

Haptoglobin Genotype Determines Long-Term Survival and Affects Cardiac Remodeling after Myocardial Infarction in Diabetic Mice

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Introduction: Hp genotype predicts long term survival and congestive heart failure after myocardial infarction (MI) in individuals with diabetes mellitus. We have determined that Hp genotype determines the extent of myocardial necrosis after Ischemia-Reperfusion injury in diabetic mice. **We hypothesized** that Hp genotype would play a role in cardiac remodeling and left ventricular (LV) dysfunction after MI in diabetic mice.

Methods: The Hp 2 allele exists only in man. Wild type C57Bl/6 mice carry the Hp 1 allele. We genetically engineered a murine Hp 2 allele and targeted its insertion by homologous recombination to the murine Hp locus to create Hp 2 mice. MI was produced by occlusion of the left anterior descending artery in diabetic mice. MI size was determined with TTC. LV function and dimensions were assessed by echocardiography before the MI, 4 days and 30 days after the MI.

Results: MI size was similar in diabetic Hp 1 and Hp 2 mice 24 hours after MI. However, diabetic Hp 2 mice had a higher mortality rate than diabetic Hp 1 mice 30 days after the MI. Mortality rate was similar in sham operated mice. There was no significant difference in LV function between diabetic Hp 1 and Hp 2 mice at the different time points. LV end-diastolic area was significantly increased in Hp 2 mice compared to Hp 1 mice 30 days after MI.

Conclusion: In diabetic mice the Hp 2 genotype is associated with increased mortality and more severe cardiac remodeling 30 days after MI.

Myocardial Mechanics Explains the Time Course of Benefit in Septal Ethanol Ablation for Hypertrophic Obstructive Cardiomyopathy

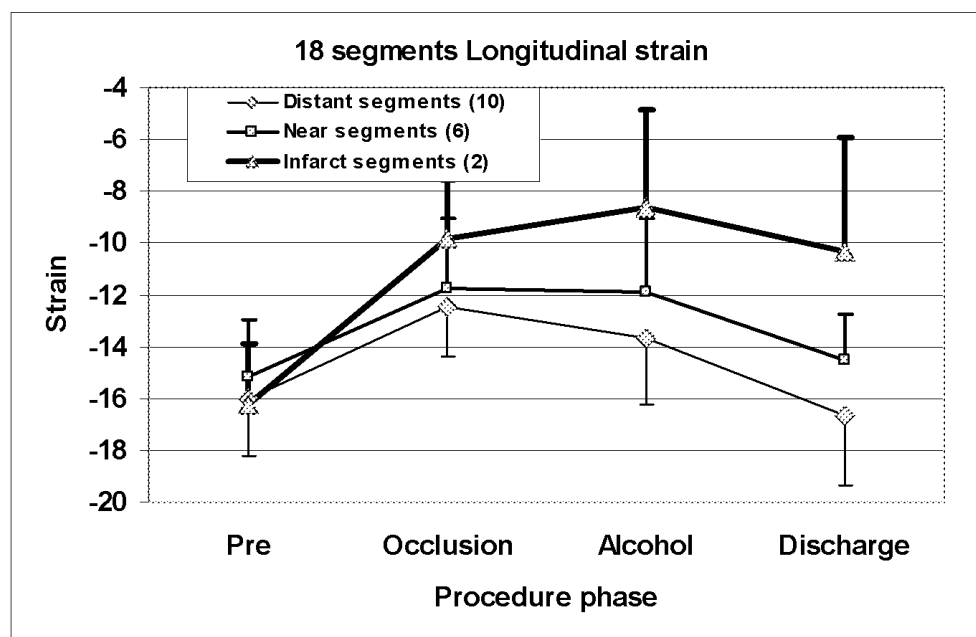
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Background Septal ethanol ablation (SEA) alleviates left ventricular outflow (LVOT) obstruction in symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) by controlled basal septal infarction. Relief of the gradient with SEA is complex and changes following ethanol injection: initially decreases during the procedure, increases pre-discharge then gradually decreases over the succeeding 6-12 months following the procedure. We hypothesized that the time course of LVOT gradient reduction during SEA is related to changes in regional and global myocardial mechanics.

Methods Baseline, immediately after septal occlusion, after alcohol injection and pre-discharge 2D echocardiograms were available in 21 patients with hypertrophic obstructive cardiomyopathy undergoing SEA. Echocardiograms were analyzed for mechanics using Velocity vector Imaging (VVI, Siemens) and correlated with hemodynamic data.

