(estimated glomerular filtration rate < 60 ml/min/1.73 m2) although not ascribed to be a cause of dyspnea, occured in 50.0% of those with elevated BNP values ≥ 500 pg/ml.
Conclusion: Markedly elevated BNP values in the absense of CHF are rare. When they occur, they tend to reflect conditions increasing RV and LV wall tension with superimposed volume overload due to chronic kidney disease.

5:00 p.m.

828FO-5 Myocardial Production of C-Type Natriuretic Peptide in Chronic Heart Failure

Paul R. Kalra, Jonathan R. Clague, Aidan P. Bolger, Philip A. Poole-Wilson, Allan D. Struthers, Andrew J. Coats, National Heart Lung Institute, London, United Kingdom, Clinical Pharmacology and Therapeutics, Dundee, United Kingdom

Background: C-type natriuretic peptide (CNP) is a vasodilator produced by the vascular endothelium. It shares structural and physiological properties with the cardiac hormones atrial and brain natriuretic peptide (BNP), but little is known regarding its pathophysiological role in chronic heart failure (CHF). We assessed the hypothesis that CNP is produced by the heart in patients with CHF.
Methods: Myocardial CNP production was determined (difference in plasma levels between the aortic root and coronary sinus) in 9 patients undergoing right and left heart catheterisation as part of their CHF assessment (all male, age 59±9y; New York Heart Association class 2.2±0.1, LV ejection fraction 29±5%, mean±SEM). BNP, established as originating from myocardium, was assessed from the same samples as a positive control. Analyses were performed using a standard competitive radioimmunoassay kit (Peninsula Laboratories, Bachem Ltd. UK).
Results: A step-up (29%) in plasma CNP concentration was found from the aorta to the coronary sinus (3.55±1.53 versus 4.59±1.54 pg/mL, p=0.035). The mean increase in CNP was 0.90±0.35 pg/mL (range 0.05 to 2.80 pg/mL). BNP levels increased by 57% from aorta to coronary sinus (86.0±20.5 versus 135.0±42.2 pg/mL, p=0.01). Coronary sinus CNP levels correlated with mean pulmonary capillary wedge pressure (r=0.82, p=0.007).
Conclusions: We have shown that CNP is produced by the heart in patients with chronic heart failure. Whilst further evaluation is required to define its full pathophysiological role in this condition, CNP may represent an important new local autocrine and/or endocrine mediator in the heart.

5:15 p.m.

828FO-6 Ventricular Endocrine and Wall Motion Function in Acute Myocardial Infarction

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Aim: To investigate ventricular endocrine function in patients with coronary artery disease during acute myocardial infarction (MI).
Methods: We studied 45 patients with acute MI ; 13 anterior (age 57± 12 years) and 32 inferior (age 58± 12 years). Atrial (ANP) and brain (BNP) natriuretic peptides were measured on admission and on day 7 after thrombolysis. No patient was in heart failure, had additional valve disease or developed serious arrhythmia during the study period.
Results: ANP increased from 13.7± 12.7 on day one to 22.4± 14.0 pmol/L (NS) on day 7 in anterior MI, and from 5.9± 4.6 to 16.2± 10.6 pmol/L (p<0.001) in inferior MI. BNP increased from 15.4± 26.1 to 61.7± 54.3 pmol/L (p<0.02) in anterior MI and from 8.5± 10.3 to 51.4± 52.4 pmol/L (p<0.001) in inferior MI. ANP and BNP levels correlated with left free wall long axis excursion in anterior MI (both r= -0.8, p<0.001). Whereas only BNP correlated with the anterior wall excursion in inferior MI (r= -0.5, p<0.005). There was no significant difference in peak CK level or fractional shortening between the two groups.
Conclusion: Acute MI is associated with a delayed rise in ANP and BNP in a pattern unrelated to the extent of myocardial damage. This rise is related to the severity of adjacent segmental systolic dysfunction, thus suggesting either a compensatory mechanism for the myocardial loss or an ongoing remodeling process.

ORAL CONTRIBUTIONS

830 Mechanisms of Vascular Injury and Healing

Monday, March 31, 2003, 4:00 p.m.-5:30 p.m.
McCormick Place, Room S404

4:00 p.m.

830-1 Genetic Background Is a Major Determinant of Arteriogenesis After Femoral Artery Ligation in Inbred Mice

Armin Helisch, Shawn Wagner, Ulrike Brandt, Matthias Heil, Tibor Ziegelhoeffer, Georg Bachmann, Wolfgang Schaper, Max-Planck-Institute for Physiol. & Clinical Research, Bad Nauheim, Germany, Kerckhoff-Klinik, Bad Nauheim, Germany

