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

with severe heart failure (HF) in the COPERNICUS study, of whom 132 had a SBP of 85-95 mm Hg and 264 had a SBP of 96-105 mm Hg at the time of randomization. Following initiation of treatment, SBP increased (CRV>PBO) in the patients with low SBP and fell transiently (CRV>PBO) in the patients with higher SBP. Results (see table):

	All-Cause Mortality		Death or HF Hospitalization	
	1-year PBO rate	Hazard ratio (CRV:PBO)	1-year PBO rate	Hazard ratio (CRV:PBO)
85-95 mm Hg	34%	0.77	61%	0.74
96-105 mm Hg	25%	0.61	43%	0.75
106-115 mm Hg	18%	0.65	37%	0.78
116-125 mm Hg	17%	0.61	40%	0.54
> 125 mm Hg	15%	0.60	32%	0.68

Patients with low baseline SBP were at extremely high risk of a major clinical event, the magnitude of risk decreasing with increasing SBP. However, CRV decreased the risk of death and of death or HF hospitalization in all SBP subgroups, the magnitude of benefit being independent of SBP (interaction P=0.64 and P=0.80 for mortality and for death or HF hospitalization, respectively). The rate of permanent withdrawal decreased with increasing baseline SBP (P=0.0001), similarly for PBO and CRV (interaction P=0.25). Hypotension was reported as an adverse effect more with CRV than PBO overall; this difference was not accentuated in the low SBP subgroups.
Conclusions. These results provide the first evidence that CRV is effective and well tolerated in patients with severe HF and a low SBP.

4:45 p.m.

839-4 The Carvedilol Hibernation Reversible Ischemia Trial: Marker of Success (CHRISTMAS)

John G. Cleland, D. J. Pennell, S. G. Ray, A. J. Coats, A. Lahiri, P. W. Macfarlane, J. Dalle Mule, Z. Vered, G. Murray, for the CHRISTMAS Investigators, *Castle Hill Hospital, Kingston Upon Hill, United Kingdom.*

Background: Improved left ventricular ejection fraction (LVEF) in response to beta-blockers is a consistent finding in dilated cardiomyopathy while it is less consistent in ischaemic heart disease (IHD). This heterogeneous response could be explained by the volume of hibernating myocardium or of scarred myocardium.
Methods: Patients with chronic heart failure (HF) of ischaemic etiology and left ventricular systolic dysfunction (wall motion (WM) index ≤ 1.3 by echocardiography, corresponding to a LVEF ≤ 39%) were enrolled in this international double-blind randomised trial. The primary objective was to determine whether the presence of hibernating myocardium predicted the magnitude of improvement in LVEF in response to carvedilol or placebo. Myocardial status (hibernating or non-hibernating) was assessed by correlating the echocardiographic WM findings to the results of myocardial perfusion imaging (MPI). Hibernation was defined as a regional mismatch between impaired WM with preserved myocardial perfusion by MPI. Baseline LVEF was assessed by radionuclide ventriculography (RNVG). Echocardiographic and nuclear studies were blindly assessed by core laboratories. Hibernators and non-hibernators were stratified into two treatment groups of similar size, randomised to carvedilol or placebo, and titrated up to 25 mg bid. The total duration of the trial was about 6 months.
Results: 305 patients were included in the analysis: 90% males (mean age 62 years), 73% angina-free during daily activity, 60% in NYHA class II, 29% in class III. Mean baseline LVEF was 29 ± 11% (SD). 181 (59%) were classified as hibernators. LVEF was unchanged after 6 months in patients on placebo regardless of myocardial status. Both the hibernating and non-hibernating groups showed significant LVEF improvement with carvedilol. Within the carvedilol group, patients with lower LVEF and larger volumes of hibernating myocardium had a greater LVEF response.
Conclusion: These data suggest that some of the effect of carvedilol on LVEF may be mediated through improvement of hibernating myocardium. Medical therapy may be an important adjunct or alternative to revascularisation for patients with hibernating myocardium.

5:00 p.m.

839-5 Effects of Valsartan on Morbidity and Mortality in Heart Failure Patients Not Receiving ACE Inhibitors

Aldo P. Maggioni, Inder Anand, Sidney O. Gottlieb, Roberto Latini, Gianni Tognoni, Jay N. Cohn, on the behalf of Val-HeFT Investigators, *GISSI Group, Milano, Italy, University of Minnesota Hospital and Clinic, Minneapolis, Minnesota.*

Background: ACE-inhibitors (ACE-i) reduce mortality and morbidity in pts with chronic heart failure (CHF). Nonetheless, nearly 20% of potentially eligible pts may not be prescribed on ACE-i.
Aim: To evaluate the effects of the angiotensin II receptor blocker (ARB) valsartan (V) in the pts randomized in the Val-HeFT trial not receiving ACE-inhibitors.
Methods and Results: Val-HeFT was an international, randomized, double-blind trial testing V vs placebo (P) when added to the prescribed treatment of pts with CHF. The two primary end points were all-cause mortality and morbidity defined as all-cause death, resuscitated sudden death, hospitalization for CHF, or administration of iv inotropes or vasodilators for >= 4h without hospitalization. Of the 5010 pts enrolled in the trial, 366 (9.3%) were not treated with ACE-i at baseline, but 39% were on betablockers. Pts already on treatment with an ARB were excluded. Baseline characteristics and concomitant treatments were comparable in V and P groups not taking ACE-i. Analysis of covariance was performed to assess the effect of V in this subgroup (Table).
Conclusion: Val-HeFT has provided the first placebo-controlled outcome data demonstrating a favorable effect of an ARB on mortality and morbidity in pts with CHF not treated with ACE-i. The improved left ventricular function and reduction in BNP confirm the beneficial effect of V on the progression of CHF. Thus, V can be considered a valid alternative to ACE-i in pts who cannot be treated with these recommended drugs.