Results



LV outflow tract gradient decreased with septal balloon occlusion, further decreased post ethanol injection, and partially rebounded at discharge (5-6 days post procedure). During balloon occlusion longitudinal and circumferential strain significantly decreased in all analyzed segments, significantly improved with alcohol injection only at sites distant to infarction and normalized at all segments except infarcted ones at discharge. LV twist significantly improved with ethanol injection and remained high at discharge.

Conclusions Myocardial mechanics suggest that the decrease in LV outflow tract gradient during septal ethanol ablation coincides with global LV dysfunction despite only local ischemia during septal balloon occlusion. Global dysfunction is transient and the gradient rebounds when dysfunction is limited to the basal septum.

Segmental Wall Motion Abnormalities in Echocardiography of Patients with Acute Peri-Myocarditis.

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Background

Acute peri-myocarditis is a frequent inflammatory disease that may be associated with impaired cardiac function. Echocardiography is essential for acute peri-myocarditis diagnosis, assessment of the presence and amount of pericardial fluid and confirmation of concomitant heart disease. While, regional wall motion abnormalities have been observed a detailed description of these changes have not been described. In this study a detailed analysis of wall motion abnormalities are assessed.

Methods

Thirty consecutive patients 29(96.6%) males age 31±10, with first episode of acute peri-myocarditis were enrolled. Acute peri-myocarditis diagnosis was confirmed by the following: clinical history, ST elevation and/or PR depression on EKG, elevated inflammation markers and echocardiographic findings. Patients' echocardiography including pericardial fluid, detailed chambers measurements and wall motion abnormalities were measured on admission and after clinical recovery.

Results

Pericardial effusion was present in 20 (66.6%) of the patients with the majority of them having small to minimal effusion (90%) at the time of admission. After recovery, no effusion was noted in 17 (70.8%) of the patients, while the remaining had only minimal effusion. Sixteen (53.4%) patients had regional left ventricular dysfunction, affecting mainly the posterior, lateral and inferior wall while sparing the anterior and septal walls. Diffuse wall motion abnormalities were observed in only 3 (10%) of patients.

Upon recovery significant improvement in Ejection Fraction (EF) (55.6±5.4 to 59±2.03 % (p=0.002)) and reduction in left ventricular end systolic dimensions (LVESD) were measured (3.1 ±0.51 to 2.85±0.4 mm (p=0.006)). No additional significant echocardiographic abnormalities were found.

Conclusions

Transient significant reduction in EF and increased LVESD were observed during AP. The majority of the patients with decreased left ventricular function expressed poster-lateral and inferior wall anomalies. The reason for these predominantly regional wall motion abnormalities is not yet clear.

TNF- Alpha in Systolic Heart Failure Patients; Key for Inflammation and Myocardial Cell Destruction?

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Background: TNF- α participates in the inflammatory process of heart failure (HF). We examined serum TNF- α level in systolic HF patients, assessing its relation with other prognostic clinical and laboratory markers.

Methods: We tested sera samples of 67 pts (58 males, 9 females, age 65 \pm 13) for TNF- α level during a routine follow-up at our HF center. Mean LVEF was 25 \pm 7%. Based on median serum TNF- α level, pts were divided into two groups; detectable and non-detectable serum TNF- α level (group 1 and group-2, respectively). We evaluated both pts' groups for prognostic clinical markers including body mass index, NYHA class, six minutes walk test and QRS width. We also compared the two groups' sera for several prognostic laboratory markers including: matrix metalloproteinase-9, Hs -C reactive protein, IL-10, Troponin I, NT-pro BNP, serum hemoglobin, serum total cholesterol level and renal function tests.

Results: There were no significant differences between the two groups in the clinical parameters. However, there were significant differences between the two groups in regarding to inflammatory cytokines, myocardial damage markers, serum hemoglobin and total cholesterol level as elaborated in **Table-1**:

Parameter	Group-1 (Detectable TNF- α) m \pm sd/*inter quartile range	Group-2 (Un- detectable TNF- α) m \pm sd/*inter quartile range	P Value (*p<0.05)
NT- pro BNP (pg/ml)	3666	1139	0.001*
Matrix metalloproteinase-9	791 (2)	467 (2)	0.006*
IL-10	4.3 (30*)	0.0 (2*)	0.002*
Troponin I	0.02 (0.05*)	0.0 (0.00*)	0.001*
Hs-CRP (mg/dl)	0.6 (3)	0.8 (5)	0.6
Hemoglobin (gm/dl)	11.8 (1.6)	13 (1.7)	0.007*
Total cholesterol (mg/dl)	135 (32)	155 (36)	0.033*

Conclusions: Elevated serum levels of TNF- α in HF pts are associated with elevated markers of inflammation and myocardial cell destruction. This data reinforces the pivotal role of TNF- α in HF pathogenesis.

