08:30 - 10:00 S16 - Arrhythmias and Genetics Hall G

Chairs: **N. Freedberg**
B. Strasberg

08:30 **Optimizing CPVT Therapy in Calsequestrin-mutant Mice**

G. Katz [1], E. Kurtzwald [1,2], E. Hochhauser [2], Y. Chepurko [2], E. Porat [2], A. Shainberg [3], J. Seidman [4], M. Eldar [1], M. Arad [1]
[1] Tel Hashomer, [2] Tel Aviv, [4] Boston

08:45 **Post Pacing Abnormal Repolarization in a Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Family Associated with a RyR2 Mutation**

E. Nof [1,3], B. Belhassen [2], M. Arad [1], Z.A. Bhuiyan [4], C. Antzelevitch [3], R. Rosso [2], R. Fogelman [5], D. Luria [1], D. El-Ani [1], S. Viskin [2], M. Eldar [1], A.A.M. Wilde [4], M. Glikson [1]
[1] Ramat Gan, [2] Tel Aviv, [3] Utica NY, [4] Amsterdam, [5] Petach Tikva

09:00 **Incessant Bidirectional Ventricular Tachycardia as the Presenting Arrhythmia of Andersen-Tawil Syndrome in Two Families**

A. Laish-Farkash [1,3], E. Nof [1,3], D. Luria [1,3], N. Constantini [3], H. Yonat [2,3], M. Fridman [2,3], M. Eldar [1,3], C. Antzelevitch [4], M. Glikson [1,3]
[2] Ramat gan, [3] Tel Aviv, [4] Utica, NY

09:15 **Triple Mutation of SCN5A Associated with Sinus Bradycardia and Conduction Disease**

E. Nof [1,3], A. Laish-Farkash [1], D. Marek [2], E. Pras [2], M. Eldar [1], C. Antzelevitch [3], M. Glikson [1], D. Luria [1]
[2] Ramat Gan, [3] Utica, NY

09:30 **Genetic Screening of Familial Sinus Bradycardia**

A. Laish-Farkash [1,2], E. Nof [1,2], D. Marek-Yagel [1,2], E. Pras [1,2], S. Viskin [2], M. Berger [1,2], O. Gurevitz [1,2], H. Reznik-Wolf [1,2], M. Eldar [1,2], C. Antzelevitch [3], M. Glikson [1,2], D. Luria [1,2]
[1] Ramat Gan, [2] Tel Aviv, [3] Utica NY

09:45 **Is Grapefruit "The Forbidden Fruit" for Patients with Long QT Syndrome?**

D. Fourey, R. Rosso, O. Rogowski, S. Viskin
Tel Aviv

Optimizing CPVT Therapy in Calsequestrin-mutant Mice

Guy Katz [1], Efrat Kurtzwald [1,2], Edith Hochhauser [2], Yeleno Chepurko [2], Eyal Porat [2], Asher Shainberg [3], Jonathan Seidman [4], Michael Eldar [1], Michael Arad [1]

[1] Leviev Heart Center, Sheba Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Hashomer, [2] Felsenstein Medical Research Center, Cardiac Research Lab, Sackler School of Medicine, Tel Aviv University, Tel Aviv, [3] Department of Life Sciences, Bar Ilan University, Israel, [4] Department of Genetics, Harvard Medical School, Boston, USA

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a lethal human arrhythmia provoked by physical or emotional stress and mediated by spontaneous Ca^{++} release and delayed after-depolarizations. Beta-adrenergic blockers are the therapy of choice for human CPVT, but achieve complete arrhythmia control in <50% of cases. Using a murine model of recessively-inherited CPVT caused by either a D307H mutation ($CASQ2^{D307H}$) or CASQ2 knock-out ($CASQ2^{\Delta}$), we conducted a pharmacological screen to optimize the therapy for CPVT.

Heart rhythm telemetry was obtained in awake animals at rest, during treadmill exercise and after intra-peritoneal (IP) injection of epinephrine [0.5μg/g]. The protocol was repeated after IP injection of different anti-arrhythmic agents. The primary end-point was the ability to induce CPVT, defined as VT recorded in an animal during any one of the stress protocol stages.

