

Table

	LVol (ml)	LVMass (gm)	C.O.(L/min)	FS (%)	VCF (circ/sec)	LVESV(gm/cm <sup>2</sup> )	VCF:LVESV ratio	LVEF (%)by MUGA
Baseline	221 ± 68	168 ± 73	3.0 ± 0.9	17.1 ± 6.3	0.63 ± 0.24	234 ± 87	0.0032 ± 0.0021	28.2 ± 8.4
6 Months	197 ± 70 *	163 ± 63	2.9 ± 0.8	23.4 ± 8.0 *	0.78 ± 0.22 *	191 ± 67	0.0048 ± 0.0017 *	35.8 ± 12.9 *

**1012-123 Safety and Tolerability of Fast Up-Titration of Carvedilol in Patients With Heart Failure**

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**Background:** Although beta-blockers (BB) are now the cornerstone in the treatment of congestive heart failure (CHF), many patients are still receiving inadequate doses, probably due to cautious prescription. We designed this study to evaluate the safety and tolerability of a fast up-titration of carvedilol soon after compensation.

**Methods:** After compensation, 31 consecutive hospitalized patients (pts) with left ventricular ejection fraction (LVEF) <= 0.45 who had never used BB to treat CHF and with no contraindication to BB were selected. Mean age was 55.5 years; 21 were men, and in 54.8% (n=17) inotropic support was needed for compensation. Mean LVEF was 0.29±0.07; mean left ventricular diastolic diameter was 7.0±0.7 cm. The initial dose of 3.125 mg bid was doubled each 2 days until day 8 (target dose of 25 mg bid). Criteria for increment were HR >= 55 bpm, systolic blood pressure (SBP) >= 90 mmHg and no worsening of CHF. A 6-minute walk test was performed on day zero, day 5, day 8 and day 30; 24 hours blood pressure continuous monitoring was performed on day zero and day 8.

**Results:** It was possible to reach the daily dose of 25 mg in 23/31 (74.2%) and 50 mg in 19/31 (61.2%) pts. The dose reached on day 8 was not different between pts who did or did not require inotropic support for compensation. In the patients who reached the dose of 25 mg/day the distance walked did not differ between days zero, 5, 8 and 30 (373.6±86.5 vs. 408.7±108.8 vs. 396.3±145.5 vs. 420.0±153.8 meters - p=0.18, 0.48 and 0.22). Mean weight gain was 2.1 kg (p=0.52), and SBP tended to be lower on day 8 (98.5±15.2 vs. 93.2±17.4 mmHg - p=0.06). The same tolerability was observed on day 30. The dose could not be increased in 9 patients, had to be reduced in 1, and had to be withdrawn in 2.

**Conclusion:** Introduction and the fast up-titration of carvedilol can be done even after inotropic support. Rapid up-titration was safe and can be done on lower intervals than currently recommended.

**1012-124 Carvedilol Improves Myocardial Perfusion in Conscious Dogs With Pacing Induced Dilated Cardiomyopathy**

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**Background:** Both combined (β1, β2, α1, Carvedilol) and selective (β1, Metoprolol succinate) adrenergic blockade have been associated with improved survival and clinical outcomes in DCM. Whether there are important differences between the subclasses remains controversial. Little is known with respect to differences in regional myocardial perfusion between agents, especially in non-ischemic DCM. We have shown previously that DCM in conscious dogs is associated with reduced subendocardial perfusion in the absence of CAD.

**Methods:** We studied 15 conscious, chronically instrumented dogs with severe DCM induced by 29 days of rapid pacing (240 min<sup>-1</sup>). We measured regional (subendocardium: ENDO, subepicardium: EPI) myocardial perfusion in the LV and RV using neutron activated microspheres before and after treatment with carvedilol (CARV: 25 mg po BID) or metoprolol (MET: 100 mg po QD) for 3 days. Measurements of coronary perfusion pressure (CPP=MAP-LVEDP-RA) and heart rate (HR) were recorded simultaneously to insure comparable flow determinants.

**Results:** Both treatments were associated with significant (p< 0.01) decreases in HR (CARV: -49±6 from 126±26 min<sup>-1</sup>; MET: -42±3 from 124±6 min<sup>-1</sup>) and LVEDP (CARD: -17±4 from 35±2 mmHg; MET: -14±3 from 36±2 mmHg) and significant increases in CPP (CARV: +12±3 from 44±4 mmHg; MET: +14±3 from 41±3 mmHg).

CARV treatment increased LV ENDO (1.26±0.15 to 1.49±0.22 ml/min/g) but not LV EPI flow (1.06±0.15 to 1.05±0.11 ml/min/g). In contrast, MET decreased LV ENDO (1.17±0.12 to 1.05±0.13 ml/min/g, p<0.05 compared to CARV) but did not change LV EPI (0.96±0.18 to 0.95±0.11 ml/min/g). CARV also increased RV ENDO (0.98±0.15 to 1.56±0.14 ml/min/g) while MET had no effect (1.18±0.19 to 1.12±0.25 ml/min/g, p< 0.05 compared to CARV).

**Conclusion:** Despite comparable effects on HR and CPP, CARV improves LV and RV ENDO perfusion compared to MET. These differences are likely explained by α1 adrenergic blocking effects and may help to explain differences in clinical outcomes between CARV and MET.

