardiopro-
Functional Proteomic Analysis of Protein Kinase Cε Signaling Complexes in Preconditioning.
Peipei Ping, Jun Zhang and Roberto Bolli

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