1046-157 Expression of Hypoxia-Inducible Factors and of Vascular Endothelial Growth Factor in Infants With Congenital Cardiac Defect

Qing Ma, Agnes Görlach, Kathrin Schumacher, Jaime F. Vazquez-Jimenez, John Hess, Götz von Bernuth, Marie-Christine Seghaye, German Heart Center Munich, TUM, Munich, Germany

Background: Hypoxia and mechanical stress could up-regulate mediators of angiogenesis such as VEGF in the myocardium of infants with congenital cardiac defect. This study was aimed to test this hypothesis.
Methods: Expression of VEGF-mRNA was detected by RT-PCR in the right atrial- and ventricular myocardium of infants with a cyanotic cardiac defect (tetralogy of Fallot (TOF)) (n=7) or with an acyanotic cardiac defect (ventricular septum defect (VSD)) (n=7). Levels of VEGF, and of its transcriptional activators HIF-1a and HIF-2a were measured by Western blot and their localization in the myocardium by immunocytochemistry. Levels of the activators of HIF-1a (phospho-Akt and MAP-kinases) were also measured by Western blot.
Results: VEGF-mRNA was expressed in both atrial and ventricular myocardium of all patients but VEGF levels tended to be higher in infants with TOF than in those with VSD (p=.09). Levels of HIF-1a and HIF-2a were also higher in the former (p=.03, p=.06) as were levels of phospho-p38 and phospho-Akt (p=.03; p=.02, respectively). In all patients, levels of HIF-1a and VEGF correlated inversely with preoperative arterial oxygen saturation (Spearman: -.64, p<.02; -.76 p<.004, respectively). HIF-1a was present in the nuclei of cardiomyocytes, and HIF-2a also in endothelial cells and macrophages. VEGF was found in the cytoplasm of cardiomyocytes and endothelial cells.
Conclusion: Our results suggest that in infants with congenital cardiac defect chronic hypoxemia leads to over-expression of HIF-1a and HIF-2a via the Akt- and MAP-kinase p38 signaling pathways. This is responsible for increased VEGF synthesis in cardiomyocytes and myocardial endothelial cells, and could regulate myocardial remodeling in this age group.

1046-158 Superoxide Dismutase Reduces Reoxygenation-Induced Cardiopulmonary Dysfunction in the Immature Heart

Jeffery M. Pearl, Connie J. Wagner, Jerri L. McNamara, Jodie Y. Duffy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background: Superoxide radicals and their interaction with nitric oxide (NO) during hypoxia and reoxygenation result in cellular damage and cardiac dysfunction. The hypothesis was that superoxide dismutase (SOD), a superoxide radical scavenger, could improve cardiac recovery after reoxygenation in a neonatal piglet model incorporating cardiopulmonary bypass (CPB).
Methods: Neonatal piglets underwent 90 min of hypoxia followed by 1 hr reoxygenation on CPB. Animals were maintained for 2 hr after reoxygenation. One group (n=6, SOD) received 15,000 units/kg/hr of SOD during hypoxia and reoxygenation. Control animals received saline (n=10). Nitric oxide levels were measured in exhaled air with chemiluminescent detection and systemically with in vivo NO-permeable probes. Peroxynitrite production was estimated by scoring intensity and localization of nitrotyrosine immunohistochemical staining in cardiac tissue.
Results: SOD administration reduced cardiac dysfunction associated with reoxygenation injury. Control LV +dP/dt decreased from a baseline mean of 1242 +/- 101 to 646 +/- 80 mm Hg/sec at 2 hr after reoxygenation (P<.05). SOD animals maintained ventricular systolic function at 944 +/- 30 mm Hg/sec after reoxygenation (P<.05 vs controls). RV +dP/dt was also maintained in SOD animals at 520 +/- 31 compared with controls at 281 +/- 11 mm Hg/sec (P<.05). Oxygen delivery 2 hr after reoxygenation was preserved in SOD animals (718 +/- 82 mL/min) compared with controls (452 +/- 62 mL/min; P<.05). The SOD group had higher systemic and exhaled NO levels than controls after hypoxia and 2 hr after reoxygenation (P<.05). Nitrotyrosine immunohistochemical scores from LV tissue collected 2 hr after reoxygenation were lower in animals receiving SOD (1.4 +/- .8) than controls (3.7 +/- .6; P<.05).
Conclusions: Administration of a superoxide scavenger during hypoxia and reoxygenation reduced cardiac dysfunction associated with reoxygenation injury and preserved systemic NO levels. Recovery of cardiac function might partially result from reducing the interaction of superoxide and NO to form peroxynitrite, a cytotoxic oxidant, as well as preserving beneficial NO levels.

