5:00 p.m.

838FO-5 Immediate Postinfarction Shape Changes Predict the Outcome of the Remodeling Process

Sina L. Moainie, T. Sloane Guy, IV, Joseph H. Gorman, III, Martin St. John-Sutton, Robert C. Gorman, *University of Pennsylvania, Philadelphia, Pennsylvania.*

INTRODUCTION: Post-infarction left ventricular (LV) remodeling causes heart failure as a result of LV aneurysm (LVA) formation, ischemic mitral regurgitation (IMR) or ischemic cardiomyopathy (ICM). We hypothesized that early post-infarction changes in LV shape predict the ultimate outcome of the remodeling process. METHODS: Three groups of 5 sheep underwent infarction (MI) of 23% of the left ventricle. Infarction in Group I led to LVA, in Group II it led to progressive IMR, and in Group III it led to ICM without IMR or LVA. All animals underwent echocardiography at baseline and 1 hr, 2, 5 and 8 weeks after MI to assess remodeling and LV shape changes. LV shape was assessed by the ratio of the LV internal diameter at end-systole to the left ventricular long axis length at end-systole (sphericity index). RESULTS: Group I (LVA) had immediate decline in ventricular sphericity after MI that persisted throughout the remodeling. Group II (IMR) had an increase in LV sphericity immediately that progressed over eight weeks. Group III (ICM) animals did not experience early changes in left ventricular sphericity but had a progressive increase in sphericity over the eight-week study period. CONCLUSION: After MI, early changes in LV sphericity predict the final result of LV remodeling. An immediate increase in LV sphericity is correlated with the development of IMR while a delayed increase is seen with ICM. An early decrease is associated with LV aneurysm.

Left Ventricular Sphericity Index

Timepoint	Group I (LVA)	Group II (IMR)	Group III (ICM)
Baseline	0.49(±0.04)	0.48(±0.03)	0.47(±0.08)
1 Hour Post-Infarction	0.44(±0.06)*	0.52(±0.04) *	0.47(±0.09)
2 Weeks Post-Infarction	0.44(±0.04)	0.54(±0.06)	0.48(±0.09)
5 Weeks Post-Infarction	0.40(±0.08)	0.54(±0.06)	0.49(±0.09)
8 Weeks Post-Infarction	0.41(±0.07)^	0.56(±0.08) ^	0.54(±0.06) ^

*p<0.05 1 hour compared to baseline ^p<0.05 8 weeks compared to baseline

5:15 p.m.

838FO-6 Endothelin Antagonism With Bosentan Improves Myocardial Mechanics and Ventricular Remodeling in Rats With Chronic Heart Failure

Ingeborg Schafhalter-Zoppoth, John R. Teerlink, *San Francisco VA Medical Center, San Francisco, California, UCSF, San Francisco, California.*

Background: The effect of ET antagonists on ventricular remodeling in CHF remains controversial and there has been limited investigation of the functional effects of ET blockade in CHF. We hypothesized that chronic therapy with bosentan would not only result in attenuation of progressive ventricular dilation, but would also result in functional improvements in myocardial mechanics.
Methods: Adult male Sprague-Dawley rats (270-300g) underwent coronary artery ligation (CAL) and rats with ejection fraction <40% on conscious echocardiography at day 5-7 after surgery were assigned to the CHF group. One week after surgery the animals were randomized to Placebo(P) or Bosentan (B;100 mg/kg/d) as a food additive. After 8 weeks of treatment, the animals underwent conscious echocardiography and in vivo hemodynamics and assessment of cardiac mechanics with a conductance catheter. The hearts were excised and diastolic pressure-volume curves were obtained (n>9 in all groups).
Results: Baseline data (EF, body weight) showed no differences between the treatment groups. There were no differences in body weight at 8 weeks, but echo EF was higher in the bosentan group (B, 26.4±2.3%, vs. P, 19.4±1.7%; p=0.028) and LVEDP was lower (B, 20.2±3.4 mmHg, vs. P, 29.5±2.5; p=0.05). Conductance catheter measurements demonstrated that bosentan treated rats had increased stroke volume (p=0.02), cardiac output (p=0.03), and increased maximal power (B, 93.5±17.5 mW, vs. P, 36.6±5.3; p=0.006; preload adjusted, p=0.01). Vena caval occlusions demonstrated a trend toward increased Ees (p=0.12) and ex vivo passive pressure-volume curves demonstrated marked reductions in ventricular volumes (LVEDVI@20mmHg: B, 2.17±0.17 ml/kg, vs. P, 2.78±0.13; p=0.01) in the bosentan treated group, but no differences in stiffness constants over the 10-30 mmHg range.
Conclusion: These data demonstrate that chronic ET blockade with bosentan results not only in significant attenuation of ventricular dilation, but also markedly improves ventricular function. Whether this improvement translates into symptomatic benefit in patients is being studied in current clinical trials.

ORAL CONTRIBUTIONS

839 Heart Failure Trials II

Monday, March 18, 2002, 4:00 p.m.-5:30 p.m.
Georgia World Congress Center, Room 364W

4:00 p.m.