Adult CASQ2 mutant mice suffered from complex ventricular arrhythmia at rest and developed bidirectional and polymorphic VT on exertion. Class I antiarrhythmic agents (procainamide, lidocaine, flecainide) were ineffective in controlling arrhythmia. Propranolol and sotalol attenuated arrhythmia at rest but failed to prevent CPVT during sympathetic stimulation. The calcium channel blocker verapamil showed a dose-dependent and genotype-dependent protection against CPVT. Verapamil was more effective than the dihydropyridine L-type Ca^{++}-channel blocker nifedipine, and its activity was markedly enhanced when combined with propranolol.

We conclude that verapamil is the drug of choice in CASQ2 mice. Beta-adrenergic blockers have little benefit in murine CPVT but markedly enhance the effects of verapamil. L-type Ca^{++} channel blockade is only one of the mechanisms participating in CPVT suppression.

Post Pacing Abnormal Repolarization in a Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Family Associated with a RyR2 Mutation

Eyal Nof [1,3], Bernard Belhassen [2], Michael Arad [1], Zahurul A Bhuiyan [4], Charles Antzelevitch [3], Raphael Rosso [2], Rami Fogelman [5], David Luria [1], Dalia El-Ani [1], Sami Viskin [2], Michael Eldar [1], Arthur A.M Wilde [4], Michael Glikson [1]

[1] Heart Institute, Chaim Sheba Medical Center, Ramat Gan, [2] Heart Institute, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel, [3] Experimental Cardiology, Masonic Medical Research Laboratory, Utica NY, USA, [4] Cardiology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [5] Pediatric Cardiology, Schnieder, Petach Tikva, Israel

Introduction: CPVT is characterized by exercise induced ventricular arrhythmias. EPS is not known to be of value. We present a CPVT family in which post pacing abnormal repolarization during EPS was the only consistent phenotypic manifestation of RyR2 mutation carriers

Methods: A family presenting with 5 cases of SCD was evaluated using exercise, flecainide, epinephrine and adenosine provocative testing. EPS included ventricular pacing at various cycle lengths and extrastimulation using a short-long sequence. Genetic screening involved direct sequencing of *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, CACANA1C* and *RyR2* genes.

Results: Basic QTc was in normal range (410± 33 ms). Non-invasive clinical tests were normal in the 9 patients evaluated except for exercise induced ventricular arrhythmias in 1. Six patients demonstrated a marked increase in QT and QT $_{peak\text{-}end}$ only in the first beat after cessation of ventricular pacing and/or extrastimulation (Table). All 6 were found to have a heterozygous missense mutation (M4109R) in RyR2. Two of them, presenting with aborted SCD, also had a 2nd missense mutation (I406T- RyR2). Two family members without RyR2 mutations did not display prominent post-pacing QT changes.

Conclusions: M4109R- RyR2 is associated with a high incidence of SCD. The contribution of I406T to the clinical phenotype is unclear. Arrhythmias during exercise testing, considered as the hallmark of CPVT were not present in most affected family members. Marked post pacing repolarization changes in a single beat accurately predicted carriers of M4109R- RyR2 in this family.

RyR2	Post pacing QT interval (ms)		Average increase between 1st and 2nd beat (%)	Post pacing T $_{peak\text{-}end}$ interval (ms)		Average increase between 1st and 2nd beat (%)
	1st beat	2nd beat		1st beat	2nd beat	
M4109R	**516± 31**	**355± 41**	**47± 2.1***	**195± 17**	**105± 10**	**88± 3.1***
WT	**380± 0**	**360± 14**	**5± 0.4**	**95± 7**	**85± 7**	**11± 0.1**

*$p<0.05$

Incessant Bidirectional Ventricular Tachycardia as the Presenting Arrhythmia of Andersen-Tawil Syndrome in Two Families

Avishag Laish-Farkash [1,3], Eyal Nof [1,3], Davis Luria [1,3], Naama Constantini [3], Hagit Yonat [2,3], Moshe Fridman [2,3], Michael Eldar [1,3], Charles Antzelevitch [4], Michael Glikson [1,3]

[1] Heart Institute, [2] Genetic Institute, Sheba Medical Center, Ramat gan, [3] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [4] Masonic Medical Research Molecular Biology Laboratory, (MMRL), Utica, NY, USA

Introduction: Familial bidirectional VT (BDVT) is commonly associated with catecholaminergic polymorphic VT secondary to mutations in RyR2 and *CASO2* genes. We evaluated 2 families who presented with incessant BDVT and dysmorphic features.

