852 The Hemodynamics of Mitral Valvular Heart Disease: Influence of Pharmacology and Physiology

Tuesday, March 31, 1998, 2:00 p.m.–3:30 p.m.
Georgia World Congress Center, Room 364W

2:00

852-1 A Prospective Trial on the Effects of Losartan on the Degree of Mitral Regurgitation

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Vasodilators have been used clinically in pts with mitral regurgitation (MR), but their efficacy in reducing volume overload caused by MR is not quantitatively documented. In a prospective pilot trial, 29 pts (23 men, age 68 ± 14) underwent a quantitative echocardiogram at baseline and four hours after 50 mg losartan orally. The regurgitant volume (RVol) and effective regurgitant orifice (ERO) were quantified using two methods (flow convergence and quantitative Doppler). Measurements included indexed left ventricular end-diastolic (EDVI) and end-systolic volumes (ESVI), ejection fraction (EF) and mean blood pressure (MBP). In 24 pts, the echocardiogram was repeated after continued oral losartan therapy 50 mg QD for 30 ± 13 days. The effects of losartan are tabulated below.

	Baseline	4 hours	P*	1 month	P*
MBP (mmHg)	107 ± 11	91 ± 11	< 0.0001	93 ± 7	0.0001
ERO (mm2)	43 ± 17	36 ± 16	< 0.0001	37 ± 18	< 0.0001
RVol (cc)	75 ± 29	64 ± 27	< 0.0001	69 ± 29	< 0.0001
EDVI (ml/m2)	128 ± 20	115 ± 18	< 0.0002	117 ± 16	0.0029
ESVI (ml/m2)	48 ± 26	42 ± 23	0.034	40 ± 20	0.14

* P-value for the comparison with baseline using a paired t-test.

Conclusions: We concluded that treatment of mitral regurgitation using the angiotensin II blocker losartan, 1) has favorable effects with a significant reduction of regurgitant volume, regurgitant orifice and left ventricular remodeling; 2) these favorable effects appear to persist with time, 3) are of moderate magnitude, suggesting that 4) the evaluation of the clinical effects of the medication in a controlled trial is warranted.

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852-2 Long-term Therapy With Enalapril in Asymptomatic Patients With Moderate to Severe Chronic Mitral Regurgitation

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Background: Vasodilators acutely reduce regurgitant volume and improve left ventricular (LV) performance in mitral regurgitation (MR), but more data are necessary about their long-term efficacy.

Methods: To assess the long term effect of ACE inhibition in asymptomatic patients (pt) with moderate to severe MR we compared) echocardiographic left ventricular (LV) performance in 30 pt before and after 6 months. After randomisation 15 pt were allocated to enalapril (E) therapy (24 ± 7 mg/day) and 15 pt served as control (C).

Results: There were no differences in baseline Echo measurements of LV diameters, volumes, mass and mean wall stress (MWS) between E and C groups. After 6 months pt receiving E had a reduction in end-diastolic diameter (EDD) (from 63.9 ± 6.7 to 60.5 ± 4.1 mm, p = 0.02) and volume (EDVI) (from 115.9 ± 21.4 to 102.9 ± 13.6 ml/m^2, p = 0.02). LV mass (from 176.5 ± 41.0 to 151.4 ± 22.6 g/m^2, p < 0.02) and MWS (from 253.0 ± 36.1 to 223.6 ± 26.8 kdyne/cm^2, p < 0.01). End-systolic diameter (ESD), volume (ESVI) and EF were not altered. In C group EDD, ESD, EDVI, ESVI, EF, mass and MWS did not change significantly after 6 months. In addition, there was a clear difference between E and C group in EDD (60.5 ± 4.1 vs 65.3 ± 7.1 mm, p = 0.03), ESD (37.7 ± 4.1 vs 40.5 ± 4.2 mm, p = 0.07), EDVI (102.9 ± 13.6 vs 117.9 ± 28.2 ml/m^2, p < 0.05), mass (150.4 ± 22.6 vs 168.3 ± 29.5 g/m^2, p < 0.05) and MWS (223.6 ± 26.8 vs 257.3 ± 31.0 kdyne/cm^2, p < 0.01) after 6 months.