1046-159 Left Atrioventricular Valve Function Following Repair of Atrioventricular Septal Defects: A 22-Year Experience

Christopher B. Mahnke, Janine E. Janosky, Frank A. Pigula, Ralph D. Siewers, Prapti Kanani, Children's Hospital of Pittsburgh, Pittsburgh, PA

Background: Left atrioventricular valve (LAVV) function is crucial for long-term clinical success following repair of atrioventricular septal defects (AVSD). We reviewed our experience with AVSD repair to identify predictors of poor post-operative LAVV function.
Methods: A retrospective chart review was performed on all patients who underwent biventricular repair of complete and partial AVSD at our institution from 1980-2001. Anatomic, hemodynamic, and surgical variables were correlated with post-operative LAVV function and repeat LAVV surgery.
Results: Two-hundred seventy patients underwent AVSD repair during the study period. There were 24 peri-operative deaths. Long-term outcome data was available for 220 patients (109 complete AVSD, 111 partial AVSD). Twenty-seven survivors required repeat LAVV surgery (12.3%; 24 for LAVV regurgitation) with no deaths. Absence of Down syndrome, abnormal papillary muscles, and moderate/severe pre-operative or immediate post-operative LAVV regurgitation were each associated with repeat LAVV surgery (p<0.05). In addition, repeat LAVV surgery was more common in patients with partial AVSD (p=0.077) and unbalanced AVSD with small LV (p=0.064). In the 24 patients requiring repeat surgery for LAVV regurgitation, repair of the LAVV was accomplished in 14 (58%). Successful LAVV repair (versus replacement) was more common in patients with Down syndrome (Down syndrome 7/8, non-Down 7/16; p=0.08). For most patients, the degree of LAVV regurgitation remained stable over time. Progression to severe LAVV regurgitation was rare (24 patients; 1.4% per pt yr) and usually developed within the first 5 post-operative years (19/24, 79%). LAVV stenosis occurred in 3.6% of survivors, and was associated with unbalanced AVSD and papillary muscle abnormalities.
Conclusion: Following AVSD repair, LAVV regurgitation requiring repeat surgical intervention was associated with the absence of Down syndrome, abnormal papillary muscles, partial AVSD, unbalanced AVSD with small LV, and moderate/severe pre-operative or immediate post-operative LAVV regurgitation. Progression to severe LAVV regurgitation over time was rare.

1046-160 Anomalous Origin of the Left Coronary Artery From the Pulmonary Trunk: A 25-Year Single Institution Outcome Study Following Surgical Restoration of Dual Coronary Antegrade Flows

Subash C. Reddy, Gerard A. Boyle, Steven A. Webber, Sang C. Park, Lee B. Beerman, William H. Neches, Children's Hospital of Pittsburgh, Pittsburgh, PA

