The Utility of Prophylactic Pacemaker Implantation in Right Bundle Branch Block Patients Pre-Transcatheter Aortic Valve Implantation

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ABSTRACT: **Background:** Patients with right bundle branch block (RBBB) prior to transcatheter aortic valve implantation (TAVI) are at high risk for immediate post-procedural heart block and long-term mortality when discharged without a pacemaker.

Objectives: To test whether prophylactic permanent pacemaker implantation (PPI) is beneficial.

Methods: Of 795 consecutive patients who underwent TAVI, 90 patients had baseline RBBB. We compared characteristics and outcomes of the prophylactic PPI with post-TAVI PPI. Need for pacing was defined as greater than 1% ventricular pacing.

Results: Forty patients with RBBB received a prophylactic PPI (group 1), and in 50 the decision was based on standard post-procedural indications (group 2). There were no significant differences in clinical baseline characteristics. One patient developed a tamponade after a PPI post-TAVI. A trend toward shorter hospitalization duration in group 1 patients was observed ($P = 0.06$). On long-term follow-up of 848 ± 56 days, no differences were found in overall survival ($P = 0.77$), the composite event-free survival of both mortality and hospitalizations ($P = 0.66$), or mortality and syncope ($P = 0.65$). On multivariate analysis, independent predictors of the need for pacing included baseline PR interval increase of 10 ms (odds ratio [OR] 1.21 per 10 ms increment 95% confidence interval [95%CI] 1.02–1.44, $P = 0.028$), and the use of new generation valves (OR 3.92 95%CI 1.23–12.46, $P = 0.023$).

Conclusions: In patients with baseline pre-TAVI RBBB, no outcome differences were found with prophylactic PPI. On multivariate analysis, predictors of the need for pacing included baseline long PR interval, and the use of newer generation valves.

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KEY WORDS: conduction disturbances, pacemaker, prophylactic, right bundle branch block (RBBB), transcatheter aortic valve implantation (TAVI)

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For editorial see page 829

The use of transcatheter aortic valve implantation (TAVI) continues to increase, as the indications for the procedure are becoming broader [1]. New conduction disturbances following the procedure and the need for permanent pacemaker implantation (PPI) have been described [2]. Although mortality and major complication rates have decreased with the new generation valves, the rate of pacemaker implantation remains high in both the EvolutR (Medtronic, Minneapolis, MN, USA) and the Edwards S3 (Edwards Lifesciences, Irvine, Ca, USA) valves [1,3-6].

The presence of right bundle branch block (RBBB) prior to the procedure is a known risk factor for developing complete heart block and the need for PPI post-TAVI [7,8]. Researchers have found that baseline RBBB is independently associated with higher all-cause and cardiovascular mortality [9,10]. In addition, patients with RBBB without PPI at hospital discharge had a higher rate of 2 year cardiovascular death [9]. Thus, the management of patients with pre-procedural RBBB is unclear, and the benefit of a prophylactic PPI has not been assessed. In this study we compared the outcomes of patients with baseline RBBB who underwent prophylactic PPI prior to TAVI to patients with baseline RBBB who underwent a PPI for post-procedural indications.

PATIENTS AND METHODS

Our study comprised 795 consecutive patients who underwent TAVI at our medical center. Informed consent was obtained from all individual participants included in the study. The study was approved by the institutional ethics committee. Patients were recruited as part of their participation in the Tel-Aviv Prospective Angiography Study (TAPAS).

The diagnosis of severe aortic stenosis was based on clinical, echocardiographic, and hemodynamic criteria. Suitability and eligibility for TAVI was determined by a joint team including an interventional cardiologist, a cardiac surgeon, and a senior echocardiographist.

