Trends and Outcomes in Heart Transplantation over the Past Three Decades: A Single Tertiary Center Experience in Israel

Yael Peled MD[1,2], Dov Freimark MD[1,2], Yedael Har-Zahav MD[1], Eyal Nachum MD[1,2], Alexander Kogan MD[1,2], Yigal Kassif MD[1,2] and Jacob Lavee MD[1,2]

[1]Heart Transplantation Unit, Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Heart transplantation (HT) is the treatment of choice for patients with end-stage heart failure. The HT unit at the Sheba Medical Center is the largest of its kind in Israel.
Objectives: To evaluate the experience of HT at a single center, assess trends over 3 decades, and correlate with worldwide data.
Methods: Between 1990 and 2017, we reviewed all 285 adult HT patients. Patients were grouped by year of HT: 1990–1999 (decade 1), 2000–2009 (decade 2), and 2010–2017 (decade 3).
Results: The percentage of women undergoing HT has increased and etiology has shifted from ischemic to non-ischemic cardiomyopathy (10% vs. 25%, $P = 0.033$; 70% vs. 40% ischemic, for decades 1 vs. 3, respectively). Implantation of left ventricular assist device as a bridge to HT has increased. Metabolic profile has improved over the years with lower low-density lipoprotein, diabetes, and hypertension after HT (101 mg/dl, 27%, and 41% at decade 3, respectively). There has been a prominent change in immunosuppressive treatments, currently more than 90% are treated with tacrolimus, compared with 2.7% and 30.9% in decades 1 and 2, respectively ($P < 0.001$). Cardiac allograft vasculopathy (CAV) rates have declined significantly (47% vs. 17.5% for decades 1 and 2, $P < 0.001$) as have the combined endpoint of CAV/death. Similarly, the current incidence of acute rejections is significantly lower.
Conclusions: Our analysis of over 25 years of a single-center experience with HT shows encouraging improved results, which are in line with worldwide standards and experience.

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KEY WORDS: cardiac allograft vasculopathy (CAV), heart transplantation (HT), single-center study, transplant rejection

In 2017, the world celebrated the 50th anniversary of the first heart transplantation (HT), which was performed in 1967 in South Africa by Christiaan Barnard [1]. Over the years, HT has grown to become the treatment of choice for patients with end-stage heart failure, with an increase in the median survival of HT patients from 15 days to 11 years [2].

Worldwide, the number of patients on the waiting list for HT today is over 4000, almost twice the number of patients who will actually undergo HT [3]. In Israel, the shortage of heart donors is even worse. In 2016, there were 73 patients on the national waiting list, while only 22 patients eventually underwent HT [4]. The cause is a lack of donors to meet the increasing number of patients awaiting HT. Finding a balance between maximal individual survival benefit and maximal utility is of great importance for maximum utilization of this rare, and life saving resource. Therefore, it is extremely important to identify clinical, demographic, and histopathological characteristics to predict the success of HT.

The Heart Transplantation Unit at the Sheba Medical Center was established in 1992, and has since become the largest of its kind in Israel, having performed more than 220 adult heart transplants. In addition, patients who underwent HT at various medical centers worldwide have been followed at the unit since 1990. Collectively, our HT program features a unique pool of HT patients of diverse ethnic, national, and religious origins, transplanted over a period of more than 25 years, with all medical records documented and stored at our institute.

The aim of this study was to evaluate the experience of HT at a single center, assess trends over the years, and correlate with worldwide data.

PATIENTS AND METHODS

STUDY POPULATION AND REGISTRY DESIGN

Between December 1990 and May 2017, 285 patients who underwent HT were enrolled and prospectively followed in the tertiary center of the Sheba HT registry.

DEFINITIONS

Study groups according to year of heart transplantation

Patients were grouped by year of HT into three groups:

- Decade 1:1990–1999 (n=97)
- Decade 2: 2000–2009 (n=118)
- Decade 3: 2010–2017 (n=70).

