The Right Atrium of Patients with Various Heart Diseases Retain Progenitor Cells with Regenerative Capacity

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BACKGROUND: The notion that the adult human heart contains a pool of cardiac progenitor cells (hCPC) can be translated into an attractive approach to repair damaged hearts. However, significant amount of data regarding the characterization and function of hCPC are lacking, and no efficient, reproducible method exists to isolate CPC from human hearts.

OBJECTIVE: To determine whether the hearts of patients with ischemic and non-ischemic heart disease contain cardiac progenitor cells with regenerative capacity.

METHODS AND RESULTS: We developed an efficient and reproducible method to isolate hCPCs from the myocardium of patients with ischemic and non-ischemic heart disease, heart failure and diabetes. Following patients' consent tissue samples were donated during all kinds of open heart surgery and percutaneous RV septum biopsies. Isolated cells created typical clones, possessed self-renewal capacity and expressed stem cell markers including C-Kit, CD133, MDR1, and GATA 4.

Following *in-vitro* manipulation, hCPC successfully differentiated into the osteogenic, adipogenic and myogenic lineages.

Cell cultures from the right atrium were found to have larger amounts of C-Kit^{+} cells (17%) compared with the left atrium (5.7%) or septum (7.9%). Correspondingly, right atrium cells had better *in-vitro* differentiation capabilities.

hCPC were injected into nude rat myocardium to examine myogenic differentiation. After one week, some cells still expressed stem cell markers while others expressed specific human cardiac markers, such as human cardiac troponin I and human fetal cardiac α-actin with early sarcomere formation, indicating that some of the implanted human cells developed into cardiomyocytes *in vivo*.

CONCLUSIONS: Our preliminary findings suggest that adult human heart, especially the right atrium, retains a unique cell population with stem cell markers and multi-lineage differentiation capability. These cells, which can be isolated, expanded and stored, could be used to treat patients with heart disease.

The Impact of the NT-proBNP Assay in the Emergency Department on the Diagnosis of Heart Failure and on Outcomes in Patients Admitted for Dyspnea: A Prospective Randomized Placebo-controlled Double-center Trial (BNP4EVER)

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We have evaluated prospectively the impact of the NT-proBNP assay on the diagnosis of HF in patients presenting to the ER with dyspnea. NT-proBNP assay was performed in all patients randomized in 2 hospitals to open or blinded NT-proBNP. A preliminary diagnosis was made in the ER prior to obtaining result. Throughout the 17-month study, 485 recruited patients (72.5±14 years, 236 males and 249 females) presented 517 times to the ER. Validated NT-proBNP cutpoints determined the HF-unlikely (17% of patients), HF-less likely (24%), and HF-likely (59%) groups. Corresponding NT-proBNP levels were 115±94, 809±391, and 8318±8243 pg/ml. Diagnosis of HF in the ER was made in 18%, 54.5%, and 75% of patients in the 3 groups. Admission rates were 80%, 87%, and 96% ($p<0.01$), with HF as discharge diagnosis in 11%, 24%, and 66% in the 3 groups, respectively. Assay availability did not affect admission within group. 60% of blinded and 74% of unblinded patients among admitted HF-likely patients were diagnosed as HF patients ($p<0.007$). The assay did not confer a survival benefit at 21 months
in the HF-likely patients. However, if this group was divided by median NT-proBNP level (5000 pg/ml) there was a survival difference between subgroups ($p=0.0003$) and the lower than median subgroup benefited if NT-proBNP level was known ($p=0.05$). These preliminary results show that appropriate diagnosis of HF was missed in 40% of patients when NT-proBNP level was unknown. In general, survival in the HF likely patients was not altered by assay unless NT-proBNP level was less than median, in which case HF patients could be salvaged if correctly diagnosed and treated. These findings suggest underdiagnosis of HF in dyspneic patients and improved diagnostic accuracy by NT-proBNP assay.

Echocardiographic and Plasma N-Terminal Pro-B Type Natriuretic Peptide Evaluation During Pregnancy in Patients with Preexisting Dilated Cardiomyopathy