Everolimus as Maintenance Therapy in Heart Transplant Recipients: From Investigational Status to Everyday Practice, a Case Series.

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Purpose: Everolimus is a proliferation signal inhibitor recently approved for the use in heart transplantation (HTx). Besides its potent immunosuppression it has anti-cancer properties, it reduces the incidence of cardiac allograft vasculopathy and CMV infections and may improve renal function (RF). The purpose of the present study is to assess the role of everolimus in the common practice of HTx therapy.

Methods and Materials: The immunosuppressant protocol of the 75 pts transplanted at our center was assessed during their visits at the HTx clinic. Everolimus was introduced in 19 (25%) pts: 8 (42%) in the reduced CNI dose (CNIRD) and 11 (58%) in the CNI free (CNIF) protocols. The proposed trough levels of the CNI and everolimus were maintained.

Results: Results: Change to CNIRD was due to: worsening RF (n=5), mycophenolate mofetil (MMF) related symptoms (n=2), recurrent CMV (n=2), CNI induced neuropathy and delayed acute rejection (one each). Change to CNIF was due to: worsening RF (n=7), CNI related side effects (n=4), advanced cardiac allograft vasculopathy (n=4). Recurrent CMV and malignant melanoma (one each). Some had multiple reasons. Time from HTx to everolimus therapy in CNIRD and in CNIF was 57 and 75 months and mean follow up was 4 and 3.5 months respectively. The in-between therapies period was uneventful. Creatinine was reduced: from 2.02 to 1.8 and from 1.9 to 1.8 in pts with CNIRD and CNIF respectively. The MMF related symptoms and CNI induced side effects resolved. No recurrent CMV infection or acute rejections occurred in the relevant pts. CMV infection occurred in one CNIF pt so treated for reduced RF. One CNIF pt died due to septic shock and acute rejection. Acne like eruption occurred in 2 pts treated with everolimus. Its severity was dose and time dependent.

Conclusions: Conclusions: Including everolimus in the maintenance therapy of HTx recipients has the potential of improving the tailored immunosuppressive therapy for each patient thus reducing side effects and maybe even improving prognosis.

V2-Receptors Antagonists Attenuate the Capability of Lungs to Clear Edema

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Active Na⁺ transport and lung liquid clearance are regulated by apical sodium channel and basolateral Na,K-ATPase function in the alveolar epithelium. Vasopressin is a 9-amino acid neurohormone that is produced in the hypothalamus and stored in the hypophysis and plays an important role in the regulation of extracellular volume and its osmolarity. It has been shown to decrease lung liquid production in fetal lungs. Therefore, we aimed to study whether vasopressin has a role in alveolar fluid reabsorption in adult rat lungs in the isolated perfused rat lung model. Alveolar fluid reabsorption in control rats was 0.48±0.02 ml/h (all values are Mean ± SEM) and increased to 0.64±0.02 ml/h with vasopressin (P<0.04). The specific V₁ receptor antagonist, SR-49059, did not prevent the stimulatory effects of vasopressin, 0.64±0.02; whereas V₂ receptor antagonist, SR-1214638, inhibited the vasopressin effects, 0.31±0.04 (P<0.001). Treatment with amiloride (Na⁺ channel blocker) inhibited the stimulatory effects of vasopressin, 0.23±0.02 (P<0.001). The albumin flux from the pulmonary circulation into the airspaces did not change significantly in the experimental groups indicating that lung permeability for large solutes was not increased. In conclusion, vasopressin increased alveolar reabsorption, apparently by regulating the active Na⁺ transport in the alveolar epithelium. Conceivably, this effect is mediated via V₂ receptor receptors. Supported by Rappaport Institute for Research in the Medical Sciences and Chief Scientist Office; Ministry of Health, Israel.