Immunosuppression

Maintenance immunosuppression included a combination therapy including prednisone, an antimetabolite, and a calcineurin inhibitor (CNI). Cyclosporine was the first CNI used. In 2006, tacrolimus was introduced into clinical practice, and since 2010 has become the CNI of choice. Everolimus, an mTOR inhibitor, was introduced in 2009 and applied to a minority of patients later in the follow-up, combined with low dose CNIs. All patients also received induction therapy consisting of anti-thymocyte globulin.

Rejections, surveillance, and classification

Rejections were diagnosed by routine or clinically indicated endomyocardial biopsy (EMB), classified according to the revised International Society of Heart and Lung Transplantation (ISHLT) classification system for rejection [5]. Routine EMBs were performed every week for the first 4 weeks post HT, twice a month during the second and third months, once a month for the following 3 months, and thereafter every 3 months until the end of the first year. From the end of the first year until the end of the fifth year, biopsies were carried out annually. For each patient, we calculated a total rejection score (TRS) as 0R = 0, 1R = 1, 2R = 2, and 3R = 3; and any rejection score (ARS) as 0R = 0, 1R = 1, 2R = 1, 3R = 1, both normalized by dividing the cumulative scores by the total number of biopsy specimens taken during the study period [6].

Cardiac allograft vasculopathy

The institutional post-transplant care protocol includes annual invasive coronary angiography for the first 5 years following HT, along with echocardiogram and right heart catheterization. Cardiac allograft vasculopathy (CAV) was diagnosed by coronary angiography, and invasive hemodynamic assessment was performed annually, along with clinical assessment and echocardiography, combined according to the recommended nomenclature for CAV of the ISHLT consensus statement [7].

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics were produced using means and standard deviations for continuous variables (e.g., age), as well as frequencies for categorical variables (e.g., gender). Differences among groups in continuous variables were examined via Kruskal–Wallis procedures to avoid bias for non-normal distributions. Significant differences were further estimated using Bonferroni correction to avoid bias due to multiple comparisons. Chi-square tests were used to examine differences between groups in categorical variables. The Kaplan–Meier estimator was used to assess differences in mortality and CAV occurrences by year of transplantation, while groups were compared using the log-rank test. A two-sided 0.05 significance level was used for hypothesis testing. For differences between HT year groups, *P* trend was assessed.

RESULTS

CLINICAL CHARACTERISTICS OF STUDY PATIENTS BY YEAR OF TRANSPLANTATION

Baseline pre-heart transplantation characteristics

The present study population comprised 285 patients, with an age range of 17–70 years (mean 45 ± 13 years), of whom 83% (n=236) were men. Baseline characteristics of HT patients are shown in Table 1. Over the study period, the percentage of women who underwent HT increased, from approximately 10% in decade 1 to 25% in decade 3 (*P* value for trend = 0.033).

Etiology for HT has also shifted over this period, from predominantly ischemic heart disease (70%) in decade 1 to only 40% in decade 3 (*P* value for trend < 0.001) [Table 1].

Patient risk profiles have changed during the study period. Diabetes has become more frequent, with almost 30% of patients diagnosed with diabetes prior to HT during decade 2, compared to only 10% during decade 1 (*P* = 0.003). In contrast, smoking is less frequent in decade 3 vs. decades 1 and 2 (53%, 43%, 31%, respectively, *P* = 0.021).

The incidence of patients transplanted, while listed as Status 2 priority (a lower priority incidence compared to the more urgent priority of Status 1), has declined over the years, (43.6% in decade 1, 25.0% in decade 2, and 33.3% in decade 3, *P* = 0.029).

Incidence of implantation of left ventricular assist device (LVAD) as a bridge to HT has increased, as almost one-third of the patients are currently bridged to transplant with LVAD [Table 1]. Also, implantation of an internal cardioverter defibrillator (ICD) prior to HT is more than 7 times more frequent in decade 3 as compared with the earlier decades, and is currently implanted in approximately 75% of patients undergoing HT. Pulmonary capillary wedge pressure and mean pulmonary artery pressure were lower as the years progressed, yet the pulmonary vascular resistance has remained similar.

