A Novel Mutation in the HCN4 Gene Causes Familial Sinus Bradycardia in Two Unrelated Moroccan Families

Avishag Laish-Farkash [1,3], Dina Marek [2,3], Elon Pras [2,3], Michael Arad [1,3], Eyal Nof [1,3], Haya Reznik-Wolf [2,3], Michael Eldar [1,3], Osnat Gurevitz [1,3], Michael Glikson [1,3], David Luria [1,3]

[1] Heart Institute, [2] Genetic Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, [3] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background: HCN4 channel plays a major role in the diastolic depolarization of sinoatrial node cells. We and others have previously shown that mutant HCN4 channels are associated with familial sinus bradycardia (SB).

Methods and Results: Two 20 years old men of North African Jewish decent were admitted. One survived an out of hospital cardiac arrest during extreme exercise. The other presented with weakness and pre-syncopal events. Both had significant SB (minimum 35, mean 53), which was also found in several other first degree family members. Holter and exercise testing showed SB at rest with normal response to exercise. Echo demonstrated normal heart structure. Sequencing of the HCN4 gene in both patients revealed a C to T transversion at nucleotide position 1454, which results in an alanine to valine change in the protein (A485V). Multiple alignments of different species show a conserved alanine at this position. The mutation was also found in the bradycardic relatives of the second patient and was not found in the non bradycardic relatives as well as in 50 healthy controls. The mutation is located in a conserved locus in the ion channel pore. A mutation in the pore was found in expression systems to decrease the funny current.

Conclusions: We describe a new mutation in the HCN4 gene in two unrelated patients with symptomatic familial SB. The existence of this mutation in two unrelated SB individuals from the same ethnic backgrounds suggests that it may be a relatively common cause for unexplained congenital SB in this ethnic group.

Outcome of Patients with Drug-induced High-degree Atrioventricular Block

Roy Beinart [1,2], Osnat Gurevitz [1,2], Henit Yanai [1,2], David Luria [1,2], David Bar Lev [1,2], Ilan Goldenberg [1,2], Raed Abu Sham'a [1], Michael Eldar [1,2], Michael Glikson [1,2]

[1] Heart Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, [2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background: Since information is scarce regarding the natural history of patients with drug-induced (DI) AV-block (AVB), indications for permanent pacing are inconsistent. We sought to determine the outcome of patients with drug -associated AVB.

Methods: 165 consecutive patients with high-degree AVB receiving drugs that affect conduction (presumably DIAVB), were studied retrospectively. The culprit drug was discontinued and decision on permanent pacing was taken by the attending physician. Patients were followed up to pacemaker implantation or, in non-implanted cases, till death or last follow-up, and were divided into 3 groups. Group A: pacemaker implantation (PMI) during index hospitalization; Group B: Discharged without PMI, but re-hospitalized and underwent PMI later during follow up; Group C: no need for PMI till end of follow-up.

Results:

	Group A N=107	**Group B N=23**	**Group C N=35**	***P value***	***P value (B vs. C)***
Age (years±SD)	76±9	76±8	73±12	NS	NS
Males	41(38%)	8(33%)	16(47%)	0.53	0.29
Ischemic heart disease	59(55%)	6(25%)	14(41%)	0.02	0.20
Syncope	67(63%)	6(25%)	8(24%)	**0.0001**	0.89
Mobitz type II	19(18%)	3(13%)	9(27%)	0.36	0.19
CAVB	55(51%)	4(17%)	4(12%)	**0.0001**	0.59
Wide QRS	32(30%)	4(17%)	1(2.9%)	**0.003**	0.07
Chronic atrial fibrillation	27(25%)	11(46%)	6(18%)	**0.05**	**0.02**

Conclusion: Of patients discharged without PMI, 40% will need PMI at a later stage. The presence of atrial fibrillation predicted future need for PMI among those patients, while wide QRS was a borderline predictor.

