

08:30 - 10:00 S17 - Ami Cohen Award and Adult Cardiac Surgery

Hall D

Chair: **D. Bitran**
G. Bolotin

- 08:30 **TVP1022 - a Novel Cardioprotective Drug for the Treatment of Congestive Heart Failure (CHF)**
*Y. Barac*¹, *A. Roguin*¹, *S. Kostin*², *J. Schaper*², *M. Youdim*¹, *Z. Abassi*¹, *O. Binah*¹
¹ Haifa, ² Bad Nauheim
- 08:45 **Effect of Changes in Surgical Technique on Long-term Outcome of BITA Grafting**
*A. Mohr*¹, *P. Dmitry*¹, *B. Medalion*², *A. Kramer*¹, *P. Paz Yosef*¹, *N. Nesher*¹,
*I. Shapira*¹, *G. Uretzky*¹, *R. Mohr*¹
¹ Tel Aviv, ² Petah Tikva
- 09:00 **Exercise Training Improves Cardiac Function of Calsequestrin Deficient Mice Suffering from Catecholamine Dependent Polymorphic Ventricular Tachycardia (CPVT)**
E. Kurtzwald^{1,2}, *E. Hochhauser*², *G. Katz*¹, *Y. Cheporko*², *A. Shainberg*¹,
*J. Seidman*³, *M. Eldar*¹, *E. Porat*², *Arad M*¹
¹ Ramat Gan, ² Tel Aviv, ³ Boston
- 09:15 **A Potential Role for Statins in Protecting Cells following Myocardial Infarction or Ischemia during CABG, and for Inducing Apoptosis of Malignant Cells**
S. Diab, *O. Binah*, *G. Bolotin*, *O. Cohen*, *A. Ciechanover*
Haifa
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- 09:30 **Repair Of The Bicuspid Aortic Valve- Our Experience**
D. Loberman, *A. Shinfeld*, *S. Tager*, *B. Sheick-Yousif*, *A. Kogan*, *E. Raanani*
Ramat-Gan
- 09:45 **No Hemorrhagic Strokes after Cardiac Surgery:A 14 year Retrospective Study**
I. Korn-Lubetzki, *A. Oren*, *R. Tauber*, *B. Steiner-Birmanns*, *D. Bitran*, *D. Fink*
Jerusalem

TVP1022 - a Novel Cardioprotective Drug for the Treatment of Congestive Heart Failure (CHF)

Y Barac¹, A Roguin¹, S Kostin², J Schaper², M Youdim¹, Z Abassi¹, O Binah¹

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Background:

TVP1022 is the optical S-isomer of the newly developed, FDA-approved, anti-Parkinson drug rasagiline, which was recently described as “a disease modifying drug” due to its anti-apoptotic and neuro-protective effects. Since: (1) TVP1022 is neuro-protective, and (2) cardiomyocytes and neurons share many similar features, we hypothesized that TVP1022 (which has minimal MAO inhibition), can be cardio-protective.

Materials and Methods:

The therapeutic efficacy of TVP1022 was demonstrated in 2 animal models of cardiac pathologies:

Congestive Heart Failure:

- Volume overload model induced by the placement of a fistula between the abdominal aorta and the inferior vena cava in rats.
- Doxorubicin-induced cardio-toxicity in rats and mice.

Results:

CHF:

- Volume overload - Pre-treatment with TVP1022 **attenuated** the decrease in fractional shortening, remodeling, the hypertrophic response, the increase in BNP levels and the fibrosis.
- Doxorubicin-induced cardiotoxicity - TVP1022 **attenuated** doxorubicin-induced **apoptosis and the decline in diastolic and systolic functions by 50%**.

Conclusion:

The ability of TVP1022 to attenuate cardiac damage induced by different pathological insults, by means of its unique mechanisms of action, being anti-apoptotic, anti-ischemic as well as anti-hypertrophic, render this molecule a potential **cardio-protective drug for CHF patients**.