OPERATIVE AND POST HEART TRANSPLANTATION CHARACTERISTICS

Operative data

Operative data have not changed significantly over the years with regard total graft ischemic time, prolonged ionotropic support, and length of hospital stay [Table 1]. Recent in-hospital mortality following HT is 10%. Higher rates of early postoperative complications were seen in decade 3 (approximately one-third are related to prolonged chest tubes and secretions, prolonged ventilation, and wound infection), yet did not affected the length of hospital stay or early mortality.

Table 1. Patient baseline and operative data by decades of transplantation

	Decade 1 1990–1999 (n=97)	Decade 2 2000–2009 (n=118)	Decade 3 2010–2017 (n=70)	*P* value
Recipient characteristics				
Gender, female	10.3%	17.8%	25.7%	0.033
Age, year	48.96 ± 13.92	49.25 ± 14.26	47.91 ± 15.73	0.677
Race, Arab	6.8%	13.0%	13.0%	0.309
Weight, kg	72.13 ± 15.30	74.34 ± 17.12	70.07 ± 16.78	0.515
Height, cm	170.45 ± 12.92	169.07 ± 21.23	165.59 ± 27.76	0.152
BMI	24.55 ± 4.19	25.18 ± 4.27	24.13 ± 4.83	0.213
Etiology of HT (ischemic heart disease)	69.5%	60.2%	38.6%	‹ 0.001
Hypertension	40.6%	41.9%	30.0%	0.237
Diabetes	10.4%	29.1%	17.1%	0.003
Dyslipidemia	49.0%	50.0%	37.1%	0.195
Past Smoker	53.1%	43.6%	31.4%	0.021
Status prior to HT Status 1 (higher priority) Status 2 (lower priority)	 56.4 43.6	 75.0 25.0	 66.7 33.3	0.029
Creatinine, mg/dl	1.30 ± 0.51	1.30 ± 0.63	1.33 ± 1.13	0.815
Bilirubin, mg/dl	1.6 ± 3.91	1.3 ± 2.08	1.1 ± 0.64	0.320
Systolic pulmonary artery pressure, mmHg	50.0 ± 20.59	53.31 ± 17.88	47.00 ± 19.24	0.101
Mean pulmonary artery pressure, mmHg	36.31 ± 15.86	36.92 ± 12.30	31.19 ± 13.14	0.013
Pulmonary capillary wedge pressure, mmHg	26.29 ± 11.57	25.60 ± 9.71	21.73 ± 11.51	0.022
Cardiac output, L/min	3.60 ± 0.96	3.68 ± 1.06	3.44 ± 1.23	222.0
Pulmonary vascular resistance (Wood)	3.09 ± 1.95	3.04 ± 1.54	3.01 ± 2.57	0.712
ICD	9.1%	36.4%	75.0%	‹ 0.001
Family history IHD	62.5%	49.6%	38.6%	0.009
LVAD bridge to HT	5.2%	13.6%	29.4%	‹ 0.001
PRA › 30%	0.0	0.8	1.4	0.159
CMV mismatch	48.2	53.1	56.2	0.521
Blood type A AB B O	 50.0% 13.8% 20.7% 15.5%	 43.5% 14.1% 15.2% 27.2%	 39.1% 2.2% 26.1% 32.6%	0.110
Donor characteristics				
Gender, male	61.8%	79.2%	71.7%	0.106
Age, year	34.95 ± 14.01	33.65 ± 13.33	30.53 ± 11.97	0.123
Weight, kg	73.48 ± 15.04	75.60 ± 17.07	76.05 ± 22.70	0.465
Height, cm	173.96 ± 11.14	173.04 ± 14.71	167.62 ± 26.85	0.224
BMI	24.12 ± 3.58	24.91 ± 4.32	24.39 ± 3.62	0.365
Race, Jewish	83.7%	74.6%	86.0%	0.250
Operative data				
Ischemic time, minutes	153.95 ± 55.62	165.04 ± 45.93	166.93 ± 38.72	0.317
Prolonged inotropic support after HT	35.7%	28.9%	38.8%	0.352
Days from admission to discharge	53.37 ± 42.40	48.96 ± 72.89	62.07 ± 93.34	0.165
Days from transplant to discharge	22.35 ± 32.12	18.12 ± 12.73	16.89 ± 11.21	0.227
Early complications*	55.1	52.2	71.9	0.031
In-hospital death	14.4%	15.3%	10.1%	0.600