The electrocardiograms (ECGs) of the 795 patients who underwent TAVI were reviewed. The study population comprised 90 patients who demonstrated RBBB on their baseline ECG. The study population was divided into two groups based on implantation of a prophylactic permanent pacemaker prior to the procedure (usually one day prior to the TAVI). A permanent pacemaker was implanted at the discretion of the attending physician. The prophylactic PPI group comprised 40 patients. The control group comprised 50 patients who demonstrated RBBB on their baseline ECG and underwent the TAVI procedure without a permanent pacemaker. A permanent pacemaker was implanted in this group according to post-procedural indications, which included development of complete heart block, second-degree Mobitz type II, or alternating bundle branch block. PPI was performed 0–16 days after the procedure. We compared the baseline characteristics and outcomes of the prophylactic PPI group with those of the control group.

DATA COLLECTION AND DEFINITIONS

An ECG was obtained before TAVI and on a daily basis after TAVI. The diagnosis of intraventricular conduction abnormalities was based on the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations for the standardization and interpretation of the electrocardiogram [11]. PR intervals and QRS duration were measured and the presence of RBBB was noted. Changes in PR intervals were classified according to PR prolongation from baseline ECG. Data were collected from the device clinic and the post-TAVI clinic where all patient follow-up was conducted after the procedure.

PACEMAKER IMPLANTATION FOLLOW-UP

All patients underwent a chest X-ray and standard device interrogation after PPI. At the scheduled device interrogation examination 3 and 12 months after implantation, the percentage of ventricular pacing was assessed. No need for ventricular pacing was defined as < 1% ventricular pacing and intrinsic 1:1 atrioventricular conduction with the device programmed to VVI 30 beats per minute.

STATISTICAL ANALYSIS

Differences between continuous variables were assessed using a Mann–Whitney U test. Differences in proportions were assessed by either a Chi-square test or Fisher's exact test, as appropriate. To assess overall survival and event-free survival, Kaplan–Meier curves were drawn for the two treatment groups and statistical significance was assessed by a log-rank test. Continuous predictors and multivariate analysis of need for ventricular pacing during follow-up were assessed using a logistic regression model in a univariate or multivariate fashion as appropriate. Results are shown as mean ± standard deviation for continuous variables or n (%) for categorical variables. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

BASELINE CHARACTERISTICS

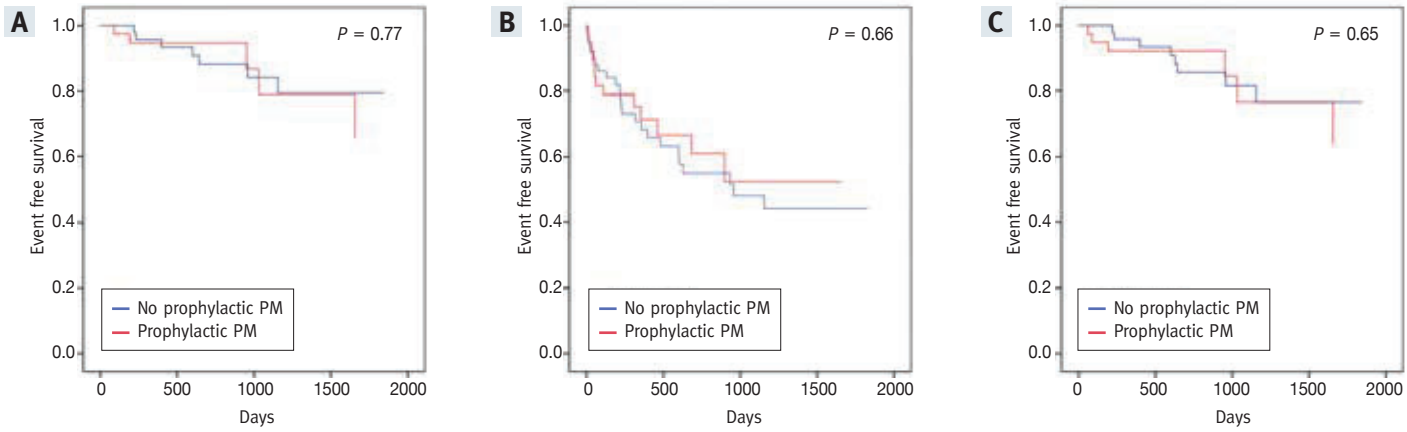
Between April 2012 and December 2016, 795 patients underwent TAVI at our center. Pre-existing RBBB was found in 90 patients (11%), 40 of whom underwent prophylactic PPI prior to TAVI (group 1). The remaining 50 patients underwent the procedure without a permanent pacemaker and the decision regarding the need for a PPI was based on post-TAVI indications (group 2). Baseline characteristics and procedural details are presented in Table 1. There were no significant differences in the clinical base-

