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 16,770 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 10 100 mcg/kg bolus and 0.125 mcg/kg/min infusion. Patients qualified by having suitable anatomy for “intent-to-treat” 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 death or non-fatal MI and the trial has 85% power to determine non-inferiority for the EPITENT trial. The primary endpoint data will be presented along with the key subgroups such as diabetics. 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**

Donald Orlic, Jan Kajstura, Stefano Chimenti, Baozhong Li, Stacie Anderson, David Bodine, James Pickel, Annarosa Cherfils-Gilberti, Piero Anversa, New York Medical College, Valhalla, NY, NIH/NHLBI, Bethesda, MD

To determine whether hematopoietic stem cells (HSC) can transform into cardiomyocytes with the potential to repair dead myocardium after infarction, Lin-Kit48 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 closely packed cells was identified at 17 days after ischemia in nearly 50% of hearts between the endocardial and epicardial surface of the injured ventricle. These cells 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 labelled by markers for myocytes, α-smooth muscle actin and myosin, endothelial cells, factor VIII, and smooth muscle cells, smooth muscle actin. The band of tissue included in the infarcted zone was similar to GFP, α-smooth muscle actin, myosin and α-actin positive cardiac muscle cells. Other GFP-positive cell populations were endothelial cells and smooth muscle cells, organized in nascent capillary structures and arterioles. Preulating 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 extent 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 to total β2-AR 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/G0. In conclusion, HSC, when injected in the heart, rapidly differentiate into myocytes resulting in significant recovery of muscle mass after infarction.

**Mutations in the R1α Regulatory Subunit of Protein Kinase A Cause Familial Cardiac Myxomas**

Carl J. Vaughan, Minaire Casey, Je He, Cathy Hatcher, Jordan M. Winter, Stanislawa Wiercinsowic, Kate Montgomery, Raja Kucherlapati, Cynthia C. Morton, and Craig T. Basson, Cardiology Division, Dept. of Medicine, Weill Medical College of Cornell University, New York, NY

Cardiac myxomas arise from primitive pluripotent mesenchymal cells within the subendocardium. In autosomal dominant Carney complex, intracardiac myxomas develop in the setting of lentigines and endocrinopathy. We previously localized the Carney complex gene defect to human chromosome 17q24. We now demonstrate that mutations in the chromosome 17-encoding gene are associated with myxomas in both familial and sporadic cases. Cardiac myxomas are the most common form of FDCM, although X-linked disease is also well described. Two genes have been identified for the X-linked forms (dystrophin and tafazzin), whereas three genes have been identified in autosomal dominant FDCM (actin, lamin A/C, desmin). We have hypothesized that DCM is a disease of the cytoskeleton and sarcopolasmia and have focused our studies on cardiac myxomas whose products are found in these structures. Here we report the screening of α-sarcoglycan, a member of the dystrophin-associated protein complex (DAPC). Methods: Blood was drawn and DNA extracted from one 4-generation family and 50 sporadic cases of DCM after informed consent. Myocardial samples were obtained after transplantation or autopsy. The α-sarcoglycan gene was screened for mutations using single strand conformation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE) and DNA sequencing. Protein structural analysis and immunohistochemistry were performed. Results: Mutation analysis of the FDCM pedigree identified a single nucleotide change in exon 8 of the α-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 α-sarcoglycan staining. Conclusions: Mutation of the α-sarcoglycan gene causes autosomal dominant FDCM. As mutations of this gene are also known to cause the Syrian hamster cardiac myopathy as well as human limb girdle 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 DCM patients and dystrophin itself, supporting our final common pathway hypothesis which suggests that DCM is a disease of the cytoskeleton/sarcolemma.

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

Wei-Zhong Zhu, Ming Zheng, Brian Kobikia, Rui-Ping Xiao, Laboratory of Cardiovacular Science, GRG, MA, NIH, Baltimore, NID 22124; Howard Hughes Medical Institute, Stanford Univ Med Cent, Stanford, CA 94305.

Cardiac β2-AR activates both Gi and Gi 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 using β1-2 double knockout mice. Using adult mouse myocyte culture and adenovirus gene transfer techniques. Stimulation of β1-AR, but not β2-AR, markedly induces myocyte apoptosis, as indicated by increased TUNEL and 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 cell survival. 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 β-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 Gβγ with JARK-1, or blocking β3 with LYS294022, indicating that β2-AR activates Akt via Gβγ-PISK pathway. Most importantly, inhibition of the Gβγ-PISK-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 Gβγ-PISK-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 Cε Signaling Complexes in Preconditioning.
Peipei Ping, Jun Zhang and Roberto Bolli

Circulation. 2000;102:2672
doi: 10.1161/01.CIR.102.21.2672-i

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/21/2672.11

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/