Methods: DNA extracted from explanted DCM hearts (n=17, 1 female; 49+/-13 years; LVEF: 18+/-5%) were investigated for clonality of the TCR-β-gene. Non-DCM-hearts (ischaemic cardiomyopathy: n=2, valvular heart disease: n=3, donor hearts: n=3) served as controls. The TCR-PCR-products analyzed by high-resolution fragment analysis (GeneScan), displayed a Gaussian-like distribution profiles in polyclonal and single dominant peaks in monoclonal T-cell populations. Clonal TCR-β PCR-products were directly sequenced.

Results: The GeneScan analysis of the TCR-β PCR-products demonstrated a clonal T-cell population in n=9/17 (53%) of the DCM hearts. In contrast, exclusively polyclonal composition of the TCR-β PCR-products were obtained from the non-DCM hearts. Sequence analysis of the clonal TCR-β PCR-products from the n=9 DCM hearts determined Vβ19.01 in n=6 cases (67%), and Vβ6-1.01, Vβ6-3.01 and Vβ10-3.04 in each of the remaining cases.

Conclusion: Clonal T-cell composition is exclusively present in DCM, as detected by PCR and GeneScan analysis of the TCR-β rearrangement. This phenomenon indicates a clonal T-cell proliferation due to specific antigen, which confirms the autoimmune hypothesis of DCM. Our results, demonstrating a clear predominance of Vβ19.01 T-cell clones in DCM, warrant the molecular analysis of the respective immunogenic sequence and eventually a TCR-based immunotherapy in DCM (e.g. with DNA vaccines).

1039-64 Prenatal Naltrexone Exposure Adversely Alters Postnatal Cardiac Development: A Model for Dilated Cardiomyopathy

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Background: Opiod Growth Factor (OGF) is an inhibitory pentapeptide that interacts with its receptor (OGFr) to target cell proliferation and DNA synthesis. Previous studies have shown that chronic disruption of the OGF/OGFr interaction by naltrexone (NTX) had a stimulatory effect on myocardial development. We hypothesized that in utero exposure to NTX alters postnatal cardiac function.

Methods: Time-mated Sprague-Dawley rats received injections of 30 mg/kg of NTX or 0.3 ml saline twice a day throughout gestation. Offspring were cross-fostered to non-injected, lactating females. Left ventricle (LV) size and function were evaluated by echocardiography in postnatal day (PD) 35, 55 and 110 NTX exposed and control rats. Six to eight male and female offspring of each group were studied for LV end diastolic dimension, LV thickness, shortening fraction (SF) and heart rate.

Results: PD 35 male and female and PD55 female offspring exposed to NTX had significantly dilated left ventricles compared to controls ($p<0.01$). PD110 NTX exposed rats had increased thickness of the LV free wall ($p<0.05$), but no changes occurred earlier. SF was significantly decreased ($p<0.01$) relative to controls in all NTX exposed rats at all ages studied. SF decreases in the NTX group ranged from 12-19%. Heart rate was significantly decreased in the NTX exposed rats compared to controls ($p<0.05$).

Conclusions: NTX exposed offspring demonstrated significant changes in ventricular size, systolic function and heart rate. The NTX exposed rats had dilated left ventricles at earlier ages .The NTX rats had decreased ventricular systolic function and decreased heart rates at all ages studied. This data suggests that in utero blockade of OGF activity by NTX leads to significant ventricular dilation and impaired systolic function. This information may provide a unique model that will allow for further study of dilated cardiomyopathies.

1039-65 Oscillatory Pattern of Respiratory Gas Exchange During Cardiopulmonary Exercise Test in Chronic Heart Failure: Clinical and Functional Correlates

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Background: In chronic heart failure (CHF), periodic oscillations in O_2 consumption (VO_2), CO_2 production (VCO_2) and ventilation may appear in the initial phases of cardiopulmonary exercise test, with controversial clinical significance. AIM: To characterize, in clinical and functional terms, CHF patients with an oscillatory gas kinetics during cardiopulmonary test. **Methods:** We evaluated 195 clinically stable CHF outpatients (171 males; mean age 62.3±9 years), with an echocardiogram and a cardiopulmonary, symptom-limited, exercise test. **Results:** Twenty-six patients had an oscillatory pattern of VO_2 and VCO_2 in the initial phases of exercise (group 1), while 169 did not (group 2). Mean age was 67.1±8.5 years in group 1 and 61.5±8.9 in group 2 ($p=0.003$). Ejection fraction (EF) was 29±8% versus 34±7% respectively ($p=0.009$). No differences existed in sex, etiology, NYHA class, cardiac rhythm and mean peak respiratory quotient (>1.11 in both groups). Patients with an oscillatory pattern had a significantly lower peak VO_2 (13.2±3.4 mL/Kg/min versus 16.8±4.8; $p=0.0003$), a higher ventilatory equivalent response (VE/VCO_2 slope)(41.0±6.2 versus 36.2±6.1, respectively; $p=0.0003$), a shorter exercise duration time (7.8±2.0 minutes versus 9.6±2.4; $p=0.0004$) and a lower peak systolic blood pressure (158.1±23.8 mmHg versus 176.9±31.8; $p=0.004$). At univariate analysis, peak VO_2 correlated with age, sex, NYHA class, EF, peak systolic blood pressure and oscillatory pattern. In a multivariate analysis model comprising all the univariate determinants of peak VO_2, the oscillatory kinetics predicted peak VO_2 independently of the other variables ($p=0.008$). At univariate analysis, VE/VCO_2 slope correlated with age, sex, NYHA class, EF, peak systolic blood pressure and oscillatory pattern. In a multivariate model analyzing the VE/VCO_2 slope and all these covariates, the oscillatory kinetics was an independent predictor of the ventilatory equivalent response ($p=0.017$). **Conclusions** In CHF, an oscillatory pattern of respiratory gas exchange during cardiopulmonary test is associated with a significantly worse exercise tolerance, independently of other known determinants of functional capacity.