Continuous variables and categorical variables are presented as mean ± standard deviation and percentage, respectively

BMI = body mass index, CMV = cytomegalovirus, HT = heart transplantation, ICD = implantable cardioverter defibrillator, IHD = ischemic heart disease, LVAD = left ventricular assist device, PRA = panel of reactive antibodies

*Prolonged ventilation, sepsis, severe coagulopathy, cerebrovascular accident, prolonged chest tubes, early wound infection

Patient characteristics after heart transplantation

Baseline low-density lipoprotein (LDL) was lower among patients who underwent HT in decade 3 (101.0 ± 32.2 mg%) compared to patients who were transplanted in decade 2 (110.4 ± 33.1 mg%) and decade 1 (123.0 ± 37.1 mg%) ($P = 0.001$) [Figure 1A]. Similarly, hypertension after HT was less frequently observed in decade 3 compared with decade 1 and 2. Diabetes mellitus was more frequent in decade 2 (49.5%) compared with patients who were transplanted in decade 1 (28.7%) or decade 3 (27.4%) ($P = 0.003$) [Figure 1B]. Cytomegalovirus (CMV) rates have been significantly lower in decades 2 and 3, comprising less than one-fifth of the incidence seen during decade 1 (6.5% vs. 20% vs. 35%, respectively; $P < 0.001$) [Figure 1B].

Marked changes are noted in immunosuppressive treatments. In decade 3, more than 90% of patients were treated with tacrolimus as the primary immunosuppression, compared with 2.7% and 30.9% in decade 1 and 2, respectively ($P < 0.001$) [Figure 1C].

TRANSPLANT REJECTIONS

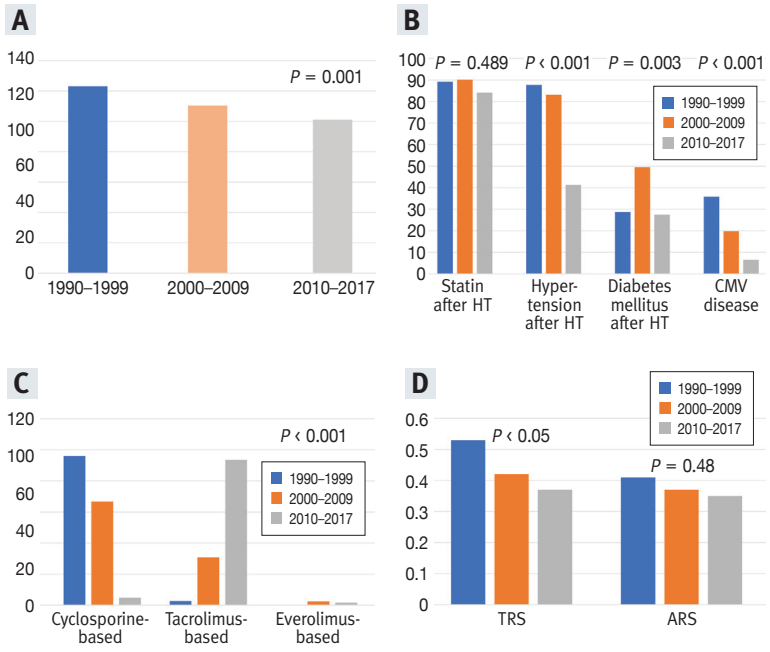
Acute rejection rates significantly declined over the years. Total rejection score, incorporating the severity of rejection, is significantly lower in patients who underwent HT during decade 3 compared to patients who underwent HT in decade 1 ($P < 0.05$) [Figure 1D]. There was a trend, although not yet significant, for reduction in any rejection, as assessed by ARS (not incorporating severity of rejection) during decade 3 compared with decade 1 [Figure 1D].