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Background: There is little experience in pregnant patientis with previously diagnosed dilated cardiomyopathy (DCM). These patients are usually advised firmly against further pregnancies.
Study aim: To exam the ussfulness of serial echocardiographic follow-up and plasma N-Terminal Pro-B-type natruiretic peptide (NT-ProBNP)evels in the management of pregnant women with preexisting DCM.
***Methods*:** We prospectevlly enrolled pregnant women with known DCM or diagnosed in the first trimester of pregnancy. Demographic, clinical caractheristics, serial echocardiographic studies and plasma ProBNP levels at base line, 30 weeks pregnancy, one and 90 day post-partum were prospectively collected.
Results: Between June 2004 to March 2007 we enrolled 7 women fulfilling the study criteria. The mean age was 33.5±3.3 years, (24 to 41), 6 caucasian, four (57%) primagravidas, two of them became pregnant after assited reproduction technique and multiple past abortions. There was a high prevalence of hypothyroidism (57%) and only one cases of diabetes mellitus, chronic hypertension, and rheumatic arthritis.
The delivery and post-partum were complicated in three patients (42%): acute heart failure resolved conservatively in two, and one with major pulmonary embolism.
The left ventricular ejection fraction (LVEF) was stable throughout the pregnancy (baseline 35% ±2.8,
30 weeks 33% ±2.9) and post-partum (1 day 35% ±2.8, 90 days 34% ±3.1). Similar stable behavior was observed regarding left ventricular dimensions, LVESD - 43.3 ±2.7 and LVEDD - 57.3±3.3 at baseline compared with 44.1±3.1 and 58.7±3.1 respectively. Two patients had demostrated good myocardial contraction reserve in pre-gestational dobutamine stress echocardiography.
The NT-ProBNP levels rised significantly in the early post-partum in all 3 patients with complications. In one additional patient the NT-ProBNP showed similar behaivor but without clinical event. In the remaining 3 patients the NT-ProBNP levels were in the upper limit range and increased only slightly one day post-partum and decreased 90 days later.
Conclusion: Serial Pro NT-BNP levels, as opposed to echocardiography, may be a better clinical tool in monitoring and management of pregnant women with preexisting DCM. An early rise in NT-ProBNP level appears to predict the occurrence of adverse events.

Early and Late Outcome of Atrial Fibrillation in Hospitalized Patients with Heart Failure

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Background: Atrial fibrillation (AF) and heart failure (HF) commonly coexist, and each adversely affects the other condition, and the interrelations between them may consititute a viscious cycle. However, the mortality, the impact of medications especially on AF subgroups have not fully investigated.

Objectives: To prospectively evaluate the impact of AF and its subtypes on management, hospital long-term mortality in hospitalized HF patients, and to identify predictors of mortality in HF-AF in comparison to HF-no AF patients.

Methods: we prospectively collected and analyzed the data of 4,102 hospitalized HF patients in a national survey conducted in all public hospitals in Israel (HFSIS 2003). AF patients were subgrouped to paroxysmal AF (PAF) (first-onset, paroxysmal or persistent) and chronic (permanent).

Results: During March-April 2003 we recorded 4,102 HF patients, 1,360 patients (33.2%) had AF: 600 patients (44.1%) PAF, 562 patients (41.3%) had chronic AF, and 198 patients (14.6%) undefined AF

Table (%):

	PAF	Chronic AF	AF-all	No AF	P (AF vs. No AF)
Male	52	52	52	60	0.0001
Age (yrs)	77	77	77	72	0.0001
Mortality					
Hospital	5.5	5.3	5.9	4.1	0.02
30-day	8.3	8.2	8.9	6.9	0.02
1-year	29.0	36.7	32.9	25.8	0.0001

Predictors of increased 1-year mortality in HF-AF versus HF-no AF patients: NYHA III-IV, renal failure, Killip class II, and III-IV, LVEF <30%, stroke/TIA anemia chronic AF COPD, age and use of furosemide and spironolactone. Hypertension, primary HF diagnosis and the use of non-dihydropyridines CCBs, anticoagulants, beta blockers and statins were associated with decreased 1-year mortality.

Conclusions: In hospitalized HF patients AF is associated with increased mortality. After adjustment to clinical variables and medications, chronic AF, Severe forms of HF, comorbidities and use of diuretics were associated with higher mortality in HF-AF patients, while PAF is tended towards lower mortality.

Correlation of Abnormal Liver Function Tests in Patients with Severe Heart Failure to Outcomes.