Background: Our group demonstrated surgical feasibility of coronary translocation in patients (pts) with anomalous origin of left coronary artery from pulmonary trunk (ALCAPA). We report our surgical results and long-term follow-up in these pts. **Methods:** Records of pts with ALCAPA and surgery between 1976-2000 were reviewed. Symptoms, left ventricular (LV) dimensions, mitral regurgitation (MR), hemodynamics, and type of repair were correlated with the immediate outcome (alive vs. dead). In the survivors we reviewed time course of improvement in LV function and MR, re-operations, exercise capacity, residual ischemia, clinical arrhythmias, sudden cardiac death, and length of follow-up. **Results:** There were 23 pts with ALCAPA and surgery. Mean age at presentation was 9.7 months. Presenting features were congestive cardiac failure in 16, MR in 16 and dilated LV with reduced shortening fraction in 20. Operations included coronary translocation in 19, and Tekeuchi in 4. There were 3 postoperative deaths. Increased LV end diastolic dimension (LVEDD) and severe MR predicted an adverse outcome (P=<0.05). The 20 survivors were followed for a mean of 91 (13 to 229) months. On serial echo evaluations the mean time period for reduction in the LVEDD and decrease in MR was 3 months, and for recovery of LV systolic function was 6 months. There were no resting LV regional wall motion abnormalities or aneurysms. Eleven pts demonstrated normal exercise capacity and no inducible ischemia on exercise testing. There were no clinically significant arrhythmias or sudden deaths, and all survivors were in NYHA functional class I at latest follow-up. All pts with Tekeuchi repair underwent reoperation between 2-14 years for supravalvular stenosis. **Conclusions:** There was an excellent outcome following surgery (87% survivors). Increased LVEDD and severe MR predicted adverse outcome. There was early recovery in LV function. All had good functional capacity and no residual ischemia, arrhythmias, or sudden deaths at long-term follow-up. Direct coronary artery translocation was superior to Tekeuchi repair.

1046-161 Oxidant Stress and Pulmonary Hypertension in Congenital Heart Surgery

Karrie L. Dyer, Rick Barr, Marshall Summar, Gary Cunningham, Thomas P. Doyle, Thomas P. Graham, Brian W. Christman, Vanderbilt University Medical Center, Nashville, TN

Background: Pulmonary hypertension (PHT) is a potentially severe complication of congenital heart surgery. Cardiopulmonary bypass (CPB) may impair endothelial function through ischemia reperfusion injury, which is mediated by oxygen radical activity. Isoprostanes are chemically stable products of arachadonic acid generated from free radical activity and thus serve as markers of oxidant stress. Pulmonary vascular tone is regulated by endothelial secretion of vasoactive substances such as nitric oxide; plasma nitric oxide (NO) metabolites therefore reflect endothelial function. In this study, isoprostane excretion is measured among infants undergoing CPB and correlated with clinical measures of pulmonary hypertension as well as plasma NO metabolites.
Methods: Isoprostane levels were measured in 41 infants preop, immediately postop, 12 , 24 and 48 hours postop. Isoprostane metabolites were quantified using stable isotope diluation methods in conjunction with gas chromatography/mass spectrometry and were normalized to creatinine. NO metabolites were measured in plasma collected at the same time points. Pulmonary artery (PA) pressures were measured directly in a subset of patients with indwelling PA lines. PHT was defined by mean PA pressure greater than 20mm Hg or greater than 50% systemic or the clinical requirement for NO.
Results: Peak isoprostane excretion occured immediately postop and returned to baseline by 48 hours. Mean isoprostane levels among all 41 patients increased by greater then 200% from pre to post-CPB (2.9 +/-1.9 ng/mg to 6.7+/-5.7ng/mg, p=.0001). Among patients with PHT (n=15), mean isoprostane excretion increased by over 300% from pre to postop (2.5 +/-2.2 ng/mg to 8.0 +/-7.6 ng/mg, p=.01). Concurrently, NO metabolites decreased from 7.4 +/-7.6 mcg to 2.4 +/- 1.4 mcg from pre to postop among all 41 patients (p=.0005) .
Conclusions: Oxidant stress is increased following CPB among infants with congenital heart disease. Patients with PHT demonstrated a more prominent increase in isoprostane excretion. The concurrent decrease in NO metabolites with peak isoprostane excretion suggests that oxidant stress may alter endothelial production of endogenous vasodilators.