Conclusions: Long term therapy with enalapril in asymptomatic pt with moderate to severe chronic MR reduces LV size and mass suggesting the potential to delay timing for mitral valve surgery.

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852-3 Beta Blockade Must be Added to ACE Inhibition to Improve Hemodynamics and Contractile Function in Experimental Mitral Regurgitation

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Although well established in the therapy of congestive heart failure, the role of ACE inhibitors and beta-blockers in mitral regurgitation (MR) remains controversial. Accordingly, we studied the sequential effects of lisinopril (L) and atenolol (A) (L + A) on 7 dogs with severe left ventricular (LV) dysfunction due to 3 months of MR.

	Baseline	3 mo MR	6 mo MR + L	9 mo MR + L + A
LV mass/BW (g/kg)	4.47 ± 0.25	5.81 ± 0.33	5.60 ± 0.43	6.13 ± 0.41*
RF (%)	60.0 ± 1.5	65.2 ± 4.1	62.4 ± 2.9	56.4 ± 4.7
PCW (mmHg)	9.6 ± 1.3	15.4 ± 1.7	12.1 ± 1.2	9.1 ± 1.4#
K index	3.48 ± 0.17	2.51 ± 0.15*	2.91 ± 0.16	3.35 ± 0.19#

*p < 0.05 vs baseline, #p < 0.05 vs 3 mo. BW = body weight, RF = regurgitant fraction, PCW = pulmonary capillary wedge pressure, K = end systolic stiffness.

We conclude that while there was a tendency for improvement in hemodynamics with L, only the combination of L + A improved hemodynamics and normalized contractility.

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852-4 Effects of Inhaled Nitric Oxide in Patients With Severe Mitral Stenosis and Normal Left Ventricular Function

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Mitral stenosis is associated with increased left atrial pressure and pulmonary hypertension in the setting of normal left ventricular function. The hemodynamic effects of inhaled nitric oxide (NO), a selective pulmonary vasodilator, in mitral stenosis are unknown. Nine women (mean age 61 ± 7 years) with severe rheumatic mitral stenosis (mean valve area (MVA) of 1.1 ± 0.2 cm^2) and normal LV function underwent right and left (via transseptal approach) heart catheterization; measurements were made at baseline, and after inhaling NO (80 ppm) for 10 minutes (mean ± SD; * = p < 0.05).

	Baseline	Nitric Oxide
Ao mean (mmHg)	96 ± 11	96 ± 13
LVEDP (mmHg)	15 ± 4	15 ± 5
LA mean (mmHg)	26 ± 3	27 ± 5
PA Systolic (mmHg)	62 ± 13	54 ± 14*
CO (Fick, l/min)	4.2 ± 1.0	4.3 ± 1.2
SVR (Wood U)	22.1 ± 7.0	21.5 ± 6.8
PVR (Wood U)	3.5 ± 2.6	2.1 ± 1.4*

In 6 patients who underwent successful balloon valvuloplasty, MVA increased from 1.0 ± 0.1 to 1.6 ± 0.3 cm^2 with a decrease in LA pressure (26 ± 2 to 19 ± 4 mmHg, p < 0.05) and PA systolic pressure (55 ± 3 to 44 ± 7 mmHg, p < 0.05). The CO (4.3 ± 1.0 l/min to 4.2 l/min, p = NS) and PVR were unchanged (3.0 WU to 2.8 WU, p = NS).

Conclusions: 1) NO reduced PVR in patients with mitral stenosis and normal LV function by decreasing PA pressure without altering LA pressure or CO. This differs from previous findings in patients with LV dysfunction in whom NO reduced PVR solely by increasing pulmonary wedge pressure. 2) PVR was unchanged immediately after valvuloplasty, despite evidence that it is not fixed as shown by the vascular reactivity with NO. This suggests a need for chronic adaptation to the reduction in LA pressure.

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852-5 Diastolic Function in the Progression From Acute to Chronic MR

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Background: The change in LV diastolic function during the progression from acute to chronic MR is unclear.

