9:15 a.m.

847-4 **Enhanced External Counterpulsation Reduces Angina and Improves Quality of Life in Elderly Unrevascularizable Patients**

Georgiann C. Linnemeier, Elizabeth D. Kennard, William E. Lawson, *University of Pittsburgh, Pittsburgh, Pennsylvania.*

Background: When treating elderly patients (E) (≥75 years) with symptomatic coronary artery disease (CAD), it is unclear whether the acute risks of revascularization are counterbalanced by better long-term survival or functional outcomes. Enhanced external counterpulsation (EECP) is a noninvasive treatment similar to the intra-aortic balloon pump, which is designed to increase myocardial perfusion pressure and decrease cardiac workload. EECP has been demonstrated to be safe and effective in treating angina; however, whether it is safe and effective in E who are not considered candidates for further revascularization is unknown.
Methods: The study group consisted of 550 patients consecutively enrolled in the International EECP Patient Registry who were ≥ 75 years and not considered candidates for further revascularization.
Results: The mean age was 79.9 (± 4.4 years). Most patients had prior revascularization: 72% prior coronary artery bypass graft surgery, 58% prior percutaneous coronary intervention. Mean left ventricular ejection fraction was 45%, and 23% of E had an ejection fraction <35%. Multivessel disease was present in 85% of patients, with 87% of E reporting Canadian Cardiovascular Society (CCS) angina class III or IV. Treatment was completed as prescribed in 80% of patients, with a mean of 32 treatment hours. The rate of major adverse cardiac events during treatment was low (<3%). Upon completion of EECP treatment, E reported: significant reduction in angina (mean CCS class, pre- 3.1 vs. post- 1.9), and significant reduction in episodes of angina (mean episodes/week, pre- 9.4 vs. post- 2.4) and nitroglycerin use (mean, pre- 9.4 vs. post- 2.7). Of 74% of E using nitroglycerin at the start of treatment, 42% of E required nitroglycerin post-EECP treatment. Patient assessed quality of life scores were also significantly improved post-treatment. All changes, pre-and post-EECP were statistically significant with p<0.001.
Conclusion: Symptomatic CAD in elderly patients is of immense public health and economic importance. In the group of elderly patients who are unsuitable for revascularization, EECP provides an innovative tool that improves functional outcome and quality of life.

9:30 a.m.

847-5 **White Coat Hypertension Increases Cardiovascular Risk in Elderly**

Jose A. Aizpurua, Tulio A. Sulbaran, Egle Silva, Gladys Maestre, *Centro de Enfermedades Cardiovasculares, Maracaibo, Venezuela, La Universidad del Zulia, Maracaibo, Venezuela.*

Background: There are no long-term follow up studies about white coat hypertension (WCH) in Venezuela; on the other hand there is a controversy about the risk provided by this condition. The aim of this study was to establish the prognostic value of Ambulatory Monitoring Blood Pressure (ABPM) for cardiovascular (CV) morbidity in elderly.
Methods: The study included a sample of 609 subjects older than 55 years who underwent non-invasive ABPM when enrolled in the study and were prospectively followed since that moment until a nonfatal cardiovascular event occurs or the ending of the study. The maximal follow up time was 31.5 months (mean 20).
Results: The comparison between morbidity rates showed a significant difference among normotensive (1.04 per 100 pac/yr), WCH (8.99 per 100 pac/yr) and ambulatory hypertension (16.76 per 100 pac/yr) groups (p < 0.01). The difference between survival curves was highly significant FIG 1. Night systolic ABP showed the best independent predictive power for CV events. Diastolic pressures were not associated to cardiovascular events risk. The risk for morbidity in WCH group was increased compared with that of normotensive group (RR 8.65; CI 95% 3.03 - 24.68; p < 0.01). Nondippers showed an increased risk compared to dippers (RR 1.73; CI 95% 1.03 - 2.88; p 0.03).
Conclusion: In this elderly population, WCH is not a benign condition, but must be considered as an important CV risk factor. Nondipper pattern showed predictive power in whole population for both sexes.

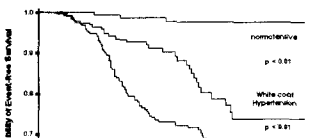

FIG1. COMPARISON BETWEEN SURVIVAL CURVES (MORBIDITY) IN THE STUDY POPULATION.

