Novel Injectable Alginate Scaffold and Fetal Cardiomyocyte Transplantation as a Staged Procedure Improve Cardiac Remodeling and Function after Myocardial Infarction in Rat

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Objective: To determine and compare the therapeutic effect of injectable alginate scaffold with staged cardiomyocyte transplantation, injectable collagen scaffold, and saline on left ventricular (LV) remodeling and function after MI in rat.

Background*:* Adverse cardiac remodeling and progression of heart failure after myocardial infarction (MI) are associated with excessive and continuous damage to the extracellular matrix (ECM). We hypothesized that injection of i*n-situ* forming alginate hydrogel into the infarct provide a temporary scaffold, and attenuate adverse cardiac remodeling and dysfunction.

Methods and Results: We developed a novel absorbable biomaterial composed of a calcium cross-linked alginate solution, which displays low viscosity and after injection into the infarct and undergoes phase transition into hydrogel after injection into the infarct. Rats (n=48) were subjected to extensive anterior MI and immediately after coronary artery occlusion, injectable resorbable alginate biomaterial (n=24), collagen (n=12), or saline (n=12) were injected into the infarct. One week later, 12 of 24 alginate-treated rats received rat fetal cardiomyocytes transplantation ($1x10^{6}$ cells) into scar (staged procedure). Echocardiography study was performed at 3 days (baseline), 1 and 2 months after MI and showed that both collagen and saline -treated animals developed significant LV dilatation accompanied by progressive deterioration in LV contractility ($p<0.01$). On the other hand, injectable alginate scaffold with and without staged transplantation of cardiomyocytes attenuated LV dysfunction. Invasive hemodynamic studies, performed with pressure-volume (PV) system (Millar instruments) two months after MI, showed that LV end-diastolic and systolic volumes were significantly smaller in animals treated with injectable alginate scaffold, with and to lesser extent without staged cell transplantation, compared with animals treated with collagen scaffold and saline. (426 ±14 and 549±42 vs 661±40 and 623±53 uL, p=0.02; and 349±2 and 448±42 vs 607±49 and 552±60 uL, p=0.01).

Conclusions: The present study shows, for the first time, that injectable alginate scaffold with staged transplantation of fetal cardiomyocytes can improve the favorable effects of injectable alginate biomaterial on cardiac remodeling and function after MI.

Baseline LDL-cholesterol Levels and Outcome in Patients with Severe Heart Failure

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Background: The prevalence of HF increases constantly in the US and Europe. Treatment by statins is well established for primary and secondary prevention of coronary events. There are controversial reports concerning low cholesterol as a negative prognostic predictor for patients with advanced HF. However there is no sufficient data to show whether low cholesterol is associated future HF admissions mortality in patients with HF. We evaluated the impact of baseline LDL-cholesterol levels on the clinical outcome in patients with HF

Methods and Results: We evaluated 297 CHF patients with an average NYHA of 2.8. Mean follow up was 3.7 years. One hundred and seven (37%) of the patients died during follow up and the mean time till first hospital admission due to HF was 25 ±17 months.
Patient cohort was divided into 3 groups (Tertiles) according to LDL levels: Group1- LDL<89 mg/dl values, group 2- 89 mg/dl<LDL<115 mg/dl group3- LDL >115mg/dl. The prevalence of diabetes mellitus, HTN, IHD was lower in latter tertile, yet there were more patients with advanced NYHA class (3-4). The best overall outcome was evident in group 3 with the highest LDL (>115 mg/dl). The same trend was observed in groups of patients with only IHD sentence to vague
Conclusion: Very low LDL cholesterol levels are associated with a reduced survival in patients with clinically controlled severe HF.

Are Statins Protective in Heart Failure Patients?

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Aim: This study aimed to investigate the impact of statin therapy before the admission to the hospital on one-year survival of patients hospitalized due to decompensated heart failure (HF).

Methods: We performed a retrospective cohort analysis of 949 consecutive patients older than 18 years hospitalized in Soroka University Medical Center with a principal discharge diagnosis of HF (acute myocardial infarction excluded) between 11/2001 and 06/2005. Two groups of patients were compared: those who received statins within 3 months before the admission (S) and those who did not (NS). The primary outcome was one-year all cause mortality. To adjust for a potential misbalance between S and NS groups in baseline characteristics, propensity score for statin therapy was incorporated into the survival model.

