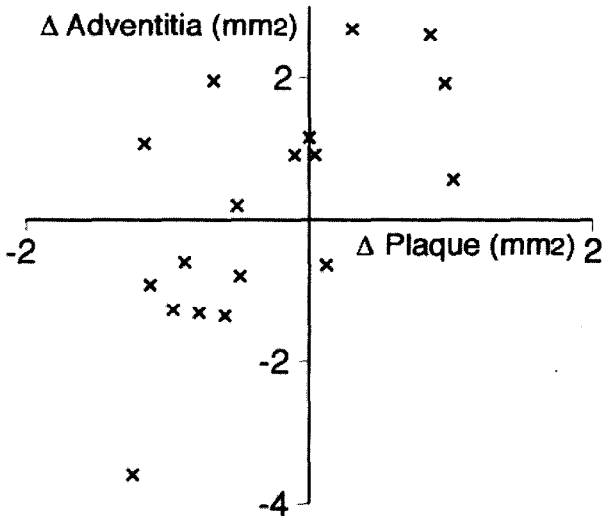
	TAC (R)	TAC (C)	p	DIFF
ALL (96)	1.21± .42	1.17± .47	NS	.03± .19
Men (47)	1.32± .40	1.31± .44	NS	.008± .19
Women (49)	1.10± .41	1.04± .48	NS	.06± .19
Young (18)	1.33± .39	1.32± .47	NS	.01± .20
Old (78)	1.21± .42	1.17± .48	<0.0001	.11± .15

Conclusions: Estimates of TAC calculated using the radial transfer function and direct carotid waveforms show 5-10% differences in women and older patients. Specific transfer functions or use of carotid pressure waveforms should be considered in these subgroups.

1179-149 **Remodeling of Human Coronary Arteries Over Time In Vivo**

David T. Linker, B. Greg Brown, University of Washington, Seattle, WA

Background: Although remodelling of coronary arteries has been deduced from examination of the variation in adventitia and plaque area along the length of the artery both histologically and on intravascular ultrasound images, it has not been observed in vivo over time. **Methods:** Intracoronary ultrasound automated pull-backs were recorded on S-VHS tape both before and after twelve months of lipid-lowering therapy in a target coronary artery in 18 subjects with known coronary artery disease. The pullbacks were digitized and calibrated, and identical segments with plaque in the target artery were identified on the pre- and post-therapy images. The lumen and adventitia-media borders were manually traced on all images in the segment that allowed image interpretation, with the longitudinal position noted. The plaque and adventitial volumes were calculated by a numerical integration of the area over the longitudinal length. The mean plaque and adventitial area were calculated based on plaque and adventitial volume and segment length. **Results:** The change in mean adventitial area was correlated with the change in mean plaque area (R = 0.647, p = 0.0037, see graph). The relationship was Change in mean adventitial area = 1.45 x Change in mean plaque area + 0.62 mm2. **Conclusions:** Remodelling occurs in the coronary arteries after one year of lipid-lowering therapy, but the change in adventitial area is greater than that of the plaque area, suggesting that remodelling is more than a simple compensatory mechanism.



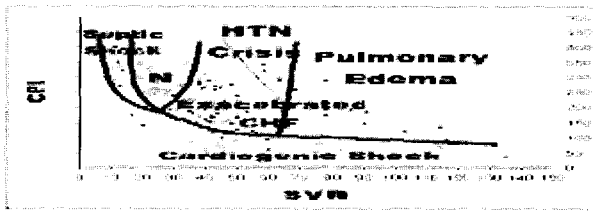
1179-150 **The Role of Cardiac Power and Systemic Vascular Resistance in the Pathophysiology and Diagnosis of Patients With Acute Congestive Heart Failure**

Gad Cotter, Yaron Moshkovitz, Edo Kaluski, Olga Milo, Ylia Nobikov, Adam Schneeweiss, Ricardo Krakover, Zvi Vered, Assaf-Harofeh Medical Center, Zerifin, Israel, Sheba Medical Center, Tel-Hashomer, Israel

Cardiac index (CI), and pulmonary capillary wedge pressure have previously demonstrated only limited value in the diagnosis of patients with acute congestive heart failure (CHF).