Table 1. Baseline clinical, electrocardiogram, and procedural characteristics of patients with and without a prophylactic PPI

		Prophylactic pacemaker		
		Yes n=40 (%)	No n=50 (%)	*P* value
Age (years)		84 ± 6	81 ± 8	0.241
Male gender		30 (75)	29 (58)	0.092
Diabetes mellitus		17 (43)	17 (34)	0.409
Dyslipidemia		22 (55)	28 (56)	0.924
Hypertension		30 (75)	35 (70)	0.599
PVD		1 (3)	0 (0)	0.444
Stroke		3 (8)	5 (10)	0.728
PCI		18 (45)	17 (34)	0.287
CABG		8 (20)	9 (18)	0.81
Heart failure		8 (20)	9 (18)	0.81
Logistic EUROSCORE		9.9 ± 10.3	9.3 ± 9.0	0.567
Heart rate (bpm)		70 ± 14	73 ± 16	0.631
Baseline rhythm	Sinus Atrial fibrillation	35 (88) 5 (13)	40 (80) 10 (20)	0.343
AVB pre-procedural	1st AVB 2nd AVB	13 (33) 1 (3)	10 (20) 1 (2)	0.362
LAHB		17 (43)	17 (34)	0.356
S in lead I		39 (98)	49 (98)	1
S in lead AVL		38 (95)	46 (92)	0.689
PR pre (ms)		201 ± 42	190 ± 39	0.249
PR post (ms)		197 ± 46	196 ± 57	0.745
Delta PR (ms)		7 ± 41	8 ± 103	0.825
QRS Pre (ms)		141 ± 12	136 ± 11	0.03
Valve type	Corevalve Edwards S3 Edwards Sapien XT Evolute R Lotus	12 (30) 12 (30) 1 (3) 12 (30) 3 (8)	10 (20) 11 (22) 23 (46) 6 (12) 0 (0)	0.273 0.387 ‹ 0.001 0.034 0.05
AVB post-procedural	1st AVB 2nd AVB 3rd AVB	7 (18) 0 (0) 18 (45)	8 (16) 4 (8) 21 (42)	0.19

AVB = Atrioventricular block, BPM = beats per minute, CABG = coronary artery bypass graft, LAHB = left anterior hemi block, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease

Figure 1. Kaplan–Meier plots of patients with or without prophylactic pacemakers **[A]** Overall survival, **[B]** composite event-free survival of mortality and hospitalizations, and **[C]** composite event free survival of mortality and syncope. No differences in clinical outcome were seen between the groups



line characteristics. There was a trend toward more male patients in group 1, 30 (75%) vs. 29 (58%) ($P = 0.09$). Mean baseline QRS width was slightly longer in group 1 (141 ± 12 vs. 136 ± 11, $P = 0.03$). No differences in PR duration were noted.

A number of differences were noted in the type of valve implanted. Patients in group 2 had significantly more Edwards XT (Edwards Lifesciences, Irvine, Ca, USA) valves implanted, 23 (46%) vs. 1 (3%), ($P < 0.001$), while patients in group 1 had more EvolutR valves implanted (12 vs. 6, $P = 0.03$). A higher number of Lotus valves were found in group 1 than in group 2 (3 vs. 0, $P = 0.05$). There was no difference in the numbers of CoreValve and Edwards S3 valves in the groups. No difference was found in development of atrioventricular block (AVB) following the procedure between the groups. Among the patients in group 2, 27 (54%) received a pacemaker before hospital discharge, 25 due to post-procedure development of second or third degree AVB. A pacemaker was implanted in two patients because of post-procedural PR prolongation, one of whom had long H-V on electrophysiological study.