Results: 297 patients (31.3%) had received statins prior to admission. Patients with ischemic heart disease (IHD) (686/949 subjects, 72.3%) had higher rate of S therapy as compared to the rest 36.2% vs. 18.6%, $p<0.001$. Overall one year mortality rate in S group was 21.9% vs. 32.7% in NS group, $p<0.001$. In the subgroup of patients with IHD statins were protective after adjustment for comorbidities and propensity score (hazard ratio [HR], 0.63; 95%CI 0.44-0.91). However, in patients with non-ischemic HF statins had a neutral effect (HR 0.79; 95%CI 0.43-1.48).

Conclusions: Statins' protective effect on one year survival in HF patients is restricted to patients of IHD etiology. As for other etiologies, statin use may be a marker of better health care, but does not improve outcome *per se*.

Mitral Valve Annulus Diameter and Mitral Valve Leaflets Lengths: Contributors of Mitral Regurgitation in Patients with Hypertrophic Obstructive Cardiomyopathy

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Introduction: The mechanism of obstruction of the left ventricular outflow tract (LVOT) in hypertrophic obstructive cardiomyopathy (HOCM) is mainly due to dynamic systolic anterior motion (SAM) of the mitral valve. Mitral regurgitation (MR) is associated with complicated abnormalities of the mitral apparatus which contributed to a high pressure gradient through the LVOT. The aim of the study to evaluate the contribution of mitral valve annulus diameter (MVAd) and leaflets length on MR.

Methods: A retrospective analysis of our hospital database (12,500 electronic transthoracic echocardiograms between11/2003 -11/2006) was performed to search for patients with combined HOCM and MR. All studies reviewed for MR grading, LVOT gradient, Left Ventricle (LV) dimensions, Ascending Aorta and Aortic Root diameters and MVAd.

Results: MR was found in 48 pts with HOCM (M/F= 9/39, aged 73.6± 15y). MR grading from1-5 (Average 2.3±1.2), MVAd = 27±4cm, MV Anterior leaflet length (MVALL) = 22±2.42 mm, MV Posterior leaflet length (MVPLL) = 17±2.17 mm, LV septum=15.6±2cm, Posterior wall thickness (PWT) =11.3± 0.7cm, LVOT gradient=60.3±23mmHg. In regression analysis the major contributors for MR were: LVOT Gradient r = 0.86, MVALL r = 0.85, MVAd r= 0.83, LV septum r = 0.64, MVPLL r = 0.63, all $P<0.05$. PWT, ascending aorta diameter, aortic root diameter, age and gender did not contribute to the MR (p = ns).

Conclusions: For patients with HOCM and MR not due to independent mitral valve disease, mitral valve annulus diameter and mainly anterior MV leaflet length are strongly related to the magnitude of the LVOT gradient and the severity of MR and thus should be considered during evaluation and management.

In vitro Model Assessment and in Vivo Safety of a New Device-Based Approach for Treating Diastolic Heart Failure

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Introduction: Diastolic heart failure (DHF) accounts for over 40% of heart failure cases, and leads to significant mortality and morbidity. Treatment of DHF patients is empirical, limited, and disappointing. We used in vitro and in vivo studies to evaluate the efficacy and safety of a new approach for treating DHF, directed towards enhancing left ventricular (LV) relaxation and filling, utilizing a passive mechanical device which stores energy during systole and releases it in a recoiling force during diastole.

Methods: The device was evaluated in vitro, utilizing a fatigue machine and ventricular model. The device was implanted on the beating heart of 12 healthy sheep, Echocardiography, Angiography and pressures measurements were conducted to evaluate long term safety, and the effects of tachycardia and acute volume overload.

Results: In vitro studies showed device durability for over 450 million cycles and a reduction in modeled end diastolic pressure. In vivo studies exhibited good clinical recuperation in all animals, Ejection Fraction was preserved up to 170 day follow-up and angiography demonstrated normal coronary flow. Average device energy transfer to the LV remained constant during follow-up.