The Utilization of ACE Inhibitors and ARB in Patients with Congestive Heart Failure: an Observational Study of Treatment Rates and Clinical Outcome

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Background: Angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) improve prognosis in congestive heart failure (CHF) and are the treatment of choice in these patients; despite this, the rates of ACE-I usage in heart failure patients remain low in clinical practice.

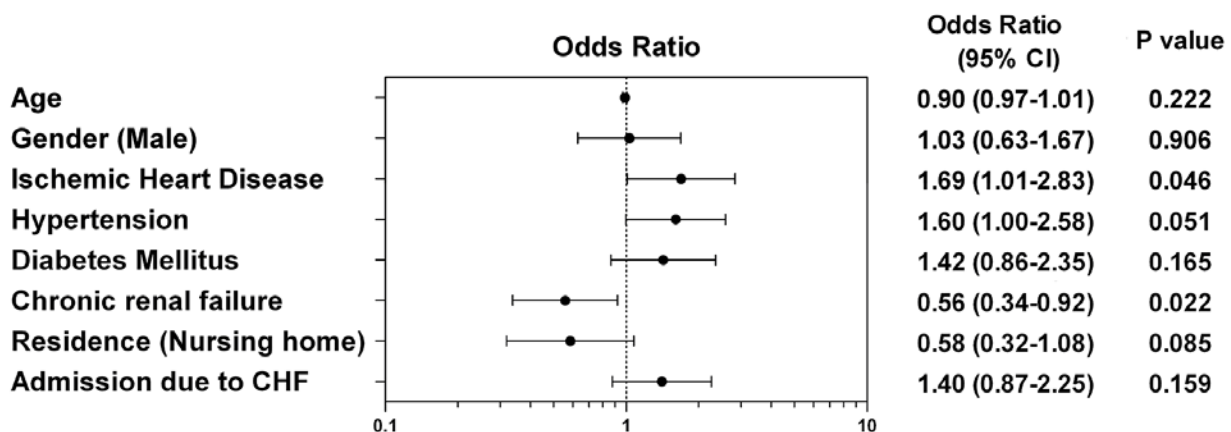
Objectives: To evaluate the rate of ACE-I/ARB treatment in hospitalized patients with CHF and analyze the causes of non-treatment.

Methods: We prospectively evaluated 362 consecutive patients hospitalized with CHF. Patients were evaluated for ACE-I/ARB usage at discharge and followed for a period of one year.

Results: On hospital discharge, 70% of the patients were prescribed ACE-I/ARB treatment. Only 69% of the patients received recommended target or sub-target dosages, proven to improve prognosis. This decreased to 63% and 59% at 6 months and 12 months of follow-up respectively, due to a shift from sub-target levels to low dosages. In the majority of patients that were not receiving optimal treatment (75%), there was no apparent justified reason for this. Common reasons for non-treatment at discharge were hyperkalemia and elevation in serum creatinine while hypotension and a cough were more prominent at follow-up. Clinical parameters associated with increased treatment rates were ischemic heart disease, hypertension and the absence of chronic renal failure. Patients receiving treatment had lower hospitalization and mortality rates.

Conclusions: ACE-I/ARB treatment is still underutilized in patients discharged from hospital with a diagnosis of CHF. Increasing the awareness of the importance of these drugs may increase the number of patients treated.

**Predictors of ACE-I/ARB Treatment at Discharge
Binary Logistic Regression**



Surface Thoracic Impedance Monitor May Enable the Prediction and Prevention of de Novo Acute Heart Failure and the Decompensation of Chronic Heart Failure

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Background – Treating patients with Acute Heart Failure (AHF) is a challenge. Presently, there is no reliable method to predict AHF. The ability to predict the development of AHF can allow medical staff to initiate early treatment, which may curtail or prevent further deterioration.

Methods and Results – We used a new Surface Thoracic Impedance Monitor (STIM) in order to monitor lung impedance (LI) in patients at risk to develop AHF. We evaluated the sensitivity of measurements and their effectiveness to trigger early administration of therapy with the intention to prevent evolution of AHF. We observed LI readings in 542 patients hospitalized for acute myocardial infarction (AMI) and in 63 out hospital clinic patients. 389 patients did not develop AHF. Their individual LI decrease was 5.6% (CI 0.8 to -12%, $p=0.7$). 114 patients developed clinically overt AHF, which was supported by roentgenological evidence. The LI decrease was 35% (CI- 14.2 to -50%, $p < 0.001$) compared to baseline. Treatment for AHF development was initiated in 39 patients at the time when LI decrease was $> 13\%$. As the result, AHF did not occur in 85% of patients ($\chi^2 < 0.01$). 75 episodes of decompensated AHF were observed in 63 hospital outpatients. Based on the accumulated evidence, LI decreased in all patients by more than 12% at 15.3 ± 10.6 days prior to clinical deterioration.