SHORT-TERM FOLLOW-UP

During follow-up, one patient had a PPI 16 days post-discharge due to sick sinus syndrome. One patient developed tamponade after a PPI post-TAVI. There was a trend toward shorter hospitalization duration in group 1 compared to group 2 (4.9 ± 1.6 days vs. 5.6 ± 1.7, $P = 0.06$). When comparing group 1 to the subgroup of patients in group 2 who underwent a post-procedural PPI, group 1 had a shorter hospitalization duration (4.9 ± 1.6 vs. 5.9 ± 2.2, $P = 0.05$).

LONG-TERM FOLLOW-UP

During a mean long-term follow-up of 848 ± 56 days, there was no difference between the two groups in overall survival (65.8 ± 14.9% vs. 79.5 ± 7.4%, $P = 0.77$), composite event-free survival of both mortality and hospitalizations (52.4 ± 11.5% vs. 44.1 ± 8.4%, $P = 0.66$), or mortality and syncope, (64.0 ± 14.6% vs. 76.8 ± 7.7%, $P = 0.65$) [Figure 1 A-C].

NECESSITY FOR VENTRICULAR PACING DURING FOLLOW-UP

In 84 of the 90 patients, follow-up data concerning the need for ventricular pacing was available. Thirty-three patients (39%) did not require pacing on long-term follow-up: 11 (32.4%) in group 1 and 22 (44%) in group 2. Patients who did not require pacing included those who were not implanted with a pacemaker (at hospital discharge and follow-up) or patients with < 1% ventricular pacing at follow-up.

UNIVARIATE AND MULTIVARIATE ANALYSIS

Univariate and multivariate analysis was performed on candidate variables for predictors of the need for pacing [Table 2, Table 3]. For the univariate analysis, predictors of the need for pacing were first degree AVB on baseline ECG, (odds ratio [OR] 3.16, 95% confidence interval [95%CI] 1.03–9.77, $P = 0.039$), the use of new generation valves (OR 3.0, 95%CI 1.17–7.7, $P = 0.02$), baseline PR interval increase of 10 ms (OR 1.21 per 10 ms increment, 95%CI 1.03–1.43, $P = 0.023$), and post-procedural increase in PR interval by 10 ms (OR 1.17 per 10 ms increment, 95%CI 1.01–1.36, $P = 0.037$). The absence of S waves in the lateral leads or QRS width in baseline ECG did not predict the need for pacing. For multivariate analysis, independent predictors included baseline PR interval increase of 10 ms (OR 1.21 per 10 ms increment, 95%CI 1.02–1.44, $P = 0.028$), and the use of new generation valves (OR 3.92, 95%CI 1.23–12.46, $P = 0.023$).

DISCUSSION

The aim of this study was to evaluate the use of prophylactic PPI for patients demonstrating pre-TAVI RBBB. We found that during

long-term follow-up there was no difference in overall survival, composite event-free survival of both mortality and hospitalizations, or mortality and syncope between patients who received a prophylactic PPI and patients who were implanted according to post-TAVI indications. In the multivariate analysis, independent predictors of the need for pacing included baseline PR interval increase of 10 ms, and the use of newer generation valves.

Patients with pre-TAVI RBBB comprise approximately 11% of the total TAVI patient population. Auffret et al. [9], who found a similar rate of patients with pre-TAVI RBBB, reported a very high incidence of 27.8% 2-year mortality in patients with RBBB and no PPI post-TAVI. Conversely, patients with RBBB and permanent pacemakers had a 2-year mortality of 18.1%, which was similar to patients without RBBB. However, in our study we were unable to prove that such policy translates into a more favorable patient outcome.

