EJCM
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E Journal of Cardiovascular Medicine

Volume 10 | Issue 3
September 2022

www.ejcvsmed.com

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CASE REPORTS

HEART AND HEALTH FOUNDATION OF TURKEY

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E-mail: info@galenos.com.tr/yayin@galenos.com.tr Web: www.galenos.com.tr | Publisher Certificate Number: 14521
Online Publishing Date: September 2022 E-ISSN: 2147-1924
International scientific journal published quarterly.

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E Journal of Cardiovascular Medicine

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Volume 10 | Issue 3 | September 2022

Research Articles

Case Reports

Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(3):100-109

DOI: 10.32596/ejcm.galenos.2022.2022-04-030

Effects of Obesity and Sports on the Left Ventricle Mass in Preadolescent and Adolescent Children

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Manisa City Hospital, Clinic of Pediatric Cardiology, Manisa, Turkey

Abstract

Objectives: An increase in left ventricular mass (LVM), a determinant of left ventricular hypertrophy (LVH) in adults and children, is a major risk factor for cardiovascular morbidity and mortality. This study evaluated LVM in athletes, healthy and obese children.

Materials and Methods: The study included 260 children aged 9-17.8 years (170 males, 90 females). No participants had diseases such as aortic pathologies, hypertension, or hypertrophic cardiomyopathy. The participants were divided into three groups: Group 1, athletes (n=89); Group 2, control (n=87); Group 3, obesity (n=84). Obese athletes were excluded from the study. The participants were further divided into the preadolescent group (n=72, aged 9-11.91 years) and the adolescent group (n=188, aged 12-17.8 years). LVM, LVM index (LVMI) were calculated using the M-mode echocardiography.

Results: The mean LVMI for all participants was 32.72±8.48 g/m$^{2.7}$. The cut-off value of 42.76 g/m$^{2.7}$, which was the 95th percentile for the control group LVMI value, was taken as the LVH criterion. There was a significant difference between Group 1-3 and Group 2-3 in terms of LVMI.

Conclusion: Because of obesity and accompanying comorbid diseases in children have increased recently, being informed about the presence of LVH is critical for the diagnosis of cardiovascular diseases that may cause morbidity in childhood and young adulthood, and for early treatment planning.

Keywords: Left ventricular mass, children, obesity, sports

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Received: 14.04.2022 **Accepted:** 27.06.2022

Cite this article as: Paytoncu Ş. Effects of Obesity and Sports on the Left Ventricle Mass in Preadolescent and Adolescent Children. EJCM 2022;10(3):100-109.
DOI: 10.32596/ejcm.galenos.2022.2022-04-030

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Introduction

The hemodynamic load is assessed with left ventricular mass (LVM)[1] in congenital and acquired heart diseases such as coarctation the aorta, aortic valve stenosis and systemic hypertension when the left ventricle is subjected to pressure overload or when it is volume overload in aortic and mitral valve regurgitation.

Left ventricular hypertrophy (LVH), defined as an increase in the LVM, is associated with age, gender, and body size and composition. The LVM index (LVMI) is the ratio of LVM (g) to body surface area (BSA, m^2). The formula of dividing LVM by body height (m) to the power of 2.7 is generally used to calculate this index [LVMI: LVM (g)/(height) $m^{2.7}$]. In adults and children, LVH is defined as an LVMI equivalent to or greater than the 95th percentile[2]. Overweight and obesity are among the most important factors contributing to diseases and adverse health outcomes, such as metabolic syndrome, diabetes mellitus, and cardiovascular disease in the medium- or long-term course. The causes of obesity in adulthood can be traced back to early childhood, as a high body mass index (BMI) in childhood is a predictor of overweight and obesity later in life. In recent decades, a substantial increase in the prevalence of childhood obesity has been observed worldwide[3].

In the study by Twig et al.[4], obese adolescents were monitored for an average of 12 years, after that period the total cardiovascular death (coronary artery diseases+stroke+sudden death) ratio was reported as 0.2% and the mean death age was reported as 45.2±9.7 years. Total cardiovascular deaths were reported as 0.18% for a total 281.033 overweight and obese adolescents[4].

It has been demonstrated that LVM is strongly determined by lean body mass (LBM). It was considered "a reference standard" scaling variable. LBM explains more of the variability in LVM than either weight or height alone[5,6].

Regular sports activities in children cause physiological changes in the heart, similar to the athlete's heart in adults[7,8]. These changes primarily include increased left ventricular myocardial thickness and LVM[9,10]. In the studies conducted so far, the relationships between hypertension and LVH, obesity and LVM, sports and LVMI have been investigated[11-16]. However, in a prospective study, LVMI was examined in normotensive obese, normal and athletic children.