CARDIAC ALLOGRAFT VASCULOPATHY

The incidence of total CAV showed a significant decline over the three study decades, from 46.9% during decade 1, to 17.5%

during decade 2, and to 1.6% during decade 3 ($P < 0.001$) [Figure 2A]. Kaplan–Meier estimates of the end-point of CAV for all patients are shown in Figure 2B, demonstrating that the rate of CAV was lowest for patients undergoing HT in decade 3, intermediate for patients undergoing HT in decade 2, and highest for patients undergoing HT in decade 1. Thus, at the 5 year follow-up, the respective rates of CAV in the three groups were 0.7%, 15%, and 18%, respectively (log-rank $P < 0.011$ for the overall differences during follow-up [Figure 2B].

Figure 1. Patient characteristics after heart transplantation. **[A]** Differences between groups in baseline low-density lipoprotein **[B]** Metabolic and cytomegalovirus (CMV) characteristics by decade **[C]** Immunosuppressive treatments by decade **[D]** Total rejection score (TRS) and any rejection score (ARS) by decade



HT = heart transplanation

blue = 1990–1999 (decade 1), green = 2000–2009 (decade 2), yellow = 2010–2017 (decade 3)

Combined endpoint: CAV/death

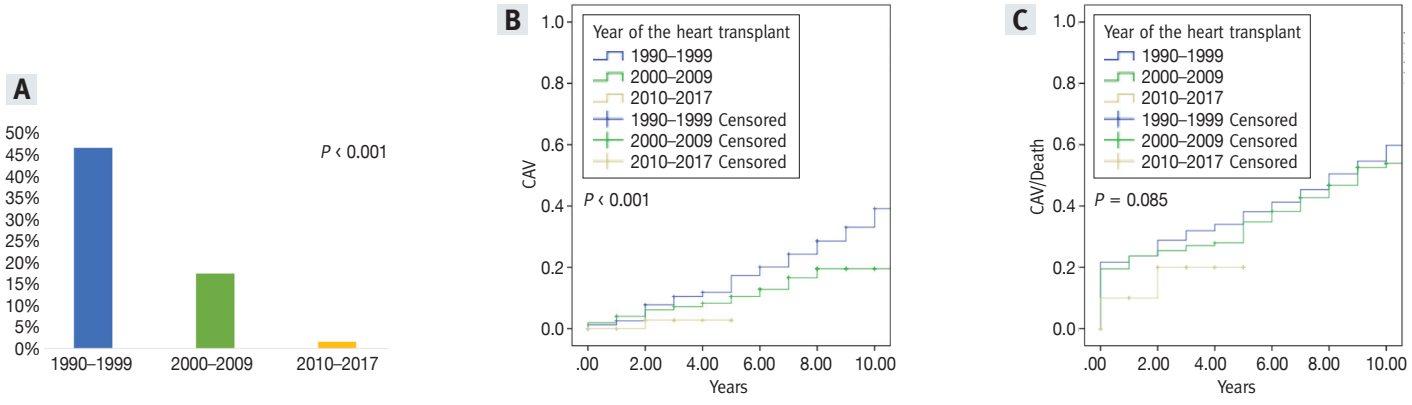
Kaplan–Meier estimates of combined endpoint of CAV or death for all patients are shown in Figure 2C, showing that the survival rates were nearly significantly different between groups (log-rank $P = 0.085$ for the overall differences during follow-up). At the 5 year follow-up, the rate of CAV/death was 33% among patients who were transplanted in decade 2, 32% for patients who were transplanted in decade 1, and 14% for patients who were transplanted in decade 3.

Consistent with these findings, multivariate analysis showed that risk for combined endpoint was significantly lower in recent years: for decade 2 (hazard ratio [HR] = 0.427, 95% confidence interval [95%CI] 0.225–0.814, $P = 0.010$), and even more prominent for decade 3 (HR = 0.127, 95% CI 0.030–0.542, $P = 0.005$) compared to decade 1 [Table 2].