1039-66 Long-Term Treatment With Selective Endothelin ETA Receptor Antagonist Suppressed NADPH Diaphorase Activity and Improved Left Ventricular Diastolic Function in Cardiomyopathy

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Background: Endothelin-1 (ET-1) receptor antagonist is expected to improve prognosis of patients with heart failure, but the effect of ETA and ETB receptor antagonist on cardiac function and structure is still controversial. We assessed the hypothesis that long-term treatment with ETA receptor antagonist could reduce inducible nitric oxide synthase (iNOS) in failing heart and improve the cardiac dysfunction in the model of dilated cardiomyopathy. Methods: A selective ETA receptor antagonist ABT-627 (ETa; 10 mg/kg/day) or a selective ETB receptor antagonist A-192621 (ETb; 15 mg/k g/day) was given in 22-week-old J-2-N cardiomyopathic (Nk) hamsters, representing severe heart failure, for 2 months. ET-1 content and NADPH diaphorase activity in left ventricular (LV) myocardium were studied by electron microscopy. Results: Though ETb showed inotropic and chronotropic effect on cardiac function, degeneration of cardiomyocytes remarkably progressed. ETa efficiently preserved the LV diastolic function and tissue damage, furthermore suppressed the NADPH diaphorase activity representing iNOS and ET-1 content in LV. Conclusions: Both ETa and ETb are potent to improve cardiac function. However, only ETa could reduce iNOS and ET-1 content, and also preserve the fine structure of LV myocardium in cardiomyopathy.

	Control (n=10)	Nk+vehicle (n=10)	Nk+ETa (n=9)	Nk+ETb (n=10)
Heart Rate (bpm)	392±9	364±18	367±20	458±9*#
LV pressure (mmHg)	152±7	109±3*	103±3	130±2*#
Ejection Fraction (%)	40±4	22±1*	24±2*	35±3#
Dct (cm/S^2)	1425±108	2517±190*	1866±105#	1908±178#
Cardiocyte Diameter (um)	17.6±0.1	26.1±0.6*	18.5±0.5#	27.3±0.7*

Values are Mean±SEM. Dct; deceleration slope. *$p<0.05$ Versus Control, #$p,0.05$ Versus Nk+vehicle.

1039-67 Novel Lamin A/C Mutations in Idiopathic Dilated Cardiomyopathy and/or Conduction Disease

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Background Idiopathic dilated cardiomyopathy (DCM) is familial in up to 30% of cases. Recent studies have shown that mutations in the lamin A/C (LMNA) gene can cause dilated cardiomyopathy with or without preceding cardiac conduction disease (CCD). Mutations in this gene are identified in up to 33% of cases with DCM+CCD. Our purpose was to assess to what extent mutations in the LMNA gene are responsible for DCM +/- CCD in our population and to test the hypothesis that LMNA mutations can be identified in patients with (still) pure CCD because CCD can precede DCM by 10 to 20 years.

Methods we studied the LMNA gene in 27 index cases with a cardiac phenotype but without overt signs of generalised myopathy using a PCR/DGGE/sequencing analysis. 10 Index patients had DCM+CCD, 14 had "pure" DCM, 3 had CCD. Patients were subclassified according to family history and additional medical information from family members (see table).

Results (see table)Novel mutations were identified in 1 family with pure DCM (1512-1513insAG) and in a patient with DCM+CCD and a positive family history (IVS7+1G>A). Mutations described before were identified in 1 large family with DCM+CCD (Asn195Lys) and 1 family with CCD (Arg225X).

Conclusions LMNA mutations were identified in families with DCM +CCD or pure DCM but also in a family with isolated CCD. LMNA mutations can be identified in patients or families with (still) an isolated CCD phenotype because CCD can precede DCM by up to 20 years. Two of the mutations identified were not described before.

results

phenotype/total no	category	no. patients	mutation
DCM+CCD (n=10)	proven familial	5	Asn195Lys
	pos. family history	2	IVS7+1G>A(novel)
	sporadic	3	-
pure DCM (n=14)	proven familial	11	1512-1513insAG(novel)
	pos. family history	1	-
	sporadic	2	-
CCD (n=3)	familial	3	Arg225X
total		27	4