**1012-125 Monotherapy With Extended Release Metoprolol Succinate Normalizes Expression of Type-1 Protein Phosphatase in Left Ventricular Myocardium of Dogs With Chronic Heart Failure**

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**Background:** We previously showed that in dogs with chronic heart failure (HF) type-1 protein phosphatase (PP1) activity is increased and that this increase is due, in part, to increased protein level of the alpha catalytic subunit of PP1 (PP1Calpha), an enzyme

considered to be a negative regulator of cardiac function. Increased PP1 activity in HF can lead to dephosphorylation of phospholamban and consequently to abnormalities of calcium cycling within the sarcoplasmic reticulum (SR) ultimately leading to LV systolic and diastolic dysfunction. In the same canine model of coronary microembolization-induced HF, we showed that chronic monotherapy with extended release metoprolol succinate (ER-MET), a selective beta-1 adrenoceptor blocker, improves left ventricular (LV) ejection fraction, reduces end-diastolic wall stress and improves myocardial relaxation. In this study, we examined whether the improvement in LV systolic and diastolic function following chronic ER-MET therapy is associated with reduced PP1Calpha protein expression. **Methods:** Protein expression of PP1Calpha and calsequestrin (CSQ), an SR protein not altered in HF, were measured in LV tissue of 6 dogs with HF treated long-term (3 months) with ER-MET (100 mg once daily), 6 dogs with HF that were untreated and 6 normal dogs. In all instances, protein expression was measured in LV homogenate using Western blots. Bands were quantified in densitometric units. **Results:** Protein expression of PP1Calpha normalized to total tissue levels of CSQ increased significantly in untreated HF dogs compared to normal dogs (0.99 ± 0.05 vs. 0.47 ± 0.02, P<0.05). In dogs with HF treated with ER-MET, PP1Calpha protein expression decreased significantly compared to untreated HF dogs (0.63 ± 0.05 vs. 0.99 ± 0.05, P<0.05), but remained higher than that measured in normal dogs (0.63 ± 0.05 vs. 0.47 ± 0.02, P < 0.05). **Conclusions:** In dogs with chronic HF, PP1Calpha protein expression is increased. Long-term therapy with ER-MET partially restores protein expression of PP1Calpha to near normal levels. Normalization of PP1Calpha expression in HF can explain, in part, the improvement of LV systolic and diastolic function seen with long-term ER MET therapy.

**1012-126 Contemporary Dosing of Angiotensin Converting Enzyme Inhibitors and Beta Blockers in Chronic Heart Failure: Report From the STAMINA:HFP (Study of Anemia in a Heart Failure Population) Registry**

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**Background:** Optimal utilization of angiotensin converting enzyme inhibitors (ACEI) and beta blockers (BB) in heart failure requires treatment of eligible patients and use of doses proven effective in clinical trials. However, doses commonly given patients with heart failure are not well studied.

**Methods:** The STAMINA-HFP Registry enrolled randomly selected patients with heart failure from 6/24/02 to 5/15/03 in 12 specialty clinics and 45 community cardiology clinics. Data on 656 return patients with EF < 40 who were taking either ACEI or BB and had information available on doses of these drugs and use of angiotensin receptor blockers (ARB) were analyzed. Doses were converted to milligram equivalents of enalapril or metoprolol CR/XL. Extent of titration in each patient was evaluated as 1) % of the clinical trial target dose in ACEI and BB mortality trials (%CTTD), (20 mg/d for enalapril and 200 mg/d of metoprolol CR/XL) and 2) % of the mean doses actually achieved in these trials (%MDA) (16.6 mg/d for enalapril and 159 mg/d for metoprolol CR/XL).

**Results:** No patients were taking ACEI + ARB and no BB. Only 2.6% of patients were taking BB + ACEI + ARB. The percentage of patients reaching at least CTTD or MDA and the mean±SD dose equivalents achieved in the other patient groups are shown.

Drug(s) (N)	ACEI CTTD ≥100%	ACEI MDA ≥100%	Enalimg (mg/d)	BB CTTD ≥100%	BB MDA ≥100%	Metocrmg (mg/d)	ACEI + BB CTTD ≥100%	ACEI + BB MDA ≥100%
ACEI (43)	42	42	17±16	--	--	--	--	--
BB (156)	--	--	--	32	33	113±82	--	--
BB+ARB (96)	--	--	--	48	49	161±114¶	--	--
BB+ACEI (344)	54	54	19±15†	39	42	136±116*§	25	27

\*Enalimg=milligram equivalents of enalapril, Metocrmg=milligram equivalents of metoprolol CR/XL, -- = not applicable.  
 †p=0.408 BB + ACEI versus ACEI alone, \*p=0.012 BB alone versus BB + ACEI, ¶p=0.001 BB alone versus BB + ARB, §p=0.080 BB + ACEI versus BB + ARB

**Conclusions.** Registry patients with documented systolic dysfunction were commonly treated with doses of ACEI and BB below MDA. Whether dose titration is limited by clinical characteristics or other factors is under investigation.

**1012-127 Neutral Endopeptidase Inhibition Augments the Vascular Actions of Bradykinin in Patients With Heart Failure on Chronic Angiotensin-Converting Enzyme Inhibitor Therapy**

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**Background** Angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) degrade kinins. ACE inhibition potentiates bradykinin mediated vasodilatation and endothelial release of the pro-lytic factor, tissue plasminogen activator (t-PA) in patients with chronic heart failure (CHF). We investigated whether additional NEP inhibition with thior-