Larger prospective studies are required to better characterize this group of patients in order to avoid unnecessary PMI

Tricuspid Incompetence after Pacemaker Implantation in 410 Patients- Incidence and Associated Factors

Marc Klutstein, Adi Butnaru, Michael Ilan, Jonathan Balkin, David Rosenmann, Dan Tzivoni
Cardiology, Shaare Zedek Medical Center, Jerusalem, Israel

Severe tricuspid incompetence (TI) after pacemaker implantation has been described in small series of patients but its incidence is not known.
We retrospectively analyzed the data of 545 patients who underwent pacemaker implantation and had an echodoppler performed before and after the procedure. We excluded 135 patients who had moderate TI or more at baseline.
Seventy-five patients (18%) had a worsening of TI by ≥ 2 grades and were defined as group1. The patients without significant change were defined as group 2.
We compared clinical and echocardiograhic data in both groups.
Patients in group 1 were older, 77 ± 7 years compared to group 2: 72 ± 10 years, $p< 0.001$.
There was no difference in systolic function, left ventricular size and function or systolic TI gradient before the implantation. The mitral E/A ratio was 0.98 in group 1 and 1.42 in group 2, $p<0.001$.
The systolic TI gradient after implantation was higher in group 1: 42 ± 12 mmHg than in group 2: 33 ± 8 mmHg, $p <0.001$.
We conclude that TI worsening after pacemaker implantation is not rare and occurs more often in older patients, with impaired left ventricular relaxation and who develop pulmonary hypertension after the procedure.

The Effects of Left Ventricular Lead Placement on QT Interval and Transmural Dispersion of Repolarization in Biventricular Pacing

Alon Barsheshet, Athanasios Michailidis, David Luria, Osnat Gurevitz, Daniel Simantov, Chava Granit, David Bar-Lev, Michael Eldar, Michael Glikson

Heart Institute, Sheba Medical Center, Ramat Gan, Israel

Background: There is controversy regarding the pro-arrhythmic effects of biventricular pacing. Left ventricular (LV) epicardial pacing using the coronary veins reverses the normal activation of the LV wall and may increase both QT interval and Tpeak-end which correlates with transmural dispersion of repolarization (TDR).

Objectives: We sought to analyze the relationship between LV lead position to QT interval and TDR in patients with cardiac resynchronization therapy (CRT) systems, with an LV lead implanted via coronary veins.

Methods: Twelve leads electrocardiograms at three pacing modes (no pacing, LV pacing only and biventricular pacing) were evaluated in 63 patients immediately following a CRT device implantation. The LV lead was located in the lateral cardiac segment in 41 patients and in the posterior segment in 22 patients.

Results: There were no significant differences in heart rate (HR), QT, QT corrected (QTc), QT dispersion, JT and Tpeak-end intervals between the two groups at baseline (no pacing). With biventricular pacing the QTc and Tpeak-end intervals were significantly greater in posterior vs. lateral position. With LV pacing only the Tpeak-end interval was significantly greater in the posterior vs. lateral position and there was a trend for longer QTc interval in the posterior vs. lateral position.

	No Pacing			Biventricular Pacing			LV Pacing Only		
LV Lead Location	HR (bpm)	QTc (msec)	Tp-e (msec)	HR	QTc	Tp-e	HR	QTc	Tp-e
Lateral Segment	67±16	482±54	113±29	71±13	499±49	114±26	80±18	558±102	128±28
Posterior Segment	68±15	496±59	119±28	70±13	530±59	143±24	85±17	602±63	148±35
P value	NS	NS	NS	NS	0.034	<.0001	NS	0.069	0.015

Data are presented as mean±SD

Conclusions: Our data suggest a pacing site-dependent increase in TDR and QTc interval in patients with both biventricular and LV pacing. Posterior lead placement may therefore be more arrhythmogenic.