In our study, higher rates of Edwards XT, but not of Edwards S3, were found in group 2. This finding is explained by the physicians' choice of the Edwards XT valve when suitable for patients with unprotected pre-existing RBBB due to its lower rate of new left bundle branch block (LBBB) and complete heart block [2]. When the patient anatomy was not suitable for implanting the Edwards XT valve, the physicians' decision inclined to a prophylactic PPI. These decisions might have also been influenced by a longer QRS duration at baseline. However, addressing the problem of pre-existing RBBB with valve selection is no longer useful since the newer generation valves have similar rates of new LBBB and heart block [5,12]. Indeed, in the current study both types of new generation valves (EvolutR and Edwards S3) were associated with higher rates of pacing.

In patients with baseline RBBB who underwent PPI following the procedure due to complete AVB, a ventricular paced rhythm at 30-day and 1-year follow-up, was present in 81% and 89%, respectively [13]. In a different study, five of six patients (83%) with RBBB developed AVB [7]. In our study, 39% of the patients did not require pacing during follow-up (32.4% and 44% in groups 1 and 2, respectively), thus there is potentially a higher percentage of patients who could be unnecessarily implanted with a permanent pacemaker. The lack of difference in long-term outcome between the groups renders both options valid. The rates of unnecessary pacemaker implantations should be weighed against the potentially slightly higher complication rate in post-TAVI implantation since post-TAVI implantations are performed urgently during complete AVB and on dual antiplatelet therapy, which was found to be associated with a four-fold hazard of bleeding during the perioperative period [14]. In addition, hospitalization duration of patients receiving a PPI following the procedure was one day longer, a difference that may be more significant with the use of the newer generation valves and their early discharge approach.

On multivariate analysis, each baseline PR increase of 10 ms was associated with an increased OR of 1.21 for the need

Table 2. Univariate analysis for predictors of the need of pacing

Categorical variables					
		Pacemaker not needed n=33 (%)	**Pacemaker needed n=51 (%)**	**OR (95%CI)**	***P* value**
Prophylactic pacemaker	No Yes	22 (44) 11 (32.4)	28 (56) 23 (67.6)	1.64 (0.66–4.08)	0.283
Baseline rhythm	Sinus AF	27 (38.6) 6 (42.9)	43 (61.4) 8 (57.1)	0.84 (0.26–2.68)	0.764
1st AVB	No Yes	27 (48.2) 5 (22.7)	29 (51.8) 17 (77.3)	3.17 (1.03–9.77)	0.039
LAHB	No Yes	21 (39.6) 11 (36.7)	32 (60.4) 19 (63.3)	1.13 (0.45–2.86)	0.79
S in lead aVL	No Yes	1 (16.7) 32 (41)	5 (83.3) 46 (59)	0.29 (0.03–2.58)	0.396
S in lead I	No Yes	0 33 (40.2)	2 (100) 49 (59.8)	-	0.517
Male gender	No Yes	15 (50) 18 (33.3)	15 (50) 36 (67.7)	2 (0.8–4.98)	0.134
Diabetes mellitus	No Yes	19 (36.5) 14 (43.8)	33 (63.5) 18 (56.3)	0.74 (0.3–1.82)	0.511
Dyslipidemia	No Yes	12 (34.3) 21 (42.9)	23 (65.7) 28 (57.1)	0.7 (0.96–1.71)	0.428
Hypertension	No Yes	12 (54.5) 21 (33.9)	10 (45.5) 41 (66.1)	2.34 (0.87–6.31)	0.088
PVD	No Yes	32 (38.6) 1 (100)	51 (61.4) 0		0.393
Stroke	No Yes	30 (39) 3 (42.9)	47 (61) 4 (57.1)	0.85 (0.18–4.07)	1
PCI	No Yes	22 (42.3) 11 (34.4)	30 (57.7) 21 (65.6)	1.4 (0.56–3.49)	0.47
CABG	No Yes	27 (39.1) 6 (40)	42 (60.9) 9 (60)	0.96 (0.31–3.02)	0.95
Heart failure	No Yes	26 (37.1) 7 (50)	44 (62.9) 7 (50)	0.59 (0.19–1.87)	0.369
Valve type	Self-expandable Balloon- expandable Mechanical expandable	15 (40.5) 18 (40.9) 0	22 (59.5) 26 (59.1) 3 (100)	0.99 (0.4–2.4) –	0.973
Valve type new vs. old	Old New	24 (50) 9 (25)	24 (50) 27 (75)	3 (1.17–7.7)	0.02
Sub-group between new valves	Edwards S3 Evolute R	6 (30) 3 (18.8)	14 (70) 13 (81.3)	0.54 (0.11–2.61)	0.7
Sub-group between old valves	Corevalve Edwards XT Lotus	12 (57.1) 12 (50) 0	9 (42.9) 12 (50) 3 (100)	1.33 (0.41–4.33) –	0.632