9:45 a.m.

847-6 **Outcome of Elderly Women With Refractory Chronic Angina Treated Invasively Versus Medically: Comparison With Elderly Men in the Prospective Randomized Trial of Invasive Versus Medical Therapy in the Elderly (TIME)**

Gabriela M. Kuster, Matthias Pfisterer, for the TIME Investigators, *University Hospital, Basel, Switzerland.*

Background: Women >75 years of age represent almost half the elderly coronary artery disease (CAD) population, yet they are severely underrepresented in clinical trials.
Patients and Methods: We prospectively randomized 301 patients age >75 years with angina CCS class II-IV despite at least two antianginal drugs to coronary angiography and revascularization or to optimized medical therapy. Six months outcome assessed as quality of life (QoL: SF 36, Rose, Duke Activity Score Index) and adverse events (AE: death, myocardial infarction (MI) or hospitalisation for acute coronary syndrome) were compared between women and men as prespecified subgroups of the TIME study.
Results: 44% (n=131) of the 301 patients were women. Age was 80±4 years (mean±SD) in both genders. More women were hypertensive (70% vs. 55%, p=0.006), and fewer smoked (12 vs. 51%, p<0.0001). Although angina severity (CCS class III-IV in 82% vs. 75% of the men, n.s.) and history of prior MI (44 vs. 49%, n.s.) were similar, the rate of prior revascularizations was lower in women (6% vs. 29%, p<0.001) and fewer coronary vessels were diseased (p<0.001). In addition, left ventricular ejection fraction was higher in women (55±12 vs. 51±12, p=0.05). Despite these findings, women judged their QoL at baseline inferior than men (p<0.01 except for Rose). During follow-up, they showed a similar improvement in QoL on therapy as men, but overall, QoL remained worse in women. AE occurred more often in women than in men with more deaths (p=0.03) and a higher rate of death and MI (p=0.01). The subgroup of medically treated women (n=64) suffered more AE (p<0.003), particularly non-fatal ischemic events (p<0.001) than women in the invasive subgroup (n=67).
Conclusions: Elderly women with chronic angina differ importantly from elderly men in disease presentation, perception and outcome: despite similar angina and lower disease severity, they judge their QoL worse than men and their outcome is worse than that of men. Still, they benefit from revascularisation similarly. These findings suggest that other mechanisms than CAD severity may be relevant in determining well-being and outcome in women.

POSTER SESSION

1156 Myocardial Prevention/Oxidative Stress

Tuesday, March 19, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1156-141 **Cytotoxic Aldehydes Aggravate Ventricular Dysfunction in an Injured Heart: Evidence From an Iron Overload Model of Heart Failure**

Mehrdad Yazdanpanah, Gavin Oudit, Andrea Lee, Fayez Dawood, Wen-Hu Wen, Peter Backx, Peter Liu, *Heart & Stroke/Richard Lewar Centre of Excellence, U of Toronto, Toronto, Ontario, Canada, Toronto General Hospital, UHN, Toronto, Ontario, Canada.*

BACKGROUND: Cytotoxic aldehydes, by-products of oxidative stress, are increased in heart failure in general, and in iron overload cardiomyopathy in particular. We tested the hypothesis that increased aldehydes exert a direct negative influence on heart function in an established iron overload heart failure model.
METHODS: On the background of cardiac iron overload, we augmented aldehyde levels by selective inhibition of tissue aldehyde dehydrogenase (ALDH) with disulfiram (Dis, 40 mg/kg ip od), cyanamide (Cyn, 50 mg/kg ip od), or administration of 12 straight chain aldehydes (0.1 mL, 2.5 mM, ip) for 3 months in B6D2F1mice, and assessed aldehyde levels together with invasive and no-invasive measures of LV function. Mice were randomized to either control (C), iron load (Fe) alone or iron load with ALDH inhibitor (Aldl).
RESULTS: Serum aldehydes increased further with ALDH inhibition (Hexanol, nmol/L, C:134±15 vs. Fe:261±37 vs. Dis:342±26, M±SEM, p<0.05). In vivo hemodynamics using a Millar catheter displayed lower LV systolic pressure with ALDH inhibition (C: 96±4 vs. Fe: 74±3 vs Cyn: 64±2 mmHg, p<0.05, and similarly with disulfiram). E/A ratio was also decreased with Aldl (C:1.4±.2 vs. Fe: 1.2±.2 vs. Dis: 1.0±.3, p<0.05). With aldehyde infusions, both +dP/dt and -dP/dt were lower (2815±547 vs 5618±776 (C), 2293±219 vs 4255±376 (C), p<0.05).
CONCLUSION: The increased levels of serum aldehydes with either ALDH inhibition or direct infusion led to further depression of both systolic and diastolic function, suggesting oxidative stress contributes to the LV dysfunction in the setting of cardiac injury, and is not merely an innocent bystander.