DISCUSSION

Heart failure has increasingly become a major public health issue, with a prevalence of approximately 5.1 million in North America [8]. Despite advances in pharmacological and device treatment of chronic heart failure, long-term morbidity and mortality remain unacceptably high. The 5 year mortality rate for patients with symptomatic heart failure is close to 50%, and may be as high as 80% for end-stage patients at 1 year [9,10]. For those patients in whom these therapies have been attempted without success, HT may be a suitable and life saving option, and is considered the gold standard for the treatment of refractory end-stage heart failure. Therefore, it is extremely important to characterize the process of HT over the years and identify factors to predict successful HT.

Figure 2. **[A]** Comparison of cardiac allograft vasculopathy (CAV) rates by decade of heart transplantation **[B]** Kaplan–Meier survival curves for CAV **[C]** Composite of CAV/death



blue = 1990–1999 (decade 1), green = 2000–2009 (decade 2), yellow = 2010–2017 (decade 3)

Table 2. Multivariate Cox proportional hazard model analysis for composite of cardiac allograft vasculopathy or death

		95%CI		
	HR	Lower	Upper	*P*
Gender, female (%)	1.222	0.578	2.585	0.600
Etiology of HT	1.229	0.703	2.148	0.470
Diabetes (%)	1.260	0.612	2.594	0.530
Past Smoker (%)	1.654	0.786	3.482	0.185
Status prior to HT	0.743	0.434	1.271	0.278
Mean pulmonary artery pressure, mmHg	1.046	1.005	1.089	0.026
Pulmonary capillary wedge pressure, mmHg	0.964	0.919	1.011	0.135
ICD (%)	1.818	0.935	3.534	0.078
Family history IHD (%)	1.069	0.477	2.398	0.871
LVAD bridge to HT (%)	4.309	1.466	12.664	0.008
2000–2009	0.427	0.225	0.814	0.010
2010–2017	0.127	0.030	0.542	0.005

95%CI = 95% confidence interval, HR = hazard ratio, HT = heart transplantation, ICD = implantable cardioverter defibrillator, IHD = ischemic heart disease, LVAD = left ventricular assist device

In the present study, we evaluated our experience at the largest single HT center in Israel over a period of more than 25 years. Our findings have several important implications that may be used to improve treatment and follow-up of patients undergoing HT. We have shown consistent changes over the years in patient characteristics and have improved long-term outcomes after HT, with an emphasis on CAV, patient metabolic profile, and rejection rates, as well as a declining trend in the combined rate of vasculopathy and mortality over the years.

PATIENT AND DONOR CHARACTERISTICS

An increase in the percentage of women undergoing heart transplantation and of non-ischemic etiology for HT

The percentage of women undergoing HT over the years has increased significantly, as did the incidence of non-ischemic cardiomyopathy as etiology for HT. These two findings may complement and explain each other. Our findings are also supported by the results of the NEW HEART study, in which women were younger and less likely to have ischemic cardiomyopathy compared to men at the time of HT [11].

The rising number of women who underwent HT in our cohorts is in line with a recently published study showing that more women (44% vs. 25%, $P < 0.0001$) [12] were hospitalized with heart failure, compared to ambulatory chronic heart failure during the years 2011–2013. Furthermore, in a study including more than 2000 patients enrolled in the Heart Failure Survey in Israel (HFSIS), women tended toward an increased risk for early mortality compared to men, which might partially explain the higher early complications seen in recent years [13].

We found a clear and significant trend in the rise of non-ischemic cardiomyopathy as etiology for HT, constituting approximately 60% of the HT in our center in recent years. These findings are consistent with the recent ISHLT registry data [2] showing non-ischemic cardiomyopathy as etiology of 50% of the HT performed worldwide during 2009–2016. Our cohort also showed that patients undergoing HT in recent years smoked less and had a lower incidence of family history of ischemic heart disease. These findings might also be related to the concurrent increase in the frequency of transplanted women and prevalence of non-ischemic cardiomyopathy. The prevalence of diabetes among patients undergoing HT in decade 3 was 17%, similar to the percentage of diabetic patients who underwent HT in Europe [2].