Left Ventricular Strain Signatures in Dilated Cardiomyopathy Predict Response to Cardiac Resynchronization Therapy: Timing is Not Everything

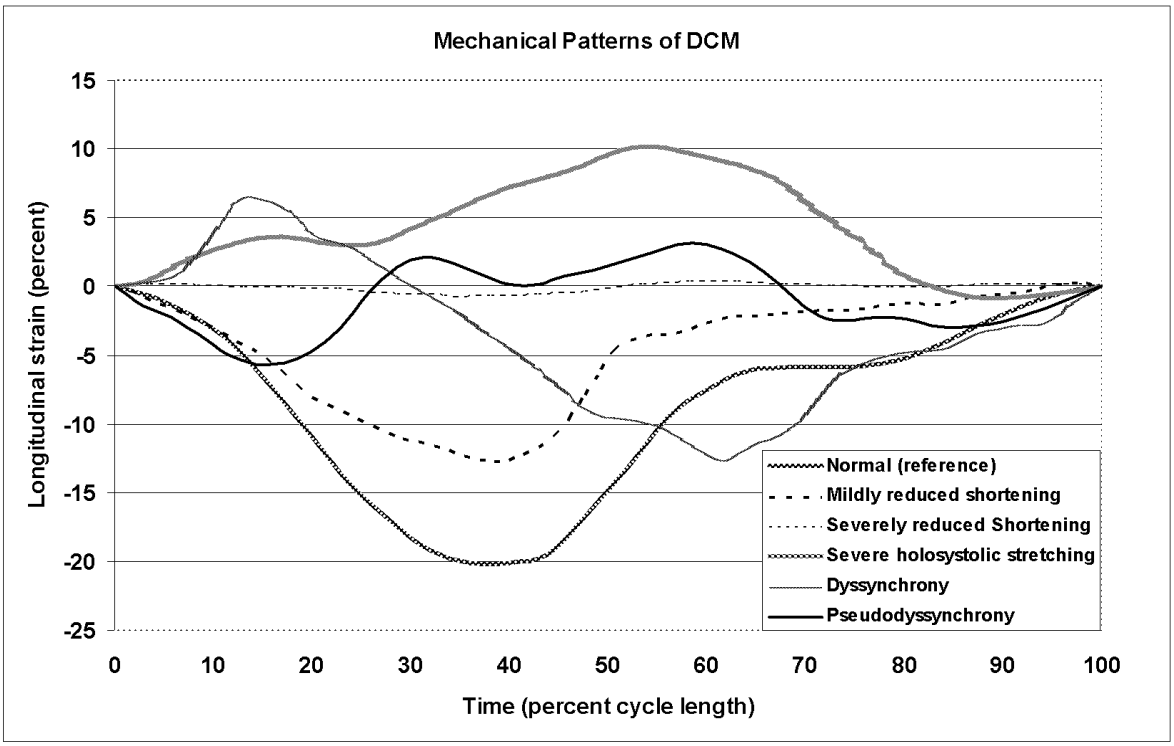
Shemy Carasso [1], Harry Rakowski [1], Klaus K Witte [1], Paul Smith [1], David Carasso [2], Zion Sasson [1], John D Parker [1]

[1] *University Health Network, Ontario, Toronto, ON, Canada,* [2] *Technion, Israel Institute of Technology, Haifa, Israel*

Background Cardiac resynchronization therapy (CRT) is helpful but not uniformly successful in patients with heart failure and ventricular dyssynchrony. Determination of dyssynchrony for patient selection does not consistently improve CRT success rate. We aimed to develop prediction rules for successful CRT based on mechanical strain patterns of LV function rather than just the timing of regional ventricular activation.

Methods 76 consecutive patients undergoing CRT were studied. Paired baseline and 3-6 months post procedural echocardiographic studies were analyzed. CRT response was determined by a ≥15% improvement in ejection fraction and/or a ≥15% decrease in end systolic volume. Longitudinal strain was measured using 2D speckle-tracking software (GE, Milwaukee) and Strain patterns correlated with CRT response.

Results Clinical and conventional echocardiographic characteristics were similar in responders (n=44) and non-responders (n=32). Resynchronization was achieved in both groups. Different strain patterns were identified and correlated with response.



Nonresponders had segments stretching ≥5% throughout systole. Absence of holosystolic stretching segments at baseline was 98% sensitive and 88% specific predicting response to CRT. When combined with presence of lateral delay pattern this model increased its sensitivity to 100% and specificity to 94% for response.