1156-142 **NF-kB Activation Is Involved in Inflammatory Skeletal Muscle Alterations in Patients With Chronic Heart Failure**

Volker Adams, Ulrike Späte, Nicolle Kränkel, Gerhard Schuler, Rainer Hambrecht, *University Leipzig, Heart Center Leipzig, Leipzig, Germany.*

Background: In advanced stages of chronic heart failure (CHF) the expression of inducible nitric oxide synthase (iNOS) in skeletal muscle (SM) may contribute to exercise intolerance and early fatigue. In vitro studies and promotor analysis demonstrated that the

transcription factor NF-kB is essential for the transcription of iNOS . The aim of this study was to assess wether NF-kB is activated in skeletal muscle of patients (pts) with CHF and linked to the expression of iNOS.
Methods: Skeletal muscle biopsies were obtained from 7 CHF-pts (NYHA II-III; LVEF 19 ± 2%; VO2max 14.0 ± 1.3 ml/kg/min) and 7 healthy controls (HC) (LVEF 71 ± 2%; VO2max 28.3 ± 2.7 ml/kg/min). Nuclear proteins were isolated and the content of activated NF-kB was analyzed by electrophoretic mobility shift assay (EMSA). iNOS expression in SM was determined by real time PCR and TNF-a concentration in the serum was measured by ELISA.
Results: The expression of iNOS and the activation of NF-kB in the SM was significantly increased in CHF pts as compared to healthy controls (iNOS: 0.30 ± 0.04 vs. 0.09 ± 0.03 relative RNA expression, p<0.01; NF-kB: 0.48 ± 0.10 vs. 0.12 ± 0.05 relative units). Additionally serum TNF-a was significantly increased in CHF pts (CHF: 5.2 ± 0.6 vs. HC: 1.5 ± 0.2 pg/ml; p<0.001). Furthermore, a signifcant linear correlation was observed between NF-kB activation and iNOS expression (r=0.71, p<0.01) as well as between serum TNF-a and NF-kB activation (r=0.8, p<0.01)
Conclusion: The results of this study indicate for the first time that in skeletal muscle of patients with chronic heart failure the activation of transcription factor NF-kB is increased and may represent one important regulatory factor for the expression of iNOS.

1156-143 Exposure of Normal Adult Cadiomyocytes to Active Caspase-8 Triggers the Release of Cytochrome C From Mitochondria Suppresses Mitochondrial Respiration

Victor G. Sharov, Anastassia V. Todor, Sidney Goldstein, Hani N. Sabbah, *Henry Ford Health System, Detroit, Michigan.*