Methods: Fifteen dogs underwent placement of 20 LV myocardial markers. MR was created by puncturing the posterior leaflet with a Cope biopsy needle. Biplane videofluoroscopic studies, performed at 1 week (acute MR) and 3 months (chronic MR), were used to assess LV volume and wall stress. Diastolic function was assessed by the maximum time derivative and time constant of isovolumic pressure decay (τ; -dP/dt), time constant of

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isovolumic wall stress decay (τ_c), early LV filling fraction (EFF), and chamber and myocardial stiffness constants (K_c, K_m).

Results: Chronic MR increased diastolic filling volume (FV) by 27% ($P < 0.05$). Chronic MR decreased minimum -dP/dt and increased both τ and τ_c. No statistically significant differences were observed in K_c or K_m (Table). [mean ± SD; *$P < 0.05$; ¶P = N.S. by t-test].

	(-)dP/dt* (mmHg/s)	τ* (ms)	τ_c* (ms)	EFF*	K_c¶	K_m¶
Acute	-1596	39.3	38.9	0.55	0.90	22.2
MR	+279	+4.5	+4.7	+0.21	+0.44	+17.3
Chronic	-1424	45.0	45.6	0.74	0.82	22.5
MR	+308	+8.3	+7.9	+0.22	+0.56	+15.7

Conclusion: Diastolic function is impaired in the progression from acute to chronic MR without changes in myocardial or chamber stiffness properties in this canine model of MR. Diastolic dysfunction in chronic MR is associated with changes in LV filling pattern as evidenced by the increase in EFF.

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852-6 Importance of Mitral Annular Performance in Determining the Mechanism of Functional Mitral Regurgitation

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The mechanism of functional mitral regurgitation (MR) is not well defined. Both an increase in annular diameter and changes in mitral valve apparatus geometry as a result of changes in LV shape have been implicated in the past. Dobutamine stimulation would be expected to change LV systolic function and mitral valve geometry, therefore, comparing the LV shape, and mitral annular diameter at rest and peak dobutamine dose would aid in understanding the mechanism of functional MR. We studied 12 male patients without significant angiographic coronary artery disease with at least mild functional MR. Standard TEE views were obtained at rest and peak dobutamine infusion (25 ± 9 ug/kg/min). Dobutamine decreased LV end systolic volume (LVESV) from 130 ± 55 ml to 103 ± 45 ml ($p < 0.01$) and increased the LV ejection fraction (EF) from 20 ± 10% to 31 ± 12% ($p < 0.01$) and significantly decreased the MR jet area from 3.1 ± 1.6 cm^2 to 1.0 ± 1.5 cm^2 ($p < 0.001$). However, the changes in LVESV and EF did not correlate with the reduction in MR severity ($r = 0.39$ and -0.28, respectively). Dobutamine also significantly decreased the mitral annular diameter in systole (3.9 ± 0.3 cm to 3.6 ± 0.3 cm; $p < 0.01$) and in diastole (4.1 ± 0.3 cm to 3.8 ± 0.3 cm, $p < 0.02$). Mitral annular shortening and shortening fraction also improved with dobutamine and correlated well with changes in MR severity ($r = 0.80$, $p < 0.01$ and $r = 0.79$, $p < 0.01$). We conclude that functional mitral regurgitation appears to be more closely related to changes in annular diameter and contractile state than changes in LV systolic shape or function. Therefore, in patients with significant functional MR, therapeutic attempts at altering LV size or function may be less effective than changing the size of the mitral annulus with an annuloplasty.

853 Transplant Vasculopathy: Clinical Studies

Tuesday, March 31, 1998, 2:00 p.m.–3:30 p.m.
Georgia World Congress Center, Room 254W

2:00

853-1 Development and Progression of Transplant Vasculopathy: Serial Intravascular Ultrasound Study

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Background: Although transplant vasculopathy is a major factor limiting outcome after cardiac transplantation, new lesion formation and disease progression over time have not been thoroughly described.

Method: Serial ultrasound was performed 4 weeks, 1 year and 2 years after transplantation (mean 28 ± 17, 370 ± 31, and 761 ± 49 days, respectively). At a series of matched sites, maximum intimal thickness (Pmax) and intimal area were measured at all three time points. Intimal area was defined as the difference between external elastic lamina and lumen areas. A new transplant vasculopathy lesion was defined as Pmax >0.5 mm on follow-up examination at a previously normal site. The availability of 4 week ultrasound measurements enabled exclusion of sites containing donor-transmitted atherosclerosis.