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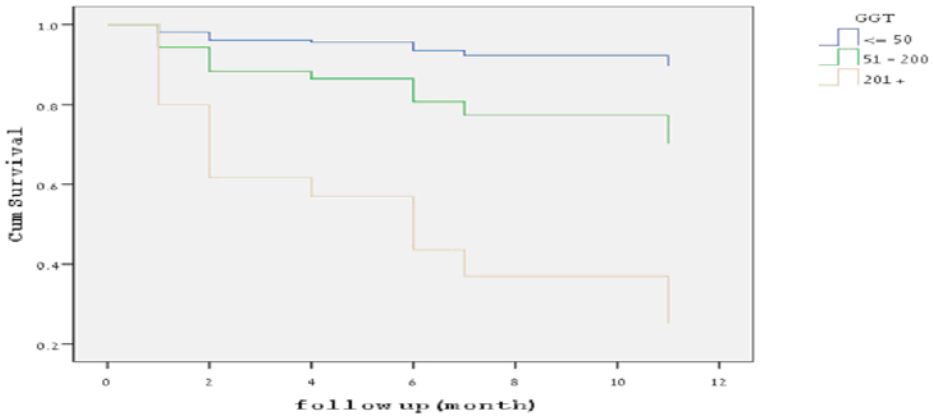
Background- Patient selection is crucial for the success of heart transplantation.
The relation of abnormal liver function tests (LFT) to outcomes of pts with severe heart failure waiting for heart transplantation is unclear yet.
Aim- To assess the relation of LFT to mortality or heart transplantation in pts with severe heart failure.
Methods and results: We analyzed all clinical, hemodynamic and laboratory data of pts with severe heart failure on the Rabin Medical Center waiting list for heart transplantation from 1/2006 -05/2007. There were 69 pts (86% males) at a mean age of 53.7± 10.0 years. The etiology was coronary artery disease in 44 (64%) pts. Mean time on the list was 4.8± 3.2 years. Mean left ventricular ejection fraction was 24%±7. 24 pts (35%) had significant pulmonary hypertension, 30 pts (43%) right ventricular dysfunction and 17 pts (25%) had significant tricuspid regurgitation. Clinical signs of right heart failure were present in nearly quarter of the pts. During the study period 12 pts (17%) underwent heart transplantation, and 5 pts (7%) died. We assessed the relation of different LFT (taken at: 1. entrance to waiting list; 2.peak results during follow-up; 3. last results) to mortality and heart transplantation. Only peak GGT, (304± 265 u/l for pts who died/transplanted vs. 136± 165 u/l for all other pts, p=0.04) was significantly related to survival or heart transplantation
Figure 1 demonstrates the relation of GGT tertials to combined outcomes:



Conclusions: In pts with severe heart failure, even mildly elevation in GGT is significantly related to mortality or heart transplantation, and thus can be used as a simple surrogate of high-risk pts, who need closer surveillance, and perhaps more aggressive interventions.

Major Adverse Events in Patients with Peripartum Cardiomyopathy: Clinical Profile and Risk Predictors

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Background: Clinical profile and predictors of major adverse events (MAE) associated with Peripartum Cardiomyopathy (PPCM) have not been characterized

Methods: A review and analysis of clinical data of 182 patients with PPCM.

Results: Forty-six patients had ≥ 1 MAE, including death (13), heart transplantation (11), temporary circulatory support (4), cardiopulmonary arrest or fulminant pulmonary edema (23), thromboembolic complications (4) and defibrillator or pacemaker implantation (10). Diagnosis of PPCM was delayed ≥ 1 week in 60% of patients and MAE preceded the diagnosis in 50% of patients. Seven (32%) of the surviving patients had residual brain damage. Patients with MAE were younger (27±8 vs. 30±7, p=0.03); more often non-Caucasians (61% vs 37%, p=0.005), had lower left ventricular ejection fraction (LVEF) (24±10% vs. 31±11%, p<0.001) and higher incidence of LVEF ≤ 25% (63% vs 31%, p=0.001) at time of diagnosis. Significant predictors of MAE were: LVEF ≤ 25% (HR = 4.20, CI: 2.04 – 8.64) and non-Caucasian background (HR = 2.16, CI: 1.17 – 3.97). These predictors in addition to diagnosis delay (HR = 5.51, CI: 1.21 – 25.04) were also associated with death or heart transplantation.

Conclusion: 1. PPCM may be associated with mortality or severe and lasting morbidity. 2. Incidence of MAE is higher in non-Caucasians and in women with LVEF ≤25%. 3. Diagnosis of PPCM is often delayed and preceded by MAE. 4. Increased awareness of PPCM is required for early diagnosis and aggressive therapy in order to improve outcome.

	No MAE n=136	**MAE n=46**	**P-value**
Age (years)	30±6	27±8	0.03
Age > 30 years	53%	42%	0.3
Non-Caucasian	37%	61%	0.005
Multipara	53%	41%	0.3
Twin Pregnancy	19%	4%	0.02
Gestation Hypertension	46%	32%	0.2
Tocolytic Therapy	18%	17%	1.0
Caesarian delivery	21%	15%	0.7
Diagnosis delay (weeks)	1.7±3.0	3.8±6.1	0.02
LVEF (%) baseline	31±11	24±10	<0.001
LVEF ≤ 25%	31%	63%	0.001
LVDD (mm) baseline	57±6	61±9	0.01
LVEF (%) at ≥ 6month	47±13	32±14	<0.0001
LVDD (mm) at ≥ 6 month	52±10	64±5	0.004
LV Recovery (LVEF ≥ 50%)	45%	18%	<0.001