Methods: Clinical and genetic evaluation of family members.

Results: In the first family (n=30), 3 females presented with incessant BDVT and dysmorphic features. 3 males presented with PVCs on Holter monitoring.
All displayed normal QT intervals. There were no symptoms related to arrhythmia, no family history of sudden death or evidence of structural heart disease (SHD). Screening for RyR2, *CASO2*, *triadin-1 (Trd)* and *junctin (Jn)* gene defects were negative. Screening of all exons and intron borders of *KCNJ2* revealed a missense mutation M307V in affected family members only, corresponding with Andersen Tawil syndrome (ATS).
In the second family (n=13), 2 females presented with incessant BDVT. Males presented with few PVCs on Holter monitoring. No cases of SCD were reported. The female proband presented with recurrent syncope in her fifth decade, intermittent prolonged QT interval as well as dysmorphic features, and no evidence of SHD. Screening for the genes of LQTS revealed mutations in the *KCNJ2* gene (R67W, associated with ATS) and *CACNA1C* gene (N2091S) in 3 affected family members, but also a G490R mutation in *CACNA1C* in the proband only.

Conclusion: We describe two families with BDVT as the main presenting arrhythmia of ATS, secondary to mutations in *KCNJ2*. In addition to BDVT there were also dysmorphic features. Interactions with other mutant ion channel defects and / or female gender likely underlie the variability in phenotypes.

Triple Mutation of SCN5A Associated with Sinus Bradycardia and Conduction Disease

Eyal Nof [1,3], Avishag Laish-Farkash [1], Dina Marek [2], Elon Pras [2], Michael Eldar [1], Charles Antzelevitch [3], Michael Glikson [1], David Luria [1]

[1] Heart Institute, Chaim Sheba Medical Center, [2] Institution of Human Genetics, Chaim Sheba Medical Center, Ramat Gan, Israel, [3] Experimental Cardiology, Masonic Medical Research Laboratory, Utica, NY, USA

Introduction: Mutations in SCN5A have been associated with a wide variety of rhythm disorders, including Brugada syndrome, LQT3 and conduction disease. The role of SCN5A in sinus node dysfunction is still in debate. Furthermore, it is not known whether mutations in SCN5A may interact to cause a more severe phenotype.

Methods: An 18 year old man with long-standing bradycardia presented with syncope during physical exercise and a documented wide complex tachycardia (WCT) on exercise testing. Evaluation included echocardiography, exercise testing, 24-hr Holter recording, EPS and cardiac MRI. Genetic screening involved direct sequencing of all exons and intron borders of HCN4, KCNJ2, KCNJ12 and SCN5A.

Results: ECG demonstrated junctional rhythm with a RBBB pattern. 24- hr Holter recording showed an average heart rate of 50 (range: 24 – 110) due to sinus bradycardia and occasional junctional rhythm with sinus pauses up to 5.8 seconds. Exercise testing did not reveal any chronotropic incompetence but induced a hemodynamically stable WCT (CL: 310 ms, RB & northwest axis). Echocardiography and MRI did not reveal any structural defects. EPS demonstrated a prolonged A-H of 260ms and H-V of 75 ms. During rapid pacing (420 CL) the H-V interval increased to over 100 ms. Atrial flutter (AFL) was inducible with 1:1 conduction leading to "clinical" WCT. Genetic screening revealed that the father had 2 missense mutations (V1251M, V1924T) and the mother had a K1492del in SCN5A. The proband inherited all 3 variations. 24-hr Holter recording showed no bradycardia in either parent, but the father displayed 1700 VPCs with a RBBB pattern.

Conclusions: Mutations in SCN5A may cause not only conduction disease but also sinus node dysfunction. Only a combination of the 2 SCN5A mutations and the amino acid deletion resulted in clinical bradycardia. Despite a markedly diseased conduction system the proband did not have any chronotrpic incompetence and had fast AV nodal conduction during AFL. This suggests that other ion channel currents may compensate or a may have a similar role to I_{Na} under hyper adrenergic states.

