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

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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

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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

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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

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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?

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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

that systolic dysfunction is common in DHF. Methods: Echocardiography with tissue Doppler imaging was performed in 339 subjects, in whom 92 had systolic heart failure (SHF) (ejection fraction <50%), 73 had DHF (ejection fraction =>50% with diastolic abnormalities on Doppler echocardiography), 68 had isolated diastolic dysfunction (DD) and 106 normal controls. Regional myocardial velocity curves were constructed offline using a 6-basal, 6-mid segmental model. Results: The peak regional myocardial sustained systolic (Sm) and early diastolic (Em) velocities were significantly lower in patients with SHF, DHF and DD than controls in almost all the myocardial segments. Likewise, the mean Sm (SHF < DHF < DD < Controls: 3.3 ± 1.0 < 4.6 ± 1.3 < 5.4 ± 1.0 < 6.3 ± 1.0 cm/s; all p <= 0.001) and mean Em (SHF = DHF < DD < Controls; 3.6 ± 1.2 = 3.9 ± 1.3 < 5.3 ± 1.6 < 7.2 ± 1.7 cm/s; all p < 0.001) from the six basal segments were decreased in all the disease groups. A mean Sm of 4.4 cm/s (-2 standard deviation of controls) predicted the presence of systolic dysfunction in 92% of patients with SHF, 52% with DHF and 14% with DD. Conclusions: Using tissue Doppler imaging, systolic abnormalities were evident in patients previously labeled as DHF, and to a much lesser extent, isolated DD. This indicates the common coexistence of systolic and diastolic dysfunction in a spectrum of different severity in the pathophysiologic process of heart failure.

1157-155 Prevalence, Clinical Characteristics, Quality of Life, and Prognosis of Patients With Congestive Heart Failure and Isolated Diastolic Dysfunction

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Background. Prevalence of isolated LV diastolic dysfunction (IDD) has been reported to be as high as 1/3 of all chronic congestive heart failure (CHF) cases, with an increasing prevalence in the elderly population. However, there is a paucity of prospective data about the prevalence and prognosis of IDD in an unselected population of pts admitted to hospital with CHF.

Methods. We prospectively evaluated 179 consecutive pts admitted in medical departments of our hospital for CHF. Among them, 135 (59% males, median age 74 years) showed sinus rhythm, and no significant valvulopathy (except heart valve prosthesis or secondary mitral regurgitation). CHF was diagnosed using a modification of the Framingham criteria, and IDD according to the European Study Group on Diastolic Heart Failure echo criteria (Eur Heart J 1998;19: 990). Six-month survival of CHF pts was compared with that of age- and sex-matched general population living in Udine in 1995.

Results. Twenty-nine pts (22%) had IDD; 102 (76%) LV systolic dysfunction (i.e. LV ejection fraction <45%. There was no difference in age, gender and NYHA functional class between pts with IDD or LV systolic dysfunction. Six-month rehospitalisation rate (50% and 48%) and median in-hospital length-of-stay during readmissions (10 and 10 days) was similar between the 2 groups. Using the Minnesota Living with Heart Failure score, quality of life was similar between the 2 CHF pt groups both at discharge (39.4 and 34), and at 6-month visit (10.4 and 10.4). Six-month survival, adjusted for age and gender, was similar between pts with IDD or LV systolic dysfunction (90% and 89.8%, Hazard Ratio= 0.99; 95%CI 0.27-3.61), and significantly reduced (Log Rank= 8.58; p<0.001) in comparison to that of the general population (Figure). Two pts (7% of pts with LV ejection fraction< 45%) did not show any echo evidence of cardiac dysfunction.

Conclusions: our data show that, using standardized echo diagnostic criteria, prevalence of IDD in pts admitted to hospital with CHF seems to be lower than previously reported. CHF pts with IDD showed clinical symptoms, self-perceived quality of life, re-hospitalization rate, and 6-month mortality similar to pts with prevalent systolic dysfunction.

1157-156 What Is Late Mortality After Hospitalization for Heart Failure in the Real World? A One-Year Report From the Lady Davis Carmel Medical Center Registry

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Background: Heart failure (CHF) is common cause of morbidity and mortality but current prevalence and long-term outcome are largely unknown in general population as opposed to pts selected for clinical trials.

Patients and Methods: 362 consecutive pts discharged from hospital with clinical CHF or suspected CHF (drug treatment compatible with CHF/LV dysfunction) were enrolled in CHF registry by prospective screening of internal medical, cardiac, intensive care and cardiac surgical departments in 2 hospitals (1 tertiary center with cardiac surgery, 1 referral hospital) over 6 week period in each. Survival status at 1 yr was ascertained by telephone and from governmental records.

Results: A quarter (90/362, 25%) of CHF pts died within 12 mths, a death rate higher than that reported in most recent clinical CHF trials. Pts who died were older (77±10 vs 75±11 yrs, p=0.03), but death was not predicted by new acute myocardial infarction (AMI) or new atrial fibrillation (AF)/paroxysmal AF at time of entry to registry or by presence of diabetes mellitus (31/90, 34% vs 74/272, 27%, NS), nor following correction for age and sex in stepwise multivariate model.

Conclusions: In pts hospitalized for CHF or suspected CHF in the real world: 1. Late (12 mth) mortality was higher than expected. 2. Mortality was higher in older pts. 3. Death was not predicted by acute event at entry to database and was marginally but not significantly higher in diabetics.

