were analysed immunohistochemically by confocal laser microscopy for the composition of the cardiac endomyocardial tissue components using specific antibodies against collagen type III, factor XIIa, TGF beta and laminin.

Results: The main component of the cardiac collagen is collagen I, followed by collagen III, laminin and type IV collagen. The layer is extremely rich with nuclei. In the subendocardium the laminin surrounds hypervascular and pycnocell mitochondria. The regular structure of normal endocardio-myo-capillary system is destroyed, thereby enhancing a prominent feature. The cardiac membrane itself does not contain laminin, however. In the borderzone between the cardionic membrane and the myocardium the lining of TGF beta positive cells is found regularly. From these factors XIIa positive cells disperse into the surrounding myocytes.

Conclusion: To the best of our knowledge this is the first description that the 2 proteins TGF beta and factor XIIa are regular constituents in the cardiac fibrosa plaque in right ventricular endomyocardium. Both proteins are known to contribute to inflammation and healing in general. Their presence in the endomyocardium substantiates the ‘response to injury hypothesis’ for the pathogenesis of the cardiac heart.

Enhanced Instability of Membranous Type 1 Matrix Metalloproteinase in Response to Mechanical Loading in Left Ventricular Myocardium

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Methods and Results: Unloading (UL, n=5) and loading (LO, n=5) of the left ventricle in dogs were achieved by constriction of the inferior vena cava and by rapid ventricular pacing (180 beats/min) for 10 days, respectively. Although the expression of the active form (37-40 kDa) of MT1-MMP in UL and LO did not differ from control (n=6), the inactive form of MT1-MMP (43-40 kDa) significantly (p<0.01) increased by 158% in LO, and significantly (p<0.05) decreased by 55% in UL, assessed by Western blotting. In addition, tissue inhibitor of MMP (TIMP)-2 significantly (p<0.01) decreased by 56% with the reduction of zymographic MMP-2 activity in LO.

Conclusion: In summary, mechanical loading initiates the autocaltivation of active MT1-MMP into inactive form concomitant with TIMP-2 reduction, resulting in decreasing MMP-2 activity. These in vivo findings suggest that ECM degradation pathway mediated by MT1-MMP down-regulates in response to mechanical loading to counteract the overload. Thus, we speculate the important compensatory biological system of MMP/TIMP for maintaining the adequate ECM circumstance in the development of heart failure.

Assessment of Ventricular Untwisting Recoil Velocity by Doppler Tissue Echocardiography: An Index of Relaxation Time Constant

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Methods and Results: We obtained micromotion-registered recorded LV pressures and DTE data in 4 anesthetized closed-chest dogs at baseline, during right and left ventricular pacing, and during dobutamine and esmolol infusion (total 21 stages). τ was calculated by the equation: LVp = PdV/T (τ) + P. LV-VU (rad/s) was defined as the difference between rotational velocities at the basal and apical short-axes levels of the LV. The rotational velocity was calculated from the septal and lateral regional velocity obtained from the LV short-axis and corrected by the instantaneous LV radius. The LV-VU showed a strong nonlinear relation with τ (r = 0.80, p < 0.001, see figure). LV-VU showed moderate correlation with minimum dp/dt (r = 0.41, p = 0.05 by repeated-measures linear regression).

Conclusion: Ventricular untwisting recoil rate, as determined by DTE using our novel method, may facilitate measurement of LV pressure decay as an index of relaxation. This method may provide an estimation of ventricular relaxation in individual patients, allowing serial noninvasive evaluations.

Improved Calcium Homeostasis and Antiarrhythmic Effects of a Novel Chimeric Molecule That Inhibits Both Type III Phosphodiesterase and L-Type Calcium Channel in Failing Hearts

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Background: Congestive heart failure (CHF) is becoming an increasing contributor to mortality rate as a function of the aging population. Because of their ability to improve cardiac performance and symptoms of decompensation, phosphodiesterase inhibitors (PDEIs) have been used in the treatment of patients with severe CHF. However, several trials have shown that PDEIs result in a +25% increase in mortality rate, apparently due to arrhythmias. We have developed a novel dual-pharmaco-compatible compound (ATI21207) designed to simultaneously inhibit the cardiac phosphodiesterase PDE3 and the L-type calcium channel (LCC). We hypothesized that ATI21207 would preserve the beneficial effects of a pure PDEI, while minimizing deleterious responses through antagonism of LCC.

Methods: Hemodynamic, echocardiographic, and electrocardiogram data were measured in anesthetized dogs with tachycardia-induced (220-240 bpm ± 5 weeks) CHF. Effects of graded intravenous doses of ATI21207 were measured, and a pure PDEI, milrinone (MI), on hemodynamic and arrhythmia indices were compared to those of vehicle control.

Results: Both ATI21207 and MI resulted in a comparable decline in mean arterial pressure and left ventricular end-diastolic pressure, while heart rate increased <5% in both groups at all doses. However, MI infusions resulted in non-sustained ventricular tachycardia (frequency of 173±12 bpm, mean(SEM)± at all doses, while none were observed with ATI21207. ATI21207 produced a dose-dependent increase in the rate of ventricular relaxation [dP/dt]min with a maximal increase of 120±7% of control, 87% of the maximal effect of MI (138±11%). ATI21207 also produced a dose-dependent increase in +dP/dtmax, ejection fraction, and fractional area shortening, with the maximal increase in contractile reserve at the highest dose being only 65-70% of the maximal effect of MI.

Conclusions: ATI21207 improves hemodynamic indices in dogs with CHF, and has selective ionic effects. This novel pattern of hemodynamic action, coupled with a reduced arrhythmogenic profile, may make ATI21207 a promising agent for CHF therapy, particularly in patients with a significant component of diastolic dysfunction.

POSTER SESSION

1088 Heart Failure: Treatment

Monday, March 08, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

Partial Fatty Acid Inhibition by Trimetazidine Improves Left Ventricular Function in Patients With Heart Failure of Different Etiologies

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We assessed whether the addition of the partial fatty acid inhibitor trimetazidine (TMZ) to standard conventional therapy (CT) in patients (pts) with heart failure, can effectively improve symptoms, restoring left ventricular function and exercise tolerance. Forty-one pts (37 males, age 64±4 yrs) were randomly allocated in an open label fashion to either CT (21 pts) or conventional therapy plus TMZ (20 mg tid) (20 pts). All pts underwent 2D-echocardiography and exercise testing before and at follow up (11±3 months). NYHA functional class, ejection fraction (EF-%), exercise time (ETsec) and metabolic units during and after exercise (MET5-3.5 ml O2/kg * min) were evaluated. Physicians performing functional tests were blind to patients’ treatment arm. At baseline NYHA class, EF (37±8 vs 38±6), exercise time (411±129 vs 397±143) and METS (7.2±3.1 vs 7.8±2.5) were not different in the TMZ and CT groups, respectively. At follow-up, in the TMG group 11 pts improved NYHA class and none worsened, while in CT NYHA class improved only in 2 pts and worsened in other 2. EF significantly increased in TMZ pts compared to CT (43±9 vs 35±8, p=0.008). Finally, although not significantly, exercise time (414±166 vs 369±137, p=0.026) tended to be higher in TMZ pts. In conclusion, long term TMZ, by shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism, improves left ventricular function and symptoms in pts with heart failure, regardless of its etiology. The observed TMZ benefits contrast with the natural history of the disease, as confirmed by the mild but consistent decrease of EF in pts when on CT only. Whether these benefits would translate into improved survival should be ascertained by a multicenter trial.