Genetic Screening of Familial Sinus Bradycardia

Avishag Laish-Farkash [1,3], Eyal Nof [1,3], Dina Marek-Yagel [2,3], Elon Pras [2,3], Sami Viskin [3,4], Michael Berger [1,3], Osnat Gurevitz [1,3], Haya Reznik-Wolf [2,3], Michael Eldar [1,3], Charles Antzelevitch [5], Michael Glikson [1,3], David Luria [1,3]

[1] Heart Institute, Sheba Medical Center, Ramat Gan, [2] Genetic Institute, Sheba Medical Center, Ramat Gan, [3] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, [4] Heart Institute, Tel Aviv Medical Center, Tel Aviv, Israel, [5] Masonic Medical Research Molecular Biology Laboratory, (MMRL), Utica NY, USA

Background: Familial sinus bradycardia (FSB) is a relatively rare phenomenon. We and others have previously shown in sporadic families that mutant hyperpolarization-activated nucleotide-gated (*HCN4)* channel, is associated with FSB. In this study we systematically screened families with SB for mutations in this channel as well as in others related to sinus node function.

Methods: Clinical evaluation and routine genetic screening of Israeli Jewish families with FSB.

Results: Twelve families with FSB were followed and screened for mutations in the HCN4 gene. Five of them, all of Jewish Moroccan descent, demonstrated A485V mutation of the HCN4 gene. Most of the carriers of this mutation were symptomatic. One additional family was positive for the G480R mutation. The carrier members were asymptomatic and had favorable prognosis without the need for pacemaker implantation during long-term follow-up. Six families did not have any mutations in HCN4. One of them was also screened for *KCNJ2, KCNJ12* and *SCN5A* genes. The screening revealed that only a combination of two *SCN5A* missense mutations (V1251M, V1924T) and an amino acid deletion (K1492del) in *SCN5A* resulted in clinical bradycardia with syncope and atrial tachyarrhythmias during physical exercise.

Conclusions: Genetic screening of families with FSB in Israeli Jewish population reveals a high yield of mutations in candidate genes of ion channels that participate in diastolic depolarization of SAN cells. The genotype-phenotype correlations will probably have a clinical role in risk stratification of FSB. Whether these findings apply to FSB in other populations remains to be determined

Is Grapefruit "The Forbidden Fruit" for Patients with Long QT Syndrome?

Dana Fourey, Rafael Rosso, Ori Rogowski, Sami Viskin
Cardiology, Electrophysiolgy, Sourasky Medical Center, Tel Aviv, Israel

Introduction: Numerous drugs prolong the QT interval and cause long QT syndrome (LQTS) by blocking a specific potassium channel named "IKr." Patients with congenital LQTS are at increased risk for this iatrogenic complication and are strongly advised to avoid all medications that block IKr. Recently, some flavinoids contained in grapefruit juice were shown to block IKr in cell preparations and prolong the QT interval in healthy volunteers. Consequently, one could argue that, until proven otherwise, patients with LQTS should avoid drinking grapefruit. Methods: We studied 19 patients with congenital LQTS and 9 age- and gender-matched healthy volunteers. All participants drank one liter of fresh pink grapefruit juice as quickly as possible and remained under electrocardiographic surveillance for 3 hours. The effects of grapefruit on heart rate, QT and QTc were measured. Results: As expected, the QTc of patients with congenital LQTS was longer at baseline than the QTc of healthy volunteers. However, grapefruit juice did *not* affect the heart rate, QT or QTc in any patient with congenital LQTS or in any volunteer at 1, 2 or 3 hours (Table). Conclusions: Drinking a single large bolus of grapefruit juice does *not* appear to cause QT-prolongation in patients with LQTS. Studies including larger number of patients and repeated drinking of grapefruit juice should be conducted to determine the long-term clinical significance of grapefruit juice for patients with LQTS.

Effect of grapefruit on QTc interval

	Controls	LQT Syndrome
	Median [25th - 75th Percent.]	Median [25th - 75th Percent.]
Baseline	416 [401 - 425]	447 [412 - 485]
1 hour	417 [397 - 423]	453 [428 - 476]
2 hours	419 [407 - 430]	443 [422 - 481]
3 hours	421 [409 - 435]	435 [419 - 472]