Effect of Changes in Surgical Technique on Long-term Outcome of BITA Grafting

Aya Mohr¹, Pevni Dmitry¹, Benjamin Medalion², Amir Kramer¹, Paz Paz Yosef¹,
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Background: Learning curve can affect early and long term outcome of surgical procedure. In order to evaluate the effect of learning curve on long term outcome of BITA grafting, we compared two cohorts of patients: those operated between 1996-1999 (early period) and those operated between 2000-2001 (late period).

Methods: 1163 consecutive patients underwent BITA grafting in the early period. They were compared to 352 BITA patients operated in the late period. Occurrence of emergency and acute MI cases, EF <25%, and repeat operations was higher in the early period. Prior PCI, 3 vessel disease and PVD were more common in the later period. In order to control between groups for preoperative risk factors, propensity score was used. After propensity score matching, two groups of 342 patients each were used for comparison between the early and late periods.

Results: The two groups were similar in all preoperative characteristics. However, more patients in the early period had sequential grafting. Saphenous vein graft for right system revascularization and the off-pump technique were more common among patients in the later period. Eight years Cox adjusted survival in the later group was better and timing of surgery was found to be an independent predictor of better long term survival (H.R. 1.635, 95% CI 1.136-2.353).

Conclusions: Simplification of surgical technique and the use of off-pump revascularization are probably related to better long term outcome of patients undergoing BITA grafting.

Exercise Training Improves Cardiac Function of Calsequestrin Deficient Mice Suffering from Catecholamine Dependent Polymorphic Ventricular Tachycardia (CPVT)

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CPVT is a lethal ventricular arrhythmia evoked by physical or emotional stress. Recessively inherited CPVT is caused by either missense or null-allele mutations in the cardiac calsequestrin (CASQ2) gene. Defects in CASQ2 causing protein deficiency impair Ca²⁺ uptake to the sarcoplasmic reticulum and Ca²⁺-dependent inhibition of ryanodine channels, leading to diastolic Ca²⁺ leak, after-depolarizations and arrhythmia.

To examine the effect of exercise training on left ventricular remodeling and arrhythmia, CASQ2 knockout (CASQ^{□E9}) mice and wild-type controls underwent echocardiography and heart rhythm telemetry before and after 6 weeks training protocol using treadmill exercise. Left ventricular fractional shortening was impaired in CASQ^{□E9} (35±3% vs 41±8% in controls, p<0.05) but improved after training (44±5% and 51±3 in CASQ^{□E9} and control mice, respectively, p=NS). The exercise tolerance was 16±1 min in CASQ^{□E9} mice vs 29±2 min in controls, p<0.01, but improved in trained animals (26±2 vs 30±3 min, respectively, p=NS). CPVT prevalence in mutant mice was 67% at rest and 100% at stress. Exercise training did not change the arrhythmia prevalence but decreased CPVT severity at rest and the number of ventricular beats during exercise (p<0.05). The hearts of CASQ^{□E9} mice had an increased basal expression of the A and B-type natriuretic peptide genes which were markedly decreased after training (tested by RT-PCR). Although connexin 43 protein levels remained the same, the β1 adrenoreceptor tended to decrease in exercise-trained hearts (Western blot). We conclude that in CASQ^{□E9} mice, exercise training is beneficial and could offer a strategy for prophylactic and therapeutic interventions.

A Potential Role for Statins in Protecting Cells following Myocardial Infarction or Ischemia during CABG, and for Inducing Apoptosis of Malignant Cells

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Background: Protein degradation via the ubiquitin system involves their covalent tagging by ubiquitination following by their proteasome degradation. Hdm2/Mdm2 is a ubiquitin ligase that plays a key role in the regulation of cell growth/death and in malignant transformation. Overexpression of Hdm2/Mdm2 in cardiomyocytes provides protection from death caused by ischemia/reperfusion. Recent studies have shown that 3-hydroxy-3-methyl-glutaryl-CoA(HMG-CoA) reductase inhibitors (statins) induce overexpression of Hdm2/Mdm2. This post-translational effect led us to hypothesize that statins are acting at the level of the degradation/stabilization of Hdm2. In this study we investigated the effect of statins on the Hdm2-p53 pathway in cultured cells.