Background: This study was performed to define the differences that may affect the recovery of the collateral-dependent hindlimb perfusion after arterial occlusion in inbred strains of mice.
Methods: We ligated the right femoral artery (FA) of C57BL/6 (n=15) and BALB/c (n=15) mice. Perfusion was assessed by laser Doppler imaging (LDI) and calf blood flow by MRI (MRflow) on days 0, 3, 7, 14, and 28. MR angiography was performed in the 4^{h} week. Furthermore, BALB/c and C57BL/6 mice (n=5 per group) were fed with BrdU per drinking water starting one day prior to right FA ligation. After 7 days the left FA was also ligated and the animals were sacrificed. Postmortem angiograms were performed utilizing a bismuth-gelatin contrast agent. Arrival of contrast in the left FA distal to the acute ligation site was timed and distal filling quantified by x-ray. BrdU stained cells were identified on cross-sections of adductor muscles.
Results: BALB/c had more severe ischemia immediately after occlusion and the poorest recovery, as reflected by LDI and MR-inflow (p<0.05, all timepoints). Distal collateral-dependent filling on postmortem angiography immediately after FA ligation was observed in 4/4 C57BL/6 and 0/5 BALB/c mice. Angiographically, similar patterns of preexistent and grown collateral vessels were identified in both strains, however. C57 mice tended to have better formed interarterial collateral connections in the quadriceps 4 weeks after FA ligation. In C57 mice, BrdU uptake during the first week after FA occlusion was seen in all layers of growing collateral arterioles and in infiltrating surrounding cells but not in capillaries. Only in BALB/c capillary BrdU uptake was also observed in regions of focal perinecrotic cellular infiltrates. The proliferation index (BrdU positive cells/total vascular cells) in growing arterioles was higher in C57BL/6 (0.67) than in BALB/c (0.40, p < 0.05).
Conclusion: Collateral artery growth in mouse hindlimbs of C57BL/6 and BALB/c mice is independent of capillary proliferation. The improved recovery of C57BL/6 mice is associated with a better preformed collateral network, less acute ischemia, and an increased proliferation index in preexistent collateral arterioles.

4:15 p.m.

830-2 The Early Growth Response-1 (EGR-1) Gene Is Critical to Reperfusion Following Acute Vascular Obstruction: Results From a Knockout Mouse Ischemia Model

Paul Schaich, Ramaswamy Ramchandran, David Y. Kim, Gerald Patejunas, Mauricio A. Retuerto, Jeffrey D. Milbrandt, Ronald G. Crystal, Todd K. Rosengart, Evanston Northwestern Healthcare Research Institute, Evanston, IL, Weill Medical College of Cornell University, New York, NY

Background: Angiogenesis induced by growth factor upregulation has been implicated as an important biological response mechanism to acute vascular occlusion. The mechanism underlying this process is unclear, because tissues immediately surrounding vascular occlusion sites that are the locus of collateral vessel formation are typically not ischemic. The early growth response-1 gene (Egr-1) encodes for an immediate-early response transcription factor that is upregulated by changes in vascular strain, and which in turn upregulates the downstream expression of growth factors such as VEGF. We therefore hypothesize that Egr-1 may be an early messenger which translates post-ligation changes in vascular shear stress into growth factor upregulation and angiogenesis.
Methods: A hind limb ischemia model consisting of proximal and distal ligation and excision of the femoral artery was applied to 2-3 month old wild-type C57 BL/6 mice (n=10) or mice deficient in the Egr-1 gene ("knockout", n=5). Distal hind limb perfusion was serially assessed using laser Doppler perfusion imaging and expressed as an index of the mean perfusion in the ligated versus the non-ligated limb.
Results: The pre-ischemic perfusion index for both the Egr-1 knockout and control mice was 1.00 ± 0.03. Egr-1 knockout mice demonstrated a perfusion index immediately post-ligation of 0.15 ± 0.02, compared to a post-ligation value of 0.23 ± 0.02 in control animals (p = 0.008). All Egr-1 knockout mice developed necrosis of the ligated limb between 1 and 4 days after the procedure, but none of the control animals developed necrosis (p=0.001). The perfusion index failed to improve in knockout mice, while control mice demonstrated significant improvement from baseline in the perfusion index at day 4 (0.32 ± 0.04, p = 0.01) and day 35 post-ligation (0.77 ± 0.02, p=0.0001).
Conclusion: Mice lacking expression of the Egr-1 gene exhibit a profound deficit in vascular collateralization and reperfusion following acute peripheral arterial occlusion. These findings suggest that Egr-1 plays a pivotal role in vascular recovery in response to acute vascular occlusion, and could represent a potential target for therapeutic intervention.

4:30 p.m.

830-3 Constitutive Overexpression of Hypoxia Inducible Factor-1a/VP-16 Enhances the In Vitro Angiogenic/ Arteriogenic Effects of Mesenchymal Stromal Cells

Tim D. Kinnaird, Eugenio Stabile, Mary Susan Burnett, Yi Fu Zhou, Richard Baffour, Cheol Whan Lee, Shmuel Fuchs, Stephen E. Epstein, Cardiovascular Research Institute, Washington, DC

Background: We have recently demonstrated that mesenchymal stromal cells (MSCs) release a broad spectrum of angiogenic/arteriogenic cytokines and augment collateral response to ischemia. Constitutive over-expression of the hypoxia inducible factor-1a/ VP-16 construct in MSCs may enhance their therapeutic potential. Methods and Results: Murine MSCs were purified using double magnetic bead separation of cultured bone marrow. Flow cytometry confirmed absence of CD34, CD45, CD31 and CD117 surface markers, and the presence of SH2 and Sca-1 surface markers. MSCs were replated and transduced with Ad.HIF-1a/VP16 vector, exposed to normoxia or 1% O2 for 24 hours and conditioned media (CM) collected. Using ELISA, CM VEGF and bFGF levels were increased following HIF-1a/VP16 transduction (fig 1); a cytokine/viral dose-dependant