Background: We previously showed that mitochondrial respiratory abnormalities exist in cardiomyocytes of human with end-stage heart failure as well as in cardiomyocytes of dogs with intracoronary microembolization-induced chronic heart failure. The factors that promote these abnormalities remain uncertain. One possible factor is activation of caspase-8 which, by activating Bid, promotes the release of cytochrome c from mitochondria that, in turn, results in mitochondrial dysfunction. In the present study, we tested the hypothesis that exposure of normal adult cardiomyocytes to active caspase-8, activates bid, causes the release of cytochrome c from mitochondria and adversely impacts mitochondrial respiration.
Methods: Cardiomyocyte were enzimatically isolated from left ventricular myocardium of 5 normal dogs. Cardiomyocytes were saponin skinned, incubated under normoxic conditions (95%air/5%CO_2), and exposed to active caspase-8 (100U/ml) for one hour. Aliquotes of cardiomyocytes incubated with and without active caspase-8 were used to measure mitochondrial state 3 respiration with Clark electrode in the presence of 3 mM malate, 5 mM glutamate and 1 mM ADP. A second set of aliquotes of cardiomyocytes was centrifuged at 15,000 g and the supernatant used to measure the expression of cytosolic cytochrome c and a third set was homogenized and the homogenate used to measure the expression of Bid by Western blotting.
Results: Exposure of cardiomyocytes to active caspase-8 resulted in cleavage of Bid into 15 kDa fragments and markedly increased cytosolic cytochrome c (2.4 ± 0.3 vs. 25.2 ± 0.8, P<0.001) compared to unexposed cardiomyocytes. Exposure to caspase-8 also caused a significant decrease in mitochondrial state 3 respiration (39 ± 4 vs. 64 ± 13 ng atoms O_2/min/mg protein, P<0.001).
Conclusions: These results indicate that exposure of normal adult cardiomyocytes to active caspase-8 triggers cleavage of Bid and the release of cytochrome c from mitochondria with subsequent suppression of state respiration. This cascade of events offers an explanation for the observed abnormalities of mitochondrial respiration seen in heart failure.

1156-144 Thioredoxin: A New Marker of Oxidative Stress in Patients With Chronic Heart Failure

Andreas Jekell, Akter Hossain, Anders Rosén, Ulf Dahlström, *Linköping University, Linköping, Sweden.*

Background: It is well known that pro-inflammatory cytokines are important prognostic markers in chronic heart failure (CHF) patients and it has been shown that tumor necrosis factor-α (TNFα) is elevated in plasma of CHF patients. Elevated levels of TNFα are correlated with New York Heart Association (NYHA) functional class. Thioredoxin (Trx) is a multifunctional redox-protein, which regulate the intra- and extra cellular redox-environment. One important function of Trx is the protection from oxidative stress caused by free radicals and pro-inflammatory cytokines. Trx is upregulated both during chronic and acute oxidative conditions. However, it is not known whether Trx is elevated in systemic circulation in patients suffering from CHF. The aim of this study was to investigate possible mechanisms behind CHF with special emphasis on the activation of cytokines and to see whether oxidative stress was playing a role. In order to assess these complex processes in CHF, we analyzed plasma levels of the redox-active proteins Trx and Trx-reductase (TrxR) as markers of oxidative stress and TNFα and interleukin 6 (IL6) as pro-inflammatory cytokines.
Methods: 27 male patients with CHF, NYHA class II-III, and mean age 74 ± 5 years (range 65-82) were compared to 30 healthy subjects of similar age-groups, mean age 75 ± 5 years (range 64 - 81). Plasma samples were collected in the morning after rest for 30 min in supine position and analyzed in enzyme-linked immunosorbent assays (ELISA) for TNF, Trx, TrxR and IL6.
Results: Patients with CHF showed a significant increase of Trx in plasma, mean 32 ±5 (SEM) ng/ml, compared to healthy subjects (16 ±4 ng/ml); p < 0.0001. Variations of plasma Trx were found in patients with CHF (range 9-101 ng/ml) as well as in healthy subjects (range 4-117 ng/ml). No significant differences in TNFα, IL6 nor TrxR concentrations were seen between the two groups.
Conclusions: The most important finding in our pilot study is that Trx was significantly (p < 0.0001) elevated in patients with CHF compared to healthy subjects of similar age groups. This finding indicates that Trx may be a new sensitive marker of oxidative stress in CHF.

1156-145 Anticytokine Therapy Alleviates Oxidative Stress and Attenuates Left Ventricular Remodeling in Experimental Heart Failure

Gordon W. Moe, Andrea Konig, Marina Romanova, Peter Liu, *St Michael's Hospital, Toronto, Ontario, Canada, University Health Network, Toronto, Ontario, Canada.*