This study evaluated LVMI, identify in which group the LVMI increase is significant and to determine the percentile values of LVMI in all groups.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Health Sciences Ethics Committee of (the approval number 20.478.486) Manisa Celal Bayar University, Faculty of Medicine, Manisa, Turkey. Written informed consent was obtained from the participants before the inclusion in the study. The voluntary participation form was signed by the parents.

Patients

The study included 260, patients aged 9-17.8 (mean 13.26) years, including 170 males and 90 females, who presented to the pediatric cardiology outpatient clinic of Manisa Merkezefendi State Hospital, with the complaints of cardiac murmurs identified from previous auscultation, chest pain, palpitation and between June and October 2018. The patients were divided into three groups: athlete, control, and obesity.

None of the patients had disease-causing cardiac muscle hypertrophy, such as aortic coarctation/stenosis, systemic hypertension, and hypertrophic cardiomyopathy, or a family history of this disease. Patients with endogenous obesity pathologies and different syndromes such as Type 1/Type 2 diabetes mellitus, metabolic syndrome, insulin resistance, dyslipidemia and hypertension, were excluded from the study. In this regard, measured mean blood pressure values were 106/66 mmHg, 114/70 mmHg and 113/67 mmHg for groups, respectively.

Eighty-nine participants in Group 1 (athlete group) made up 34.2% of the total patient population. Athlete children were involved in at least one type of sports: soccer, basketball, handball and swimming (high dynamic, moderate static component) in order of frequency, and practiced sports in a sports club and/or school team. About half of the them engaged in soccer, 43.8% basketball, 6.7% handball and swimming. Sports engagement was in the form of regular and disciplined training under the supervision of an instructor and participation in competitions/matches. The participants were training for at least one and at most eleven (mean 4.46±2.37) years. They participated in training for at least two hours and at most twenty-four (mean 8.08±5.07) hours a week. Obese and hypertensive athletes and those engaged in more than one sport were excluded from the study.

Eighty-seven children in Group 2 (control group) made up 33.5% of all patients. This group consisted of children who presented with various complaints (chest pain, fatigue, syncope, etc.) had a functional murmur, and normal cardiovascular findings on examination. They attended the gym and sports classes for only two hours a week at school.

Eighty-four children in Group 3 (obesity group) made up 32.3% of all patients. 29.7% were mild, 32.1% were moderate, 23.8% were severe and 14.4% were very severe obese. Most of the children in this group were only participating in gentle warm-up exercises in sports classes.

Echocardiography and Other Examinations

The routine transthoracic echocardiographic was examined with the segmental analysis method, using a Philips Medical System Nederland BV 2005 and S4-2 MHz Broadband Sector Array transducer. Heart rate was recorded during this examination. All these echocardiographic were examined by the same pediatric cardiologist (Dr. SP). LVM and LVMI were calculated using 2D, spectral Doppler, and M-mode echocardiograms. LVM was estimated using the formula (Method I) by Devereux et al.[17], (LVM=0.8 [1.04 x (interventricular septal thickness + left ventricular posterior wall thickness + end-diastolic diameter)^3 - (end-diastolic diameter)^3] +0.6). As mentioned above, LVMI=LVM (g)/(height)m$^{2.7}$.

I used the internet site https://www.calculator.net to calculate exponential numbers. Additionally, I calculated M-mode echocardiographic LVM [Method II: American Society of Echocardiography (ASE) convention], Z-score expected LVM (expLVM), estimated LBM (eLBM) and ASE guidelines by using the internet site http://lvmassparameterz.com[5,6,18]. I used the internet site https://www.cdc.gov/healthyweight/bmi/calculator.html to calculate BMI and degree of obesity. Patients with missing data were excluded from the study.

Paraclinical parameters, such as lipid panel (total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein cholesterol), complete blood count, ferritin, iron, C-reactive protein, thyroid function tests, fasting blood glucose, and 24-hour ambulatory blood pressure measurements were performed for all obese and patients deemed necessary. The Health Sciences Ethics Committee of Manisa Celal Bayar University approval and a waiver of consent were obtained before data collection.

Statistical Analysis

All data were evaluated using the SPSS version 15.0 software. Minimum, maximum, mean, and standard deviation (SD) values were obtained by descriptive statistical methods. Continuous variables were expressed as mean ± SD. Pearson correlation test was used to evaluate correlations between variables. Weak, moderate and strong correlations are defined as having a correlation coefficient less than 0.3 (<0.3), between 0.3-0.7 (0.3-0.7), and greater than 0.7 (>0.7), respectively. The independent sample t-test was used to compare the parametric values between the groups (female-male/preadolescent-adolescent/Group 1-2/Group 1-3/Group 2-3). Variance analysis was used to compare the values of more than two independent groups. In the independent sample one-way analysis of variance, the homogeneity of the groups was analyzed using the One-Way ANOVA test, and in the

presence of a difference, the Tukey test was carried out to determine among which groups there was a difference. Logistic regression analysis, Fisher's exact test, and the chi-square test were used to determine the risk ratio (odds ratio) and confidence interval (CI) for LVH. Bland-Altman analysis was used to display harmony between means and differences for the values of LVM Method I and II, weight, and eLBM, LVM Method I, and expLVM. The level of statistical significance was set at $p<0.05$.

