A Multicenter Study of the Safety and Efficacy of
Disopyramide for Treating Symptomatic Obstructive
Hypertrophic Cardiomyopathy

Mark Stepani, Ivan Barac, Barry Morson, Susan Casey, Lida Chojnowska, Shaughan
Dickie, Perry Elliott, William McKenna, St. Luke's-Roosevelt Hospital Center, New York
City, NY

Background: Disopyramide (diso) has been shown to reduce gradient and improve
symptoms in patients (pts) with obstructive hypertrophic cardiomyopathy (HCM). It is
often administered to medically refractory pts who would otherwise need septal
myectomy or other interventions. However, the clinical course of HCM pts treated with
diso has never been investigated in a large cohort. Methods: 141 pts with HCM were
treated with diso at 4 treatment centers from 1998 to 1999. Resting echo gradient and
NYHA class were compared before diso and at follow-up on medication. Results: 141
pts (mean age 46.6) were treated with diso for a mean of 3.9 years with a mean highest
dose of 428 ± 180 mg/day. Most recent gradient on diso was 45 ± 34 mm Hg, signifi-
cantly lower than baseline gradient 78 ± 35 mm Hg. 42% reduction, p<0.0001. 74%
of pts had > 15 mm Hg reduction in gradient, and 42% had > 40% reduction. NYHA class
improved on drug. 16/65/28/19 to 36/57/13/0 for classes I, II, III, IV respectively, p<0.01.
Also, the percentage of patients in NYHA class III and IV decreased after diso from 27%
to 16%, p<0.05. There were 4 HCM-related sudden cardiac deaths that occurred on diso.
Results: mean 54 months after initiation of diso. Annual rate of sudden cardiac death
in a diso-treated HCM pts was 0.74-1.13%, vs 0.47 and annual rate of all-cause cardiac
death. ranged from 1.22-1.79%. 16/18. 93 pts (60%) were still on diso at follow-up. The majority of pts could
be managed without myectomy or other intervention, but, while taking diso, 32% ulti-
mately required intervention for relief of obstruction. Conclusions: Patients with HCM
treated with disopyramide showed a significant and persistent decrease in outflow gradi-
et of 42% and improvement in limiting symptoms. No excess sudden cardiac death
occurred. A therapeutic trial of disopyramide should be considered before proceeding to
major intervention in obstructive HCM.

ORAL CONTRIBUTIONS

809 Molecular Mechanism of Ventricular Remodeling

Monday, March 31, 2003, 9:15 a.m. - 10:30 a.m.
McCormick Place, Room S405

809-1 Early Postinfarction Ventricular Restraint Prevents
Adverse Remodeling and Preserves Borderzone
Contractile Function

Henriem M. Jackson, Joseph H. Gorman, III, Bina L. Moarve, Navneet Nanula, Jagat
Nanula, Martin G. St. John Sutton, L. H. Edmunds, Jr., Robert C. Gorman, Hospital of the
University of Pennsylvania, Philadelphia, PA, Hahnemann University Hospital, Philadelphia, PA

Background: Postinfarction ventricular remodeling is the major cause of CHF. Early inf-
farct expansion (arecthino) initiates adverse remodeling and progressive contractile dys-
function in normally-perfused borderzone (BZ) myocardium. Early LV restraint may
prevent this maladaptive phenomenon. Methods: An infarction of 20% of the LV mass known
to cause CHF and LV dilatation in normally-perfused borderzone was prevented or significantly
reduced in the animals having early postinfarction LV wrapping. Myocardial perfusion was
unchanged in the uninfarcted regions in all animals. There was no evidence of wrap-
induced diastolic dysfunction.

Conclusion: Early postinfarction ventricular restraint to prevent infarct expansion pre-
vents adverse remodeling and preserves contractile function in non-infarcted myocar-
dium. (* p<0.05 preinfarct vs. postinfarct, ** p<0.05 wrip vs. control, *** "Preinfarct" value deter-
mined immediately after infarction)

809-2 Matrix Metalloproteinase Inhibition in Transgenic Mice
With Modified Cardiac Restricted Tumor Necrosis
Factor Expression: Effects on Left Ventricular
Geometry and Function

Ahmed Diaa, Eric M. Wilson, Andrea M. Parkhurst, Patricia Escobar, Jennifer W.
Hendrik, Kathryn B. Dowdy, Abigail S. Lowry, Jennifer R. Holder, Dorelln Lee-Jackson,
Francis G. Spinale, Douglas L. Mann, Baylor College of Medicine, Houston, TX, Medical
University of South Carolina, Charleston, SC

Background: Matrix metalloproteinases contribute to adverse left ventricular (LV)
remodeling and are influenced by tumor necrosis factor (TNF) signaling; however, a
causal relationship remains to be established. We examined the effects of matrix metal-
loproteinase inhibition (MMPi) on LV geometry and function in 2 lines of transgenic mice
with myocardial overexpression of (1) secreted TNF (sTNF) that develop LV dilatation, (2)
a non-cleavable membrane bound form of TNF (mTNF), that develop concentric LV
hypertrophy. Methods: MMPi (PD166793 30mg/kg/day) was instituted from 3 to 6 weeks of age in
mTNF (n=7) and sTNF (n=7) mice. Untreated 8 week old wild type mice, sTNF (n=13), mTNF (n=11),
and mTNF (n=6) mice were controls. LV end-diasstolic volume and ejection fraction were
determined by conductance volumetry and contractility assessed by computing Emax with caval occlusion.

Results: (Table: "p<0.05 vs wild type, t vs mTNF, # vs sTNF). LV end-diastolic volume
was increased in the sTNF group and was reduced with MMPi. MMPi increased LV ejection
fraction in both the sTNF and mTNF groups, likely due in part to increased Emax.
LV hypertrophy was unaffected by MMPi.

Conclusions: MMPi reduced the amount of LV dilation in the sTNF mice, suggesting that
mTNF→mice may have better sarcomere associations in the extracellular matrix influencing myocardial structure
(dilation). MMPi resulted in an increase in contractile function in the mTNF mice and sTNF mice,
suggesting that MMP→induced alterations in the extracellular matrix influence myo-
cardial function.

Results: All values are Mean ± SEM

809-3 Testosterone Aggravates Cardiac Performance and
Remodeling in Mice After Myocardial Infarction

Maria A. Cavasin, Ai-Li Yu, Shrevidya Menon, Xiao-Ping Yang, Henry Ford Health
System, Detroit, MI

The cardioprotective effects of estrogen have been widely studied. However, little is
known about the effects of testosterone (T) on chronic remodeling and prognosis after
MI. We found that female mice given supplemental T had significantly higher mortality
due to cardiac rupture than those treated with placebo (P) during the first week after MI
regardless of ovariectomy, whereas ovariectomy significantly reduced mortality in males.
We hypothesized that testosterone may aggravate chronic cardiomyopathy remodeling
and dysfunction, whereas estrogen may be cardioprotective after MI. 4-week-old males
and females underwent either castration (castr), or sham castration (sham), and ovariectomy
(ovx) or sham ovariectomy (sham-ovx), respectively. S-ovx females were treated with either