Two Transgenic Animal Models Expressing Human Tropinin T Gene Mutations: One Exhibiting Dilated Cardiomyopathy (W141) and the Other Exhibiting Hypertrophic Cardiomyopathy (Q92)

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Background: The usual response of the heart is hypertrophy. Decompensation and subsequent heart failure often occurs after transition from hypertrophy to dilatation appears to reflect an inhibition of growth. Tropinin T (cTNt) mutations have been identified to cause familial hypertrophic cardiomyopathy (HCM) and other familial dilated cardiomyopathy (DCM). Thus, different mutations of the same gene induce different growth patterns. HCM is induced by cTNt Q92 and DCM by cTNt W141 mutations.

Methods: We generated a transgenic mouse (TM) expressing the cTNt Q92 mutation with a phenotype of HCM and a TM expressing the cTNt W141 with a phenotype of DCM using alpha MHC as the cardiac specific promoter.

Results: The HCM phenotype (cTNt Q92) has normal heart size with sarcomere disarray, fibrosis and an increased cardiac ejection rate 73.9 ± 9.4. In contrast, the DCM phenotype (cTNt W141) has a large dilated heart without fibrosis but with decreased contractility.

Echo analysis was normal at 4 weeks but at 12 weeks showed: Diastolic left ventricular dimension (LVD) in non-transgene (NT) was 3.68 ± 0.64 versus 4.77 ± 0.20 (p < .05) in TM; systolic LVD of 2.32 ± 0.09 in NT versus 4.01 ± 0.20 in TM; fractional shortening rate of NT was 0.37 ± 0.01 versus 0.16 ± 0.09 in TM; and peak ejection rate of 113 ± 5 in NT versus 84 ± 4 in TM. Gene microarray and northern analysis of myocardin gene expression in HCM and DCM were performed for markers associated with a hypertrophic growth response. Expression of IGF and ANP was normal in HCM and DCM. In contrast, skeletal alpha actin was decreased in HCM but increased in DCM. BNP normal in HCM was decreased in DCM.

GP130, increased in HCM was decreased 1 to 2 fold in DCM. Conclusion: These data suggest that resting atrial contractile function is not a determinant of functional capacity in patients with HNCM. Possibly, atrial contractile reserve associated with exercise might be a more important factor for limitation of functional capacity in these patients.

Role of Left Atrial Contractile Function in Functional Capacity of Patients With Hypertrophic Nonobstructive Cardiomyopathy

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Background: Left atrial (LA) dilatation and reduced atrial contractile function have been demonstrated in symptomatic patients with hypertrophic, non-obstructive cardiomyopathy (HNCM), suggesting the presence of a primary atrial myopathy. Since LA contractile function partially governs left ventricular (LV) preload reserve and maintenance of the Frank-Starling mechanism, LA systolic dysfunction could provide a mechanism for exercise intolerance in HNCM. We, therefore, evaluated LA contractile function in 50 patients with HNCM (mean age=37±10 years, 29 men/21 women) who were stratified for symptoms of congestive heart failure. Methods: We analyzed LA volume normalized to body surface area, active atrial ejection fraction (LAEF), ejection force (LAF), and kinetic energy (LAKE), in asymptomatic (Group 1, n=19) and symptomatic (Group 2, n=31) subjects and compared these parameters to symptom-limited metabolic stress testing performed within one week of echocardiographic examination. Results: MRI-derived LV mass was similar between Groups 1 and 2 (mean=229±68 vs. 223±78 gms, respectively; p=N.S.) and there were no differences in LAEF, LAF or LAKE in symptomatic versus asymptomatic subjects [59.8 ±19.9% vs. 60.6±22.8%, 14.7±8.7 vs. 15.6±11.2 (idynve), 16.6±19.7 vs. 10.4±13.0 (kerg), respectively]. While resting LAEF correlated weakly with exercise time (r=0.319, p=0.05), it did not predict MVQO2 or anaerobic threshold (p=N.S. for both). Neither were LAF nor LAKE associated with any objective exercise parameter. Maximum LA volume, an index of LA volumetric remodeling, was inversely correlated with peak MVQO2 (r=-0.32, p=0.05). Conclusion: These data suggest that resting atrial contractile function is not a determinant of functional capacity in patients with HNMC. Possibly, atrial contractile reserve associated with exercise might be a more important factor for limitation of functional capacity in these patients.

Anemia in Diastolic Heart Failure Is Frequent and Associated With Worse Outcome

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Background: Many patients with heart failure (HF) and a reduced ejection fraction (EF) have anemia. The prevalence and importance of anemia in patients with HF and a normal EF (diastolic HF) are not known. Thus, we hypothesize that anemia is common in diastolic HF and associated with a worse outcome.

Methods: We evaluated 137 patients with clinical evidence of HF and a normal EF (> 0.50).

Results: The age was 65±15 (mean ± SD) years, and 58% were women. Anemia (hemoglobin, Hb < 12 g/ml in women; <13 g/ml in men) was common, occurring in 45% of patients. Patients with and without anemia had similar ages (65±15 vs 65±14). EF (0.62±0.08 vs 0.61±0.07), LV mass (213±77 vs 193±85 gms), and systolic mitral annular velocity (6.8±1.5 vs 6.9±2.1 cm/sec). Patients with anemia had a higher brain natriuretic peptide (BNP) (322±330 vs 160±240 pg/ml, p<0.001), worse diastolic dysfunction grade by mitral Doppler (1.3±8 vs 0.8±7, p<0.001), and a higher ratio of peak mitral inflow velocity to mitral annular velocity (E/Eg) (13.5±6.5 vs 9.7±4.2, p=0.001) compared to patients without anemia. Reduced Hb concentration correlated with both elevated BNP (P<0.015, p=0.0001) and E/Eg (P=0.15, p=0.0001). Patients with anemia had a reduced two-year cardiac hospitalization-free survival (hazard ratio 2.0, p<0.05).

Conclusion: Anemia is common in pts with HF and a normal EF (diastolic HF) and is associated with greater elevations in BNP, more severe diastolic dysfunction, and a worse prognosis.

Hemoglobin Level Is Associated With Mortality and Hospitalization in Patients With Severe Chronic Heart Failure: Results From the COPERNICUS Study

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Background: Anemia has been shown to be a risk factor for mortality in mild to moderate chronic heart failure (CHF), but its importance in severe CHF and its ability to predict hospitalization has not been defined.

Methods: We evaluated the relationship between hemoglobin level and mortality and hospitalization in 2286 patients (1822 men, 464 women) with severe CHF enrolled in the COPERNICUS study. All enrolled patients had dyspnea or fatigue at rest or on minimal exertion for at least 2 months and a left ventricular ejection fraction <25%.

Results: There was a highly significant (P<0.0001) but small (r = 0.089) inverse relationship between baseline hemoglobin and creatinine levels. Patients with low hemoglobin were at significantly higher risk of a major clinical events, the magnitude of risk decreasing with increasing hemoglobin, both in univariate analyses (all P<0.001) and in multivariate analyses which adjusted for sex and other predictors of risk, including age, left ventricular ejection fraction, creatinine, body mass index, systolic blood pressure, CHF etiology and treatment with carvedilol (all P<0.01). Mean creatinine levels and one-year Kaplan-Meier event rates are shown below:

Conclusion: Low hemoglobin is an independent risk factor for adverse outcomes in patients with severe CHF. Whether correction of anemia improves outcomes in CHF warrants further study.

Table:

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<th>Death or HF Hospitalization (%)</th>
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