Numerical variables		
	OR (95%CI)	***P* value**
PR pre-procedural (for 10 ms increments)	1.21 (1.03–1.43)	0.023
PR post-procedural (for 10 ms increments)	1.17 (1.01–1.36)	0.037
Delta PR (for 10 ms increments)	0.96 (0.88–1.19)	0.292
QRS width pre-procedural (for 10 ms increments)	1.23 (0.98–1.06)	0.309
Heart rate	0.99 (0.96–1.02)	0.385
Age	1.04 (0.98–1.10)	0.253
EuroScore	1.01 (0.95–1.07)	0.724

AVB = atrioventricular block, CABG = coronary artery bypass graft, LAHB = left anterior hemi block, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, OD = odds ratio, 95%CI = 95% confidence interval

Table 3. Multivariate analysis for predictors of the need of pacing

	OR (95%CI)	*P* value
PR pre-procedural (for 10 ms increments)	1.21 (1.02–1.44)	0.028
Prophylactic pacemaker implantation	0.85 (0.28–2.63)	0.645
Use of newer generation valves	3.92 (1.23–12.46)	0.023

OD = odds ratio, 95%CI = 95% confidence interval

for pacing. A similar result was found in a large Framingham Heart Study community-based cohort [15], where each 20-millisecond increment in PR was associated with an adjusted hazards ratio of 1.22 (95%CI, 1.14–1.30, $P < 0.001$) for pacemaker implantation. The longer PR interval may reflect infranodal His-Purkinje disease, explaining these results [16]. This finding supports the consideration of implanting a prophylactic pacemaker in the subgroup of patients with PR prolongation in addition to the RBBB at baseline.

An ECG pattern of RBBB in lead V1 with absent S wave in leads I and aVL has been described as indicative of concomitant LBBB delay. Such patients were found to have a higher prevalence of heart block [17]. This absence of S wave was not found to be a predictor of the need for a permanent pacemaker in univariate analysis. However, lack of an S wave in lead I was found in only two patients, both of whom needed a pacemaker. Moreover, lack of an S wave in lead aVL was found in six patients, of whom five needed pacing. It is possible that in a larger study population this finding would be useful in predicting the need for a pacemaker.

Left anterior hemi block (LAHB) was noted in 34 patients (38%) and was not useful as a predictor of the need for pacing post-TAVI in patients with RBBB. The usefulness of LAHB as a predictor for PPI was inconsistent in different studies [8,18]. Thus, it seems that the main ECG parameter that is useful for predicting the need for PPI in patients with RBBB is prolonged PR interval.

LIMITATIONS

We conducted a single-center retrospective study. The decision regarding prophylactic PPI was at the discretion of the attending physician and resulted in some differences in the type of valve implanted between the groups. As in other studies [19], the need for pacing was evaluated with a cut-off < 1% cut-off for ventricular pacing, and cannot absolutely exclude short transient complete AVB. Further large randomized trials are needed to evaluate the use of prophylactic pacemaker implantation.