Results: A total of 289 sites in 50 patients were analyzed at all three time points. At one year, 54 sites in 22 patients showed new lesions with Pmax and intimal area averaging 0.76 ± 0.19 mm and 5.60 ± 1.92 mm^2, respectively. At two year follow-up, these same sites showed minimal, if any, progression with Pmax and intimal area averaging 0.78 ± 0.26 mm and 6.14 ± 2.29 mm^2, respectively, p = NS. However, completely new lesions developed at 52 sites in 28 patients at two year examination. Of the 28 patients with new disease at two years, 14 did not have any transplant vasculopathy lesions at one year. The severity of late developing lesions was similar to lesions that developed within the first year. Pmax and intimal area averaged 0.77 ± 0.36 mm and 4.83 ± 2.54 mm^2, p = NS compared to the first year lesions.

Conclusion: Transplant vasculopathy is a process characterized by continuous and relatively constant development of new lesions at previously uninvolved sites during the first two years. Typically, progression of existing lesions is very slow with barely detectable changes between the first and second years. Thus, therapy targeted at preventing new lesion formation may significantly improve outcome.

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853-2 Discrepancies Between Morphologic and Functional Changes in Cardiac Allograft Vasculopathy. Assessment by Serial Intracoronary Ultrasound and Doppler Studies

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Background: Intracoronary ultrasound (IVUS) has the potential to assess the progression of intimal proliferation in transplant coronary artery disease (TxCAD). The functional significance of TxCAD can be determined invasively by measurement of coronary flow reserve (CFR). We sought to evaluate whether a progression of TxCAD is paralleled by an impairment of CFR by means of serial IVUS and Doppler studies.

Methods: Two groups (Gr.) of patients (P) were studied sequentially: Gr. I (20 P) immediately (<3 months) and 12 months after heart transplantation (Htx). Gr. II (26 P) late (>12 months, mean 79 ± 26) after Htx and 12 months thereafter. Baseline and hyperemic coronary flow average peak velocity were measured to calculate CFR (16 µg adenosine, 0.014 in. Doppler guide wire). IVUS was performed to determine the mean plaque index (PI = [vessel area − lumen area] × 100/vessel area) of the vessel studied with Doppler. The use of a motorized IVUS pull-back system in all 92 studies allowed the identification of corresponding sites between baseline (BaseL) and follow-up (F-up) study.

Results:

	PI (%)		ΔPI (%)	CFR		ΔCFR
	BaseL	F-up		BaseL	F-up	
Gr. I	7 ± 10	17 ± 12*	10 ± 10	2.6 ± 0.7	3.4 ± 0.9*	0.8 ± 0.8
Gr. II	16 ± 13	22 ± 13¶	5 ± 11	3.4 ± 0.8	3.5 ± 0.9	0.1 ± 0.7

(*= p < 0.001, ¶ = p < 0.02 F-up vs. BaseL)

Conclusion: Despite a marked progression of TxCAD in the first year after transplantation, an improvement of CFR to high normal values was observed. Late after Htx, CFR remained unchanged, although intimal hyperplasia further increased. Thus, endothelial independent CRF is not a reliable functional parameter to assess the progression of TxCAD in the first year and late after Htx.

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853-3 Ultrasound Evidence of Comparable Lesion Severity at Proximal and Distal Sites in Transplant Coronary Disease

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Background: Necropsy studies of transplant coronary disease suggest more severe disease occurs in distal vessels, but post-mortem examination rarely encounters patients soon after transplantation.

Methods: Intravascular ultrasound was performed in 93 patients, 1 month and 1 year after transplantation (mean 27 ± 15 and 370 ± 24 days). Arteries were divided into proximal and distal segments using the Coronary Artery Surgery Study (CASS) classification. Matched sites at baseline and follow-up examinations were analyzed for maximal intimal thickness (Pmax). A lesion (Pmax >0.5 mm) present at baseline was defined as a donor lesion and a lesion identified on follow-up at a previously normal site was defined as a de novo lesion.

Results: Of 617 sites studied at 1 year, 89 had donor and 107 had de novo lesions. Pmax for both donor and de novo lesions was similar in proximal