Methods: We have measured CI, wedge pressure, right atrial pressure and mean arterial blood pressure (MAP) in 89 consecutive acute CHF patients (exacerbated systolic CHF [n=56], pulmonary edema [n=11], cardiogenic shock [n=17] and hypertensive (HT) crisis [n=5]) and in 11 patients with septic shock and 20 healthy volunteers (using a non-invasive CI monitor). Cardiac contractility was estimated by the cardiac power index (Cpi), calculated as CI * MAP (using the physical rule for fluids: Power = Flow *pressure; where cardiovascular flow = CI and pressure=MAP).

Results: In patients with any acute CHF syndrome CI was low and wedge pressure was high, however CI and wedge pressure were often overlapping between patients with exacerbated systolic CHF, pulmonary edema and cardiogenic shock. On the other hand, we have found that in patients with pulmonary edema SVRi was extremely high and in patients with cardiogenic shock Cpi was extremely low while SVRi was similar to that of patients with exacerbated systolic CHF. Two-dimensional presentation of Cpi versus SVRi showed that these 5 clinical syndromes can be accurately defined, as the paired measurements of each clinical group seggregated into a specific region on the Cpi/SVRi normogram, and each region could be mathematically defined by a statistically significant line (Lambda=0.95).



1179-151 **Aortic Stiffness Is Related With an Increased Turnover of Extracellular Matrix in Patients With Dilated Cardiomyopathy**

Stefano Bonapace, Andrea Rossi, Mariantonietta Cicoira, Luisa Zanolla, Giorgio Golia, Piero Zardini, Universita' di Verona, Verona, Italy

Background: A stiffening of the aorta was shown in patients with increasing severity of heart failure (HF) due to dilated cardiomyopathy (DCM). The amino-terminal propeptide of type III procollagen (PIIINP) plasma level, a marker of collagen turnover, is increased in DCM patients. We aimed to assess the possible relationship between PIIINP levels and aortic stiffness measured as a pulse wave velocity (PWV) in patients with DCM. Methods: 78 patients with DCM (mean age 63±9 years, 72% male) were studied. Left ventricular (LV) volumes and ejection fraction, LV outflow tract stoke volume (SV) were measured. Aortic PWV was determined as the time (t) taken by the pulse wave to travel from the descending aorta to the abdominal aorta by Doppler flow recordings and the distance (d) travelled by the pulse wave was measured over the body surface as the distance between the two recording sites: PWV=d/t. Plasmatic PIIINP levels were determined by radioimmunoassay. Results: The mean PWV was 5.7 ±2.2 m/sec (range: 2.9-12.3). PWV was associated with age (r=0.30; p=0.007), SV (r= -33; p= 0.006), heart rate (r=0.27; p=0.02) and PIIINP (r=0.35; p=0.002). No significant correlations were found with EF and aortic size. At the multivariate analysis, PIIINP predicted PWV (p=0.03) independently of age, SV and heart rate (R^2=0.29). Conclusion: Aortic stiffness is independently associated with high PIIINP levels in DCM patients. This suggests that abnormalities in the extracellular matrix turnover might involve the proximal elastic vasculature, which contributes to the progressive clinical and hemodynamic worsening of patients with DCM.

POSTER SESSION

1180 Vascular Pathophysiology: From Basic Science to Novel Intervention

Tuesday, April 01, 2003, Noon-2:00 p.m.
McCormick Place, Hall A
Presentation Hour: 1:00 p.m.-2:00 p.m.

1180-117 **Serotonin Receptor Antagonism Improves Distal Perfusion After Hindlimb Ischemia in ApoE-/- Mice**

Jean-Pierre Bidouard Pierre Lainée, Yoann Grataloup, Frédérique Dol, Paul Schaeffer, Nathalie Delesque-Touchard, Steve O'Connor, Philip Janiak, Jean-Marc Herbert, Sanofi-Synthelabo Research, Chilly-Mazarin, France

Background: Serotonin (5-HT) may contribute to peripheral arterial diseases (PAD) by vasoconstricting collateral vessels, hence impairing limb perfusion and aggravating ischemia. Since hypercholesterolemia promotes platelet aggregation and increases plasma 5-HT levels, we studied whether SL65.0472, a 5-HT_{1B}/5-HT_{2A} receptor antagonist, could reduce hindlimb ischemia in hypercholesterolemic $ApoE^{-/-}$ mice, a strain prone to atherosclerosis.