Predictors of 1 year mortality

Vital status (12 mths)	Age (yrs)	AMI on index admission	New AF/PAF on index admission	IDDM	NIDDM
Dead (N=90)	77±10	6 (7%)	7 (8%)	7 (8%)	24 (27%)
Alive (N=272)	75±11	21 (8%)	24 (9%)	21 (8%)	53 (20%)
p value	0.03	NS	NS	NS	NS

1157-157 Impaired Left Ventricular Filling Predicts Augmented Ventilatory Response to Exercise in Patients With Chronic Heart Failure

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Introduction. Augmented ventilatory response to exercise (VE/VCO_2 slope) well predicts poor prognosis in chronic heart failure (CHF). However, the mechanisms responsible for exercise hyperpnea in CHF have not been fully elucidated. The aim of this study was to determine the interrelationship between resting ECHO 2D-derived parameters and elevated VE/VCO_2 slope in CHF. **Methods and results**. In 38 stable CHF patients (33 men, 63±8 years, NYHA class II/III 26/12) prospective ECHO-2D examination (mean end diastolic diameter [EDD]: 68±8 mm, shortening fraction [SF]: 16±7%) followed by cardiopulmonary exercise testing (peak oxygen consumption: [peakVO_2]: 19.0±6.3 ml/min/kg, VE/VCO_2 slope 37.6±12.7). VE/VCO_2 slope correlated with the following echocardiographic parameters: short isovolumic relaxation time (IVRT, r=-0.47, p=0.005), decreased mitral A wave peak velocity (A_{vel}, r=-0.44, p=0.006), depressed right ventricle long axis function (RV excursion, r=-0.37, p=0.03), and left ventricular restrictive filling pattern (defined as mitral E/A ratio > 1 and deceleration time ≤120ms, r=0.47, p=0.004). There was no relationship between resting ECHO-2D indices and peak VO_2. Twenty (53%) pts with high VE/VCO_2 i.e. > 34.0) were identified: (table).

	EDD (mm)	SF(%)	A_{vel} (m/s)	IVRT (ms)	RV excursion (mm)	Restrictive mitral flow (%)
High VE/VCO_2 (n=20)	68±8	17±7	0.4±0.3**	24±59 *	12±4*	65*
Normal VE/VCO_2 (n=18)	68±8	18±7	0.8±0.3	60±25	17±4	29

Mean ± SD, *p<0.05, **p<0.01 high vs normal VE/VCO_2**Conclusion:** In CHF impaired left ventricular filling pattern and depressed right ventricle long axis function may be important factors responsible for augmented ventilatory response to exercise.

1157-158 Efficacy and Tolerability of Carvedilol in Diabetic Patients With Chronic Heart Failure

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Background: The benefits of beta blockers (BB) in patients with chronic heart failure (CHF) are well established, however, there is limited data on the impact of BB in diabetic CHF patients, a subgroup in whom BB have been considered relatively contra-indicated. The aim of this study was to compare the efficacy and tolerability of the BB, carvedilol in diabetic and non-diabetic CHF patients.

Methods: A retrospective analysis was conducted on 505 consecutive patients with CHF (434 men, 71 women) aged 55±13 years who were commenced on carvedilol between February 1996 and May 2001. Ninety-three patients (18%) had a history of diabetes mellitus (DM group). Patients were reviewed at 3, 6, 12, 18 and 24 months then annually. Vital signs, NYHA functional class, 6 minute walk distance (6MWD), carvedilol dose and echocardiographic measurements of LV dimensions (LVEDD and LVESD) and fractional shortening (FS) were recorded at each visit. In addition, survival and non-fatal adverse events were recorded.

Results: There were no significant differences between the DM and non-DM groups at baseline with respect to age, sex, duration of CHF, heart rate, diastolic blood pressure, serum Na^+ and creatinine, drug therapy, NYHA class, LV dimensions and function. The DM group were significantly heavier, had lower 6MWD, and higher systolic blood pressure at baseline. A higher percentage of diabetics had ischemic heart disease (54% v 37%, p=0.007). During a mean follow up of 32±18 months, 22% of the DM group died, 12% underwent heart transplantation (HTx) and 11% withdrew from carvedilol due to adverse events. In comparison, 19% of the non-DM group died, 9% underwent HTx and 18% were withdrawn from carvedilol due to adverse events (all p=ns compared with DM group). Mean maintenance carvedilol doses were 42±2 and 39±3 mg/day for DM and non-DM groups (p=ns). At 24 months, NYHA class and 6MWD improved significantly, LVEDD fell by 3.1±0.5 mm, LVESD by 4.9±0.6 mm and FS rose by 3±1% (all p < 0.0001 versus baseline, n=226), with no significant differences between the DM and non-DM groups.

Conclusion: The tolerability, clinical outcomes and beneficial effects of carvedilol on LV remodelling are similar in diabetic and non-diabetic CHF patients.

1157-159 Is Additional Neurohormonal Antagonism Useful in Patients With Severe Chronic Heart Failure Already Receiving a Combination of Neurohormonal Antagonists? Results of the COPERNICUS Study

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Background. The results of the Val-HeFT study suggested that broad based neurohormonal blockade may have deleterious effects in patients with heart failure (HF), but this hypothesis has not been evaluated in other trials.

Methods. The 2289 patients with severe HF in the COPERNICUS trial were randomized to placebo (PBO) or carvedilol (CRV), which were added to diuretics and an ACE inhibitor (± digitalis) for up to 29 months. Of these patients, 445 were also on spironolactone at baseline and thus received 3 neurohormonal antagonists if they were randomized to CRV. Compared with those not on spironolactone, patients on spironolactone had a