Methods: DNA extracted from explanted DCM hearts (n=17, 1 female; 49±13 years; LVEF: 18±5%) were investigated for the 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. PCR-products analyzed by high-resolution fragment analysis (GeneScan), displayed a Gaussian-like distribution profiles in polyclonal and single dominant peaks in mononuclear 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 7/17 (41%) 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 (2/9), Vβ19.02 (1/9), and Vβ19.04 (6/9) in each of the remaining cases.

Conclusion: Clonal T-cell composition is exclusively present in DCM, as detected by PCR-based analysis of the TCR-β gene. This phenomenon is indicative of 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).

1039-04 Prenatal Naltrexone Exposure Adversely Alters Postnatal Cardiac Development: A Model for Dilated Cardiomyopathy

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Background: Opioid Growth Factor (OGF) is an inhibitory pentapeptide that interacts with its receptor (OGFR) to target cell proliferation and DNA synthesis. Recent 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 would alter postnatal cardiac function.

Methods: Timed-pregnant 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) 20, 55 and 110 NTX-exposed and control rats. Six to eight male and female offspring of each group were studied for LV diastolic dimension, LV thickness, shortening fraction (SF) and heart rate.

Results: PD 25 male and female and PD6 female offspring exposed to NTX had significant increases in LV end diastolic diameter (PD 25: 17.6±0.1 vs 16.5±0.6 mm, p<0.05), LV end systolic diameter (PD 25: 17.4±0.8 vs 16.3±0.5 mm, p<0.05) and LV wall thickness (PD 25: 2.9±0.2 vs 2.5±0.3 mm, p<0.05). PD110 NTX-exposed rats had increased thickness of the LV free wall (PD 110: 3.0±0.2 vs 2.7±0.1 mm, 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 exposure demonstrated significant changes in ventricular size, systolic function and heart rate. The NTX exposed rats had dilated left ventricles at early 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 O2 consumption 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.

Methods: Data was collected in 103 patients (55 females, 48 males; age: 63±12 years) with CHF, EF, peak systolic blood pressure and oscillatory pattern. In a multivariate analysis model comprising all the univariate determinants of functional capacity

1039-66 Long-Term Treatment With Selective Endothelin ETA Receptor Antagonist Suppressed NADPH Diaphragm 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 expression in chronic heart failure and improve the cardiac dysfunction in the model of diluted cardiomyopathy. Methods: A selective ETA receptor antagonist ABT-627 (ETa; 10 mg/kg/day) or a selective ETB receptor antagonist A-19621 (ETb; 15 mg/kg/day) was given in 2-week-old J25-N cardiomyopathic (Nk) hamsters, representing severe heart failure, for 2 months. ET-1 content and NADPH diaphragm 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.

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

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Background: Atrial fibrillation (AF) is familial in up to 70% of cases. Recent studies have shown that mutations in the lamin A/C (LMNA) gene can also cause dilated cardiomyopathy with or without preceding cardiac conduction disease (CCD). Mutations in this gene are identified in up to 30% of cases with DCM+CCD. Our purpose was to assess to what extent mutations in the LMNA gene are responsible for DCM 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. 17/27 (63%) had clinical evidence for AF and 17/27 (63%) had structural heart disease (9/27 with obvious fibrosis). Results: LMNA mutations were identified in 13/27 (48%) patients with DCM+CCD (n=9), valvular heart disease: n=3, donor hearts: n=3) served as controls (n=20, PD35 male and female and PD55 female offspring exposed to NTX had significantly increased left ventricular pressure (mmHg) 152±7 109±3 103±3 130±2$, #p<0.05 Versus Control, $p<0.05 Versus Nk-vehicle.

Results (see table): Novel mutations were identified in 1 family with pure DCM (1512.313insAG and in a patient with DCM+CCD and a positive family history (VS7 and 13A)).

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 with (still) pure CCD because CCD can precede DCM by 10 to 20 years.