Methods: SL65.0472 (30 mg/kg/d, n=9) or vehicle (n=11) were administered orally for 13 days to male $ApoE^{-/-}$ mice (25-week old) submitted to lower limb ischemia (LLI) by resection of the left superficial femoral artery and ligation of the left iliac artery. Pedal perfusion deficit was measured by laser Doppler imaging before and at 7 and 14 days after LLI induction. Expression of 5-HT_{1B} and 5-HT_{2A} receptors was assessed by semi-quantitative RT-PCR in smooth muscle cells and cellular extracts from aortas of male $ApoE^{-/-}$ mice. In separate experiments, the effect of SL65.0472 (30 mg/kg/d po) on atherosclerotic lesion development was evaluated in $ApoE^{-/-}$ mice after 3 and 8 months of treatment. Atherosclerotic lesions were scored on the aortic valves using oil red O staining.

Results: LLI induction in $ApoE^{-/-}$ mice caused a severe perfusion deficit in the ischemic leg with no recovery over 14 days in the vehicle group and 100% of foot necrosis by day 14. In contrast, incidence of foot necrosis was reduced by SL65.0472 treatment (-56%, $p<0.05$) and was accompanied by an improved pedal perfusion ratio between the ischemic and the contralateral normally perfused limb. RT-PCR analysis revealed that both 5-HT_{1B}/5-HT_{2A} receptors were expressed in aorta from $ApoE^{-/-}$ mice. However neither 3 nor 8 months of treatment with SL65.0472 affected the development of atherosclerotic lesions.

Conclusion: These results suggest that 5-HT is involved hindlimb ischemia in athero-

sclerotic ApoE$^{-/-}$ mice, and that chronic blockade of 5-HT$_{1B}$ and 5-HT$_{2A}$ receptors improves ischemic outcome of PAD but does not reduce the progression of atherosclerosis.

1180-118 Effect of CC-Chemokines (MCP-1) in a Novel Porcine Model of Peripheral Vascular Disease

Michiel Voskuil, Niels Van Royen, Imo Hoefer, Brian Guth, Randolph Seidler, Klaus Scheffler, Sebastian Grundmann, Juergen Hennig, Wolfgang Schaper, Christoph Bode, Jan J. Piek, Ivo R. Buschmann, Academic Medical Center, Amsterdam, The Netherlands

Background: For an appropriate extrapolation to patients with peripheral arterial obstructive disease we tested the efficacy of monocyte chemoattractant protein 1 (MCP-1) treatment in a novel porcine hind limb ligation model. Both flow and pressure parameters were used to evaluate changes after treatment with MCP-1.

Methods: In 36 minipigs, a ligation of the femoral artery was performed, distal to the bifurcation of the deep femoral artery. An infusion catheter was inserted proximal to the ligation site to ensure a first-pass effect of the compound across the collateral vascular bed. This catheter was connected to an external infusion pump. Animals were examined after acute ligation (n = 4), after 48 hours (n=13) or two weeks (n=10) treatment with 2µg/h MCP-1 (BIWH 3) and were compared to control animals with PBS (n=9). In the terminal experiment resting flow and pressure in the iliac artery as well as peripheral arterial pressures were assessed. Arterial perfusion pressure was controlled using a pump driven extracorporal circulation that was inserted in the abdominal aorta. Vascular conductance was determined during maximal vasodilatation. The formation of collateral arteries were visualized using both in vivo and post-mortem angiography.

Results: Resting blood flows in the leg were 25%, 53%, 81% and 81% of the contra lateral leg after acute ligation, after two weeks infusion of PBS, and after 48 hours and two weeks of treatment with MCP-1 ($p < 0.05$ for PBS compared to both MCP-1 groups). Distal pressures were 46%, 73%, 75% and 76% acutely after ligation, after two weeks infusion of PBS or 48 hours and two weeks treatment with MCP-1, respectively (p = NS for PBS compared to both MCP-1 groups). Finally, collateral conductance was 158 ± 97 ml/min/mmHg after acute ligation, 645 ± 346 ml/min/mmHg after two weeks of infusion with PBS, and 1070 ± 530 and 1158 ± 535 ml/min/mmHg after 48 hours and two weeks treatment with MCP-1, respectively ($p < 0.05$).