Methods: Testing the role of a simvastatin in Hdm2-p53 pathway using cell lines [U2OS(p53+/+), HEK-293(p53+/+), H1299(p53-/-) and neonatal-rat ventricular-myocytes (NRVM)], in which the pathway is well established.

Results: We found that incubation of U2OS, NRVM and H1299 cells with simvastatin increases the levels of Hdm2/Mdm2, implying that the effect is p53 independent. On the other hand, simvastatin decreases the levels of Hdm2 in HEK-293 cells, implying that the effect of simvastatin is cell-dependent. In these cells; simvastatin inhibits the degradation of Hdm2.

Conclusions: It is accepted that in many cases, Hdm2 supports survival. Our results suggest that simvastatin increases the level of the enzyme in NRVM cells and decreases it in HEK-293 cells. Therefore, statin might be considered a potential drug to cardiomyocytes from death following myocardial infarction or ischemia during CABG. In addition, these findings maybe suggest another potential therapeutic effect for statins induction of death in certain malignant cells.

Repair Of The Bicuspid Aortic Valve- Our Experience

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Background

A bicuspid aortic valve (BAV) occurs in 2% of the population and is a common reason for significant aortic regurgitation, particularly in the third and fourth decades of life. For patients with a regurgitating bicuspid aortic valve, repair appears an attractive alternative to replacement. Preservation of the native valve has the advantage of obviating the need for anticoagulation, and there is evidence that it minimizes the overall incidence of valve-related complications. Here we evaluate the institutional results of Aortic valve repair in patients with bicuspid regurgitate aortic valves

Methods

From 2004 to 2008, 97 patients underwent aortic valve repair in our institution, out of them 21 repairs of BAV. Operative techniques included: subcommissural plications, free leaflet edge plications and pericardial leaflet augmentation. Post operative complications, and midterm follow up of clinical and echocardiography evaluation were analyzed for this group of patients.

Results

Mean age was 43 ± 13 years, 19 out of the 21 patients were males. There were no in hospital deaths in the BAV repair group. Post operative complications included 2 re-explorations due to bleeding. Mean Hospital stay was 5.7 ± 2.2 days. Mean follow up was 20 ± 15 month. Freedom from reoperation was 100%. Freedom from AR >2 was 95%.

Conclusions

BAV repair is associated with good early post operative outcome and midterm clinical and echocardiography results

No Hemorrhagic Strokes after Cardiac Surgery: A 14 year Retrospective Study

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Objective In the general population, 10-30% of strokes are hemorrhagic. We aimed to investigate the incidence of hemorrhagic strokes after cardiac surgery.

Methods All patients who developed post operative stroke in the department of cardiothoracic surgery were retrospectively assessed over 14 years for demographic and clinical features.

Results Among 5275 patients operated (mean age 63.5 ± 12 years, 70% males), 108 developed stroke or TIA (mean age 68 ± 10 years, 60 % males). All strokes (78) were ischemic. Large vessel stroke (35/78) and right hemispheric (37/78) were the most frequent type observed. Comparison of the post operative strokes with two cohorts of stroke in a general population confirmed the difference in the incidence of intracerebral hemorrhages, absent post cardiac surgery ($p= 0.02$). Most of the strokes (68%) occurred in the immediate post operative period. Strokes occurred more in patients with combined operations (coronary artery bypass graft and valve) ($p= 0.0004$). Patients with strokes suffered more from hypertension, diabetes mellitus, and previous stroke than other operated patients ($p= 0.01$, 0.003 and 0.004 respectively). Stepwise multivariate analysis of all perioperative cardiac risk factors identified only minimal temperature as predictor of stroke ($p=0.03$). Patients with strokes had a higher mortality and were hospitalized longer ($p < 0.0001$).

Conclusions Strokes after cardiac surgery occur mostly after combined procedures. Despite risk factors similar to those of strokes victims in the general population and post operative anticoagulation in all patients with valve surgery, no hemorrhagic strokes occurred after cardiac surgery