LVAD as bridge to heart transplantation

A notable change in the patient demographics is the increase in LVAD as a bridge for HT. In recent years, one-third of patients undergoing HT at our center were supported by LVAD. These findings are in line with the ISHLT data, as 40.6% of patients in 2009–2016 were bridged with LVAD and 50% of patients in 2015 were bridged with mechanical circulatory support compared with 22% at 2005 [2]. LVAD support may also partially explain the reduction of pulmonary capillaries and pulmonary artery pressure seen among our patients in recent years. It might also explain the higher early postoperative complications seen in later years, yet not having an impact on hospital length of stay or mortality.

REJECTIONS

Maintenance immunosuppression is similar to the current practice worldwide, as 93% of our patients are currently treated with protocols based on tacrolimus (similar to 94% of HT patients in the ISHLT registry).

Rejection rates have significantly decreased over time. Total rejection score, which takes into account the severity of the rejection, has significantly declined from 0.53 ± 0.41 in decade 1 to 0.37 ± 0.28 in decade 3. Our findings are in line with the ISHLT data showing significant reduction in treated rejections from 24% in 2004–2006 to 13% in 2010–2014 [5]. A consistent trend for reduction in any rejection as assessed by ARS (not incorporating severity of rejection) has also been recognized, in line with worldwide findings [2].

Of interest, although current patients carry higher risk for being immunologically sensitized prior to HT due to higher incidence of women who are mothers to children, and higher rate of LVAD implantations as a bridge to HT, there is no increase in the proportion of patients who are sensitized and there is a significant decline in rejection rates as stated earlier.

CAV AND COMBINED END-POINT OF CAV/DEATH

Contributing factors to the significant reduction in the incidence of CAV and combined endpoint of CAV/death over the years could be the dramatic decline in the incidence of CMV

disease, post HT diabetes and hypertension, with concomitant lower LDL levels.

CONCLUSIONS

Our analysis of over 25 years at a single-center with experience in HT shows encouraging results that are in line with world-wide standards and experience. Improved results of HT over the years has established the procedure as the gold standard treatment for patients at end-stage heart failure, and only the shortage of suitable heart donors prevents us from providing it to many more of this ever-growing population.

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Correspondence

Dr. Y. Peled

Leviev Heart Center, Sheba Medical Center, Tel Hashomer 5265601, Israel

Phone: (972-3) 530-2604

Fax: (972-3) 534-3888

e-mail: yael.peled-potashnik@sheba.health.gov.il

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Capsule

Female reproductive and hormonal factors and incidence of primary total knee arthroplasty due to osteoarthritis

Hussain and co-authors examined the associations of female reproductive and hormonal factors with incidence of total knee arthroplasty (TKA) for osteoarthritis to determine whether the associations differed according to overweight/obesity status. The study included 22,289 women in the Melbourne Collaborative Cohort Study. Data on age at menarche, pregnancy, parity, years of menstruation, oral contraceptive (OC) use, menopausal status, and hormone replacement therapy (HRT) were collected from 1990 to 1994. Incidence of TKA during 2001–2013 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry. Over the course of 12.7 years, 1208 TKAs for osteoarthritis were identified. Ever being pregnant was associated with increased risk of TKA (hazard ratio [HR] 1.32 [95% confidence interval (95%CI) 1.06–1.63]). Parity was positively associated with risk of TKA (*P* for trend = 0.003). OC users had increased risk of TKA compared with non-users (for OC use of < 5 years, HR 1.25, 95%CI 1.08–1.45; for OC use of ≥ 5 years, HR 1.17, 95%CI 1.00–1.37). A 1 year increase in menstruation was associated with a 1% decrease in risk of TKA (HR 0.99, 95%CI 0.97–0.99). These associations remained significant only in women of normal weight at early reproductive age. Current HRT users had increased risk of TKA compared to non-users (HR 1.37, 95%CI 1.14–1.64). The association was significant only in non-obese women at midlife. Reproductive and hormonal factors were associated with risk of knee osteoarthritis. These associations remained significant in women of normal weight at early reproductive age and in non-obese women at midlife. Further work is needed to understand the complex effect of these factors on knee osteoarthritis.

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Eitan Israeli

"Learning is like rowing upstream: not to advance is to drop back"

Chinese Proverb