839-1 Vasopressin Receptor Blockade With Tolvaptan in Chronic Heart Failure: Differential Effects in Normonatremic and Hyponatremic Patients

Mihai Gheorghiade, Marvin A. Konstam, James E. Udelson, John Ouyang, Cesare Orlandi, *Northwestern University School of Medicine, Chicago, Illinois.*

Background: We have reported that chronic vasopressin V2 receptor blockade with tolvaptan (TLV) in pts with congestive heart failure (HF) reduces body weight and edema, and increases serum Na+. However, the effects of tolvaptan in HF patients with hyponatremia are not known.
Methods: After a 3-day run-in period, 250 pts with HF and signs of congestion were randomized to placebo (n=62), TLV 30 mg (n=64), 45 mg (n=62) or 60 mg (n=62) qd for 25 days. Pts were on standard therapy, not fluid restricted, and maintained on stable furosemide (20-240 mg/day) throughout the study.
Results: At baseline, hyponatremia (serum Na+ ≤136 mEq/L) was seen in 34, 23, 23, and 32 % of the placebo, TLV 30, 45, and 60 mg pts respectively. A significant and dose-dependent increase in urine volume was observed with TLV at day 1 in both normonatremic and hyponatremic pts. Changes in body weight (kg) and serum Na+ (mEq/L) at day 1 and 25 are shown in the table. No changes in serum K+ or other laboratory values, and BP were observed. In patients with HF and signs of congestion, TLV therapy reduced body weight and edema to a similar degree irrespective of serum sodium at baseline. Although serum Na+ increased at day 1 in both groups, it returned to baseline by day 25 in normonatremic pts, while remained normalized in hyponatremic pts.
Conclusions: In addition to reducing body weight and lessening edema, TLV therapy normalizes serum sodium in pts with HF and hyponatremia.

		Day	PLC	TLV 30mg	TLV 45mg	TLV 60mg
Body Weight	Hypo	1	+0.3±1.0	-0.2±0.7	-1.2±1.5*	-0.5±1.2*
		25	+0.4±1.8	-0.4±1.7	-1.3±3.3*	-0.7±1.5
	Normo	1	+0.3±1.7	-1.0±1.0*	-0.9±2.0*	-0.9±0.9*
		25	+0.7±2.2	-1.0±2.3*	-1.0±2.1	-0.4±2.0*
Serum Sodium	Hypo	1	+1.2±1.6	+3.6±2.1*	+3.3±2.4*	+5.2±2.1*
		25	+1.0±2.8	+2.1±4.2	+1.5±2.3	+4.3±2.4*
	Normo	1	-1.8±7.4	+2.3±2.4*	+2.9±2.4*	+2.6±2.5*
		25	-0.6±2.8	+0.2±2.5	-0.5±3.0	-0.4±2.6

4:15 p.m.

839-2 Cardiac Resynchronization Therapy Reduces Morbidity in Patients With Moderate to Severe Systolic Heart Failure and Intraventricular Conduction Delays

William T. Abraham, Westby Fisher, Andrew Smith, David DeLurgio, Evan Loh, Angel Leon, Dusan Kocovic, Alfredo Clavell, David Hayes, *University of Kentucky, Lexington, Kentucky, Crawford Long/Emory University Hospital, University of Pennsylvania, Mayo Clinic.*

Background: Cardiac resynchronization therapy (CRT) has been demonstrated to improve exercise capacity, quality of life and cardiac function in moderate to severe heart failure patients with systolic dysfunction and a wide QRS. The impact of CRT on survival and hospitalization for heart failure has not been determined. Methods: The Multicenter InSync Clinical Evaluation included secondary objectives to assess survival and hospitalization. Inclusion criteria were: NYHA Class III or IV HF, LVEF ³ 35%, LVEDD ³ 55 mm, stable and optimal medical regimen, and a QRS duration ³ 130 msec, without pacing indications. All patients were implanted with a CRT system. Patients were randomly assigned to either CRT or no CR (Control) for 6 months. Using a time to event analysis our objective for this substudy was to assess the impact of CRT on survival and hospitalization in a 6 month period. Results: A total of 225 patients were assigned to the Control group, and 228 were assigned to CRT. Freedom from an event (95% CI) at 6 months for Control is 81.0% (75.1%, 85.6%), and for CRT is 87.3% (82.0%, 91.1%) with a relative risk of 0.615 (0.382, 0.990), P=0.043. Conclusion: CRT improves the freedom from major morbid events for select heart failure patients.

4:30 p.m.

839-3 Efficacy and Safety of Carvedilol in Patients With Severe Chronic Heart Failure and Low Systolic Blood Pressure: Results of the COPERNICUS Study

Jean L. Rouleau, Michael B. Fowler, Henry Krum, Hugo A. Katus, Andrew J. Coats, Michal Tendera, Paul Mohacsi, Ildiko Amann-Zalan, Terry L. Holcslaw, Ellen B. Roecker, Milton Packer, for the COPERNICUS Study Group, *Mt. Sinai Hospital, Toronto, Canada.*

Background. Since survival trials with metoprolol and bisoprolol excluded patients with a systolic blood pressure (SBP) < 100 mm Hg, many physicians are reluctant to use β-blockers in such patients, especially those with a vasodilatory effect.
Methods. We evaluated the effects of carvedilol (CRV) vs placebo (PBO) in 2289 patients