Conclusions: Intra-arterial infusion of CC-chemokines results in modulation of the process of arteriogenesis in this novel large animal model. Perfusion of the occluded leg was improved using a 48 hours infusion of MCP-1 and remained unchanged after 2 weeks of treatment.

1180-119 Intravascular Ultrasound Molecular Imaging of ICAM-1, VCAM-1, Fibrinogen, and Fibrin in a Yucatan Miniswine Model of Atherosclerosis

Andrew J. Hamilton, Shao-Ling Huang, Mark Rabbat, Drew Warnick, Ashwin Nagaraj, Bonnie J. Kane, Melvin Klegerman, Robert C. MacDonald, David D. McPherson, Northwestern University, Chicago and Evanston, IL, EchoDynamics, Inc., College Park, MD

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Background: Targeted echogenic immunoliposomes (ELIP) for ultrasonic detection and staging of active molecular components of endothelium (ENDO) and atherosclerosis (ATH) have been developed. Our purpose was to determine the extent and specificity of ELIP ATH component highlighting in vivo.

Methods: In 5 ATH Yucatan miniswine, ENDO was denuded from one femoral and one carotid artery and the animals fed a high cholesterol diet for 2 months to create early and late stage ATH. Femoral and carotid arteries were imaged using intravascular ultrasound (IVUS) prior to and 5 minutes post ELIP injection (5mg dose). Anti-ICAM, anti-VCAM, anti-fibrin, anti-fibrinogen conjugated ELIP were used depending on the degree of ATH. A blinded observer determined if each segment of the arterial ENDO was enhanced. The IVUS images were reconstructed in 3D and videodensitometric analysis of the ENDO-blood interface used to determine the mean gray scale (MGS) change in enhanced and non-enhanced segments. Immunohistochemistry was used to confirm molecular component expression.

Results: Six arteries had segments identified as enhanced, 12 arteries had no enhancement of segments. Immunohistochemical staining confirmed the expression/lack of expression of respective molecular targets in all the observer-identified segments.

Atheroma Enhancement: MGS change ELIP *vs.* Saline

	Conjugated ELIP	Unconjugated ELIP
Positive	40.4 ± 19% *	1.4 ± 3.9%
Negative	0.9 ± 7.5%	3.4 ± 5.8%

* $p<0.05$ *vs.* Saline

Conclusion: ELIP specifically enhance atheroma components. This allows for better characterization of the type and extent of active molecular ATH components and may allow for more directed therapy.

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1180-152 Oxidative Damage and Repair System in Spinal Cord Ischemia and Reperfusion Injury

Roxian Lin, Glen Roseborough, Yafong Dong, G. Melville Williams, Chiming Wei, University of Maryland, Baltimore, MD, Johns Hopkins University, Baltimore, MD

Spinal cord injury following a successful operation on thoracic and thoracoabdominal aneurysms is a disastrous complication in humans. It is believed that the cause of spinal cord dysfunction is ischemia from hypoperfusion during cross-clamping. Research has also indicated other factors as mediators of delayed cell death after central nervous system ischemia, including free radical production and apoptosis. The reactive oxygen species (ROS) plays a critical role in the pathogenesis of ischemia-reperfusion injury. Therefore, the current study was designed to investigate the DNA damage such 8-oxoG generation and its relationship with apoptosis as well as DNA repair enzyme expression in spinal cord with ischemia-reperfusion injury. Spinal cords of rabbits were removed at 1, 3, 6, 24, 48 hours after 30 min of infrarenal aortic occlusion. DNA damage was determined by 8-oxoG staining. The expression and localization of DNA repair enzymes such as MYH, OGG1 and MSH2 were studied by Western blot analysis and immunohistochemical staining. The levels of apoptosis and apoptosis-related gene expression (such as caspase-3) were determined by TUNEL study and Western blotting. Neurological functional score was investigated during spinal cord ischemia-reperfusion injury. DNA damage such as 8-oxoG level was significantly increased from 1-hr to 6-hr after reperfusion in ischemic spinal card. The levels of hMYH, hOGG1 and hMSH2 were markedly increased at 6-hr after reperfusion. Furthermore, the peak level of TUNEL was found at 48-hr after reperfusion in spinal cord. Immunoreactivity of caspase 3 was induced at 6-hr to 24-hr after reperfusion in ischemic spinal cord. The increased 8-oxoG level was correlated with neurological score in rabbits with spinal cord injury. The current study demonstrated that the DNA damage-repair system may plays an important mechanism in apoptosis and pathophysiological changes in spinal cord during ischemia-reperfusion injury.