The device was not restrictive during tachycardia and volume overload 170 days post implantation. Histopathological evaluation 6 months post implantation demonstrated mild to moderate fibrosis limited to the myocardium around device attachment.

Conclusion:

This study demonstrates that a passive mechanical device, which transfers energy to LV during diastole, reduces filling pressures in an in vitro model, is durable for cycles simulating 10 functional years and can be safely implanted.

Routine Laboratory Results and One-Year Mortality Risk Following Hospitalization with Acute Heart Failure

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Aim: The study aim was to evaluate the relationship between admission routine laboratory tests results, patient characteristics and one year mortality of patients admitted for heart failure.

Methods: All heart failure admissions to the seven major general hospitals of the Clalit Sick Fund during years 2002-2005 throughout Israel were screened. Patients with a principal diagnosis of heart failure were enrolled. Patients with acute heart failure due to myocardial infarction were excluded. Data on diagnoses, co-morbid conditions, medications, laboratory findings, in-hospital management and mortality were assessed.

Results: 8,246 patients were included into the study cohort. Hospital mortality rate was 5.7%. One year mortality rate 28.7% and was associated with patients' age, co-morbid conditions and routine admission laboratory results in Cox regression survival analysis. Three dichotomized abnormal laboratory results with highest hazard ratio for one year mortality were: hypoalbuminaemia in 36.3% (HR 1.76, 95%CI 1.60-1.97), hyponatremia in 22.0% (HR 1.65, 95%CI 1.48-1.85) and hyperuricaemia in 70.3% (HR 1.51, 95%CI 1.32-1.73) of patients. A simple prediction tool with one point assigned for each abnormal result was capable of discrimination within 0.7% to 13.9% in hospital mortality rate range, and within 11.6% to 55.6% one-year mortality rate between patients with score of 0 (1,477 patients) and score of 3 (544 patients).

Conclusions: Age, dementia and increased Charlson score are all predictive of one year mortality from HF. A small panel of easily obtainable laboratory tests can risk-stratify patients admitted to the hospital due to the heart failure.

Guidelines of Heart Failure Medications; the Gap between "Real World" Practice and Official Recommendations

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Background: Current heart failure (HF) guidelines advocate the need to maximize the doses of anti-renin angiotensin system medications; beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) and aldactone. However, "real life" HF pts are usually older and sicker than pts who participate in the clinical trials. Consequently, there is a gap between the "official" medications' doses recommendations and daily practice.

Accordingly, we examined medical records of 154 consecutive pts who are followed at our HF center. We compared the doses of BB, ACEI, ARB and aldactone between the first clinic visit and 1 year later. We also analyzed the clinical implications of the intolerance to the different regimes.

Results: Our pts mean age was 67±13 years, 110 were males. Mean ejection fraction (EF) was 32%±14% and 98(64%) pts had EF less than 30%. Ischemic etiology was present in 90(58%) pts. Anemia (hemoglobin<12 gm %) was present in 88(57%) pts, diabetes mellitus was present in 65(42%) pts and chronic renal failure (baseline Creatinine>1.5 mg/dl) was present in 51(33%) pts.

Beta blockers doses were reduced after 1 year in 33(21%) pts and were discontinued in 9(6%) pts.

The dose of ACEI/ARB was reduced after 1 year in 24 (16%) pts and in 8 (5%) pts ACEI/ARB were discontinued.

Aldactone was given in 46(30%) pts and in 20 (43%) pts was discontinued one year later. Of note, all decrease doses changes and/or discontinuation in the BB, ACEI, ARB and aldactone regimens were done due to either hemodynamic and/or renal deterioration causes.

A total of 17(11%) pts died, in 4(24%) pts, the BB regimen was stopped prior to their death. Of all the medical regimens changes, only the BB intolerance had a significant clinical implication, as it was associated with high mortality (p=0.03).

Conclusion: In almost 1/4 of our HF pts, at least one of the"official" recommended HF regimens doses had to be either reduced or discontinued as the patients did not tolerate the guidelines target recommended doses. In addition, it is important to note that intolerance for BB carries the highest risk for future mortality in HF pts and may serve as a prognostic marker for mortality.