CONCLUSIONS

In patients with baseline RBBB pre-TAVI, no difference in overall survival, composite event-free survival of mortality and hospitalizations, or mortality and syncope were found on long-term follow-up among patients who underwent a prophylactic PPI compared with those who underwent implantation according to post-TAVI indications. On long-term follow-up, 39% of the patients were not pacer dependent. On multivariate analysis, independent predictors of the need for pacing included baseline PR interval increase of 10 ms and the use of newer generation valves. A prophylactic PPI may be considered for patients with baseline PR prolongation in addition to RBBB.

Conflict of interest

Dr. Finkelstein acts as a TAVI proctor and receives consultation fees from Medtronic Cardiovascular (Minneapolis, Minnesota, USA) and Edwards Lifesciences (Irvine, California, USA)

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Capsule

Mechanical tissue matching

Implantable electronic devices that can precisely detect metabolites and biomarkers of disease in real time are an exciting prospect. However, ensuring that such devices stably interact with human tissue without causing damage is difficult because the devices need to bend and adapt to the motions of the body. To overcome this impediment, **Wang** et al. developed an implantable electrochemical sensor composed of flexible helical bundles of carbon nanotubes that mimic the fibril structure of muscle. When injected into target tissues in cats, the bundles formed a stable interface with the tissue and could detect and transmit chemical concentrations in real time through Bluetooth. Matching the mechanical properties of tissue should thus allow implantable devices to be used long-term in humans.

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Eitan Israeli

Capsule

Charting MAIT cell development

Mucosal-associated invariant T (MAIT) cells are a distinct subset of T cells that recognize vitamin B metabolites presented by major histocompatibility complex class I-related protein (MR1). **Koay** et al. used bulk and single-cell RNA sequencing and flow cytometric analysis to characterize the development of murine and human MAIT cells. In addition to providing a clearer picture of MAIT cell development in the thymus, the studies uncovered several molecules that play key roles in regulating this process. Genetic inactivation experiments in mice confirmed the functions some of these molecules – including SAP, SATB1, CXCR6, and CCR7 – in regulating MAIT cell development.

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Eitan Israeli

Capsule

No association of *HLA–DRB1* and *TNF* alleles in Mexican patients with autoimmune hepatitis

*HLA–DRB*1 alleles have been found to be implicated in susceptibility to autoimmune hepatitis (AIH) in populations from different genetic backgrounds. In Mexicans, *HLA–DRB*1*04:04 is recognized as a risk allele for AIH but, to date, there is no high-resolution data supporting this association. Also, the association of other nonclassical HLA genes, such as *TNF–LTA* locus, have not been evaluated in this population. **Mendoza-Carrera** et al. evaluated the association of *HLA–DRB*1 alleles determined by sequence-based typing and two polymorphisms in the TNF locus with AIH in a sample of Mexican patients. Fifty-six patients from Guadalajara, Mexico, diagnosed with AIH and 115 age and gender matched healthy volunteer blood donors, were genotyped for *HLA–DRB*1 by the sequencing exon 2 and for *TNFA*–308G›A and *LTA* + 252A›G polymorphisms. Increased frequencies of both *HLA–DRB*1*04:04:01 and *16:02:01:01 alleles (odds ratio [OR] = 2.91; 95% confidence interval [95%CI] = 1.08–7.84) and the haplotype (*DRB*1–*TNFA–LTA*) *04:04:01-G-A (OR = 5.33; 95%CI = 1.32–21.49) were observed in AIH patients. However, after corrections for multiple comparisons, associations were not significant. This study does not support the association of *HLA–DRB*1*04:04:01 with the susceptibility to AIH in Mexican population. More studies including patients from other Mexican regions and considering other genetic, immunological, and environmental factors should be performed.

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