Background: Increased expression of the proinflammatory cytokine tumor necrosis factor-alpha (TNF-α) and increased oxidative stress have been observed in the failing heart. TNF-α is known to induce oxidative stress *in vitro*. Accordingly, this study tested the hypothesis that TNF-α would also induce oxidative stress *in vivo* and contribute to LV dysfunction and remodeling in heart failure (HF).
Methods: Dogs were randomly assigned to: (1) no pacing (controls, n=10), (2) chronic pacing for 4 weeks to severe HF (HF, n=10), and (3) pacing with concomitant treatment with *etanercept*, a chimeric TNF-α soluble receptor, 0.5 mg/kg twice weekly SC (HF-*etanercept*, n=10). LV tissue level of aldehyde, an accurate marker of oxidative stess, was measured using gas chromatography/mass spectroscopy. LV function and remodeling was assessed by echocardiography.
Results: LV tissue total aldehyde level increased markedly in HF, indicating severe oxidative stress. Selected unsaturated aldehydes such as 4-OH hexenal and malondialdehyde were also increased. This was accompanied by reduced LV ejection fraction (LVEF) and increased LV volume (LVV), reflective of LV dysfunction and remodeling. Treatment with *etanercept* normalized LV aldehyde levels, reduced LVV, and partially restored LVEF.
Conclusion: Our data provide supportive evidence that TNF-α contributes to LV dysfunction and remodeling in canine pacing-induced CHF, mediated in part by a local increase in oxidative stress.

*** p<0.001 vs controls, ** p<0.05 vs HF**

	Controls	HF	HF-*etanercept*
LVV (ml/kg)	3.4 ± 0.5	5.2 ± 0.4*	4.0 ± 0.2**
LVEF (%)	53 ±2	19 ± 3*	26 ± 2**
Aldehydes (pmol/100 mg)	7048±448	11760±1410*	6991±516**

POSTER SESSION
1157 Heart Failure: Clinical Experience
Tuesday, March 19, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1157-153 A Simple Model to Predict Left Ventricular Systolic Dysfunction in a Multiethnic Community

Gavin I. Galasko, Roxy Senior, Avijit Lahiri, *Cardiology Research Department, Northwick Park Hospital, Harrow, United Kingdom.*

Background: Community-based programmes to screen for and treat left ventricular systolic dysfunction (LVD) have recently been advocated. However, who best to invite for screening has not yet been fully elucidated. This study was undertaken to assess this further.
Methods: 1403 subjects ≥ 45 years old were chosen at random from 7 geographical and socio-economically representative community practices to undergo a clinical assessment, symptom questionnaire, ECG, echocardiogram and fasting blood tests. A multivariate model to predict the presence or absence of LVD was then constructed using both clinical and biochemical parameters.
Results: 730 subjects (52%) attended. 515 (71%) were Caucasian and 188 (26%) South Asian. An ejection fraction (EF) was calculable by echocardiography using Simpson's apical biplane rule in 700 cases (96%). 38 subjects (5.4%) were found to have LVD. Of these 19 (50%) were entirely asymptomatic. Multivariate predictors of LVD included prior myocardial infarction, diabetes, a history of heavy alcohol usage, male sex, abnormal ECG and plasma N-terminal proBNP levels. No significant differences were seen with ethnicity. A multivariate model to predict LVD using these 6 parameters was constructed. It gave an area under the ROC curve of 0.95 for predicting significant LVD (EF <45%). A risk-score above 2.83 gave a sensitivity of 92% and specificity of 89% for predicting LVD, requiring only 14% of the population to undergo echocardiographic screening with a one-in-four pick up rate.
Conclusion: Thus left ventricular dysfunction is a common problem in multi-ethnic communities, has no racial difference in prevalence, is asymptomatic in half of cases, and has identifiable clinical and biochemical risk factors. Six simple clinical and biochemical markers can be used to successfully predict the presence or absence of LVD, potentially allowing a cost-effective targeted community-based echocardiographic screening programme for LVD.

1157-154 Is Isolated Diastolic Heart Failure Truly Stand Alone?

Cheuk-Man Yu, Hong Lin, Hua Yang, Shun-Ling Kong, Steven Wai-Luen Lee, Chu-Pak Lau, *The University of Hong Kong, Hong Kong, Hong Kong.*

Background: Definition of diastolic heart failure (DHF) relies on the use of sensitive tools to exclude the presence of systolic dysfunction. The use of ejection fraction of 50% as the cut-off point may not be adequate to address such task. We testify the hypothesis