	V (n=185)	P (n=181)	p
All-cause deaths %	17.3	27.1	0.02
Morbidity %	24.9	42.5	0.0002
HF Hospitalizations %	27.6	64.6	0.01
EF %	4:66+/-9.19	1.68+/-8.01	0.0004
BNP pg/mL	-53+/-166	64+/-337	0.0004
SBP mmHg	-8.1+/-1.2	-3.2+/-1.2	0.004

5:15 p.m.

839-6 Beneficial Effects of Spironolactone Are Independent of Baseline Aldosterone Levels in Severe Congestive Heart Failure: Results From the RALES Neurohormonal Substudy

Michel F. Rousseau, Annie R. Robert, Jean Marie Ketelslegers, Sylvie A. Ahn, Hubert G. Pouleur, *University of Louvain, Brussels, Belgium.*

Background : Spironolactone (spiro), an aldosterone (aldo) receptor antagonist, is known to improve survival in severe congestive heart failure.
Methods : To determine if this beneficial effect was also present in patients with low baseline aldo plasma levels, aldo plasma concentrations (normal value:<0.4nmol/mL) were measured in 125 patients (mean EF:25%,NYHA III-IV, all treated with ACE-Inibitors), randomly assigned to spiro (n=61) and placebo (n=64) in the RALES Trial.
Results : After 24 months of follow-up, 25% of spiro patients had died versus 42% of placebo patients (p<0.05). Further, when patients were divided according to baseline aldo levels ≥ to median (0.38nmol/mL), the benefit of spiro was present in all patients regardless of baseline values (see table). Indeed, although overall mortality tended to be higher in placebo patients with high baseline values (49%) than those with low baseline values (34%), mortality was also higher in the two placebo groups when compared to patients treated with spiro (RR for placebo vs spiro : 1.76 [0.85-3.93] and 1.58 [0.63-4.13], [95% CI] for high and low baseline values respectively). Given the 95% CI overlap, these RR indicate comparable risk reduction in both spiro groups.
Conclusions : the beneficial effects of spiro on survival are not limited to patients with high circulating aldo levels at baseline, suggesting that tissue concentration might play a key role in the pathophysiology of congestive heart failure.

	Spironolactone		Placebo	
	Death	Alive	Death	Alive
≥0.38	n=8	n=21	n=17	n=18
<0.38	n=7	n=25	n=10	n=19

ORAL CONTRIBUTIONS

845 Hypertrophic Cardiomyopathy Septal Ablation, Athletic Heart, and Doxorubicin Toxicity

Tuesday, March 19, 2002, 8:30 a.m.-10:00 a.m.
Georgia World Congress Center, Room 257W

8:30 a.m.

845-1 Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: A New Standard of Care

Nasser M. Lakkis, Jennifer Franklin, Donna Killip, Sherif S. Nagueh, Robert Roberts, William Spencer, III, *Baylor College of Medicine, Houston, Texas, MUSC, Charleston, South Carolina.*

Alcohol septal ablation for hypertrophic obstructive cardiomyopathy has been introduced in the US by our group at Baylor College of Medicine in Nov 1996. The purpose of this abstract is to report on the clinical and echocardiographic long-term outcome of the 219 patients treated at our institution. The mean age was 51+/-15 years, 133 patients were males. The peak CK post ablation rose to 1352+/-915 units. The mean resting gradient decreased from 60 +/-38 mm Hg to 19+/-28 at 6 weeks and continued to decrease at one year to 10+/- 19 mmHg and 5+/-10 mmHg at 3 years. The provoked gradients decreased from 94+/-54 mm Hg to 53+/-65, 42+/-37, and 29+/-36 at 6 weeks, one year and three years. Along with these positive results, the septal thickness decreased from 2.07+/-0.5 cm at baseline to 1.6 +/-0.4, 1.3+/-0.4, and 1.2+/-0.4 cm at 6weeks, one year and three years.
NYHA class symptoms for heart failure decreased from 2.7+/- 0.7 to 0.3+/- at 0.6 at 3 years. Twenty-four patients had a redo procedure within 4 months of the initial ablation for residual gradient, symptoms or both. One patient had a second redo for the same reasons. Ten patients underwent myomectomies for failure of the ablation procedure to relieve their symptoms significantly. Nine out of these ten patients had very small septal arteries that supplied only a limited territory of the hypertrophied septum, as evidenced by the smaller enzyme peak (443+/-354)in these patients. Nine patients died on follow-up. One patinet died after open heart surgery for failed ablation, Two patients had unwit-