Conclusions – STIM monitoring in patients at risk to develop AHF can reliably predict further deterioration. We have demonstrated that timely prediction may prompt medical professionals to administer early treatment that could successfully prevent the development of AHF.

Aldosterone Synthase Polymorphism is Associated with Atrial Fibrillation in Systolic Heart Failure Patients

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Background: Atrial fibrillation (AF) is common in heart failure (HF). The activation of the renin-angiotensin system has an important role in AF pathogenesis. Aldosterone synthase is a key enzyme in the final step of aldosterone production. The *CYP11B2* T-344T polymorphism in this enzyme is associated with increased aldosterone activity. Accordingly, we examined the impact of this polymorphism on the prevalence of AF in systolic HF patients.

Methods: We analyzed the association between *CYP11B2* T-344T polymorphism in aldosterone synthase and the presence of AF in 178 {aged 65±13 years, 145 (81%) males} consecutive systolic HF patients who were followed at our HF center. Mean LVEF was 24±7% and 97 (55%) patients were in NYHA functional class 3 or 4.

Results: Atrial fibrillation was present in 57 (32%) patients. The -344 CC genotype was a strong independent marker for AF. Almost half (45%) of the patients with this genotype subtype had AF compared to only about a quarter (27%) of patients with out this genotype (p=0.02). In a multivariate stepwise logistic regression model, the *CYP11B2* CC genotype was the most powerful independent predictor of AF after age and left atrium size (Table-1).

Conclusion: Systolic HF patients with the *CYP11B2* promoter T-344 C polymorphism have significantly higher prevalence of AF. This association may explain in-part the direct anti-aldosterone treatments success in systolic heart failure and in atrial fibrillation prevention.

Table-1:

Variable	OR	CI	P
Lt. atrium size	5.1	3.23-8.05	<0.0001
Age	1.1	1.03-1.07	<0.01
CYP11B2 -344 CC genotype	2.6	1.68-3.98	0.02

A Stable Minipig Model for Heart Failure

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Background: A number of chronic models of heart failure have been developed. Each of these models has specific limitations and in particular, is difficult, timely and expensive to create. We established a stable model based upon multiple interventions to impair compensatory mechanisms in a minipig. We sought to demonstrate that the acute heart failure model could be additionally used as a stable and recurrent chronic model.

Methods: Twelve minipigs were used in this study. All animals underwent alternate selective LAD and Cx injections of microsphere (90 µm). Fluid loading was performed with aliquots of 500cc of warmed NaCl. Afterload elevation was achieved with partial or complete descending aorta balloon occlusion. Hemodynamic parameters measured included RA, LA, aortic and LV pressures. The endpoints were stable elevation of maximum LA/LVED with maintained systemic blood pressure for a period of two hours. In selected cases TTE was performed to assess LV function. For the chronic group the animals were restudied at 4 weeks after the microsphere injection.

Results: Complete hemodynamic studies were performed acutely in 7 animals and in 4 chronic animals. A single animal was excluded due to an intercurrent illness. In the acute studies the time to stressing with afterload and fluid aliquots was longer and associated with larger amounts of preliminary IV fluid administration. LA and RA pressures (mmHg) are shown in the table.

	Baseline		Post beads		Post Volume		After load	
	RA	LA	RA	LA	RA	LA	RA	LA
Acute	13±4.7	17±4.4	15±6.0	22±7.4	19±6.7	32±8.0	21±6.2	38±9.3
Chronic			9±4.0	14±4.4	9.9±4.7	15±3.2	11±4.6	22±2.3

P<0.05 acute to chronic (non parametric)

Preliminary echocardiography was performed in 3 chronic animals prior to stressing with fluids and afterload. LV function normal to preserved in all cases.

Conclusions: The development of a stable and reproducible heart failure minipig model was achieved using a combination of selective coronary microsphere embolization, volume loading and intermittent afterload elevation apparently without impairing LV function. The model was effective both acutely and recurrently, with the chronic model providing less extreme LA pressure overload.