Conclusions LV strain pattern signatures are highly predictive of response to CRT, specifically, absence of holosystolic stretching. Strain imaging assesses the quality of resynchronization and its mechanical outcome.

Sinus Rhythm Restoration after Persistent Atrial Fibrillation: The Clinical Value of N-Terminal Pro-BNP Measurements.

Vladimir Danicek[1], Nick Theodorovich[1], Samuel Bar-Chaim[2], Asaf Miller[1], Zvi Vered[1], Nira Koren-Morag[4], Andrey Shopen[1], Nurit Brantriss[3], Edo Kaluski[1]

[1] Department of Cardiology, [2] Emergency Department, [3] Biochemical Laboratories, Assaf Harofeh Medical Center, Sackler School of Medicine, University of Tel Aviv, Zerifin, [4] Division of Epidemiology and Preventive Medicine, Sackler School of Medicine, University of Tel Aviv, Tel Aviv, Israe

Aim: To examine effects of sinus rhythm (SR) restoration on N-Terminal pro-BNP (NTP-BNP), in patients with atrial fibrillation (AF).

Methods: Subjects with paroxysmal and persistent AF in the absence of organic heart disease were prospectively studied. Chemical or electrical restoration of SR was attempted within 48h (n=37) or >3 weeks (n=73). Clinical and laboratory (N-terminal Pro-BNP, 72 hour Holter monitor and EKG) assessments were obtained at baseline and 1, 30, and 180 days after an attempt to restore SR. Patients were divided into 3 predefined "outcome groups": (a) Maintenance of SR for 1 month. (b) SR with periodical recurrent AF (PeAF) (c) Early (<30 days) recurrence AF (RAF).

Results: 110 patients enrolled; 93 had successful SR restoration. Baseline NTP-BNP was 936 pg/ml ($_{q25\text{-}75}$ 333-2026); Ratio between baseline and 30 day NTP-BNP was 10.2 ($q_{25\text{-}75}$ 6.42-22.0) for SR group, 3.3 ($q_{25\text{-}75}$ 2.45-7.34) for PeAF, and 1.07 ($q_{25\text{-}75}$ 0.87-1.22) for RAF ($p<0.001$), and was higher with early cardioversion. Patients with ratio ≤3 were more likely to have PeAF. (46% versus 3%, OR 30, $P<0.001$).

Results NTP-BNP Levels	ALL (n=110)	SR (n=38)	PeAF (n=32)	RAF (n=23)	Control (n=17)	p Value (chi²)
pre-cardioversion (pg/ml) median (q25-75) n=110	970 (344-1966)*	1415 (561-2626)*	641 (249-1410)*	896 (274-1110)*	1259 (755-2215)*	0.047
24 post-cardioversion (pg/ml) median (q25-75) n=67	471 (194-949)	451 (212-1041)	348 (164-1140)	650 (340-908)	-	0.614
1 month (pg/ml) median (q25-75) n=110	272 271-816	114 (271-816)	167 (56-290)	777 (276-1061)	1209 (749-2406)	<.001
6 months (pg/ml) median (q25-75) (n=45)	171 (53-336)	122 (15-249)	216 (89-444)	-	-	.031
12 months (pg/ml) median (q25-75) (n=25)	207 (83-474)	144 (21-376)	318 (171-1118)	-	-	.062
Ratio of pre and 1 m post CV median (q25-75) (n=110)*	2.98 1.13-8.87	10.2 6.42-22.0	3.3 2.45-7.34	1.07 0.87-1.22	1.04 0.85-1.17	<.001
*Ratio of pre and 6 m post CV * median (q25-75) (n=44)*	4.91 2.8-18.6	15.2 4.60-32.11	2.9 1.92-4.83	-	-	<.001

*CV-cardioversion

Conclusion: Patients with AF have elevated NTP-BNP, which is not predictive of SR restoration. When restoring SR dramatic reduction of NTP-BNP is observed up to 1 month. The NTP-BNP drop is partially or completely abolished by PeAF and RAF respectively. Post-cardioversion NTP-BNP may predict recurrent AF and embolic events.