1180-153 Percutaneous Aortic Valve Replacement in the Beating Heart: First Animal Results

Markus Ferrari, Gerhard Hellige, Markus Schlosser, Ines Frerichs, Eckehardt Mueller, Volker Guyenot, Gerd Eisold, Hans R. Figulla, Friedrich-Schiller-University, Jena, Germany, Fraunhofer Institute, Jena, Germany

Introduction: Due to increasing number of elderly patients with relevant co-morbidity there is need for a non-invasive technique of aortic valve replacement. Therefore, we evaluated the feasibility of transvascular aortic valve replacement in animal experiments.

Methods: Pulmonary valves from pigs were fixed in a self-expanding stent after low-pressure fixation in glutaraldehyde solution for 72 hours. The stent (6 cm in length) containing the biologiocal valve in its proximal part was implanted in 3 pigs (88-104 kg) by means of a 25F catheter via the left subclavian artery by guidance of fluoroscopy and trans-oesophageal ultrasound (TEE). During stent deployment the original aortic valve was pushed against the aortic wall.

Results: It was possible to replace the aortic valve in the beating heart without any complication or even relevant drops in blood pressure. Under standard hemodynamic monitoring we infused dopamine with doses of 5 µg/kg/min., 10 µg/kg/min., and 15 µg/kg/min. Cardiac output increased from 3.8 to 9.7 l/min., and the blood pressure rose from 96 / 54 mmHg to 138 / 111 mmHg respectively. The maximal peak to peak pressure gradient across the valve carrying stent increased from 0-2 mmHg at rest to 5-8 mmHg under infusion of dopamine. Peak aortic flow increased from 0.8 m/s to 1.7 m/s measured by TEE. No relevant aortic insufficiency of the implanted valve was observed by Doppler flow analysis. All pigs were sacrificed after 5 hours post transvascular aortic valve replacement. The chest was opened and the left ventricle and the ascending aorta were carefully inspected. There were no signs of malfunction of the implant, or of damage of the aortic vessel wall.

Conclusion: This study proves the feasibility of trans-vascular aortic valve replacement in the beating heart. Further diameter reduction of the implantation-catheter-device, and chronic animal experiments are on its way.

1180-154 Convergence and Stabilization of Cellular Proliferation Into Steady State Over the Permanent Arterial Filtration Struts of the Diverter: A Novel Percutaneous Device for Protection Against Embolic Stroke

Dagan Harris, Jonathan Leor, Yaron Assaf, Boaz Nishri, Orna Oz, David Tanne, Ygael Grad, Ofer Yodfat, MindGuard Medical Devices Ltd., Caesarea, Israel

Purpose: To prove the long term patency of a novel filtering device (the Diverter) percutaneously implanted at the carotid bifurcation. The device redirects emboli away from the internal into the external carotid artery and thus may prevent embolic stroke of central source such as afib. We have previously shown that the diverter, which is a fine structured stent like mesh is capable of arterial blood filtration up to 4 months. Our aim was to determine cellular proliferation rates over the filtering area.

Methods: Diverters (n=10) composed of fine wire meshes were successfully implanted, by percutaneous approach into the swine illio-femoral bifurcation. The bifurcations were harvested for evaluation at short, mid and long-term follow up periods (1, 3 and 23 weeks) post implantation. The animals were injected with BrdU (40mg/kg) 24h and 1h prior sacrifice. The filtering parts were embedded by paraffin and stained by hematoxilin (for total cell counting) and immunohistolabeling using an anti-BrdU monoclonal antibody. Each filtering part was tested at 4 different microscopical fields using morphometrical software. Proliferation rate was measured as the percent of BrdU stained vs. the total number of cells at the filtering area.

Results: Flow patency of the Diverter was confirmed prior to animal sacrifice by angiography and Doppler ultrasonography. Microscopical evaluation and morphometry showed that most of the filtered area of the 10 specimens remained patent, and the percent of