Results

The demographic and echocardiographic data of all patients are shown in Table 1 and Table 2. The mean age of all children (n=260) n included in the study was 13.26±2.06 years. All participants included in the study had a mean LVM of 119.53±37.68 g and a mean LVMI of 32.72±8.48 g/m$^{2.7}$. The demographic characteristics and echocardiographic findings of the male and female participants are shown in Table 3. The pre-adolescent group (n=72) included participants aged 9-11.91 years, while the adolescent group (n=188) included participants aged 12-17.8 years. In all participants, female/male and adolescent/preadolescent groups, the percentile values for LVMI were determined and are presented in Table 4.

Table 1. The demographic and echocardiographic data of all patients

	Total	Female	Male
n	260	90	170
	Minimum	**Maximum**	**Mean ± SD**
Age (year)	9	17.8	13.26±2.06
Body weight (kg)	25.3	144	59.59±16.22
Height (cm)	130	192	161.7±13.49
BSA (m^2)	0.93	2.49	1.6±0.25
BMI	14.21	48.16	22.64±4.97
w/h	68	217	108.89±25.39
IVS (cm)	0.61	1.25	0.87±0.13
LVDd (cm)	3.02	5.71	4.43±0.44
LVSd (cm)	1	3.67	2.71±0.34
LVPWd (cm)	0.6	1.25	0.84±0.11
EF (%)	59.7	81.7	68.84±4.64
FS (%)	31.7	50.7	38.42±3.77
LVM (g)	42.6	243	119.53±37.68
LVMI (g/m$^{2.7}$)	32.74	122.22	73.79±17.79
Expected LVM	76.8	311.6	183.07±44.52
Estimated LBM	19.7	92.4	41.33±10.54
LBM Z-score	-4.56	1.93	-0.56±1.03

BSA: Body surface area, BMI: Body mass index, SD: Standard deviation, LVMI: Left ventricular mass index, LVM: Left ventricular mass, LBM: Lean body mass, LVDd: Left ventricular diastolic diameter, LVSd: Left ventricular systolic diameter, LVPWd: Left ventricular posterior wall diastolic

Correlations between the entire patient group and individual groups were analyzed. There were statistically significant results for all the correlations between LVMI and height, body weight, BMI, w/h of the entire group. The correlation between LVMI and w/h was strongest and moderately statistically significant (r=0.531, p=0.001).

The analysis of variance by groups showed a significant difference between these three groups in terms of different parameters. There was a significant difference in terms of LVMI between Group 1 and Group 3 (p=0.001). The same significance in terms of LVMI between Group 2 and Group 3 was found (p=0.001).

M-mode echocardiographic LV mass, Z scores, expLVM, eLBM were examined in all groups. A statistically significant and important correlation was found between LVMI calculated based on the Devereux formula and LVMI calculated on the basis of the guideline reported by Lopez et al.[18] (there was a significant correlation between LVM calculated with calculator and LVM calculated with Devereux formula). There was a significant correlation in terms of LVM between Methods I and II (r=0.84, P=0.001).

There was a statistically significant and strong correlation between eLBM and weight (r=0.906, p=0.001). Also, there was a statistically significant and moderate correlation between LVM (Method I) and expLVM (Method II) (r=0.644, P=0.001).

Totally, there were 39 patients overweight (14.99%). There were 11 patients overweight (4.23%) in Group 1 (athlete) and 28 patients overweight (10.76%) in Group 2 (control). Since LVMI (m)$^{2.7}$ is a restrictive factor in patients whose height is less than 140 cm[2,5]. "I would like to state that there are eight patients whose height is less than 140 cm". The cut-off values for LVMI and the

incidence of LVH in the groups (in accordance with the values we accepted in our study and from various studies) are displayed in Table 5.

The mean LVM for LBM z- score values, the mean eLBM values and p values of both, girls and boys are presented in Table 1-3. The mean LVM difference between Method I and II: -1.21±4.54 (CI 95%: -1.76/-0.65, p=0.001) is displayed in Figure 1. The mean LVM difference between Method I and expLVM: -64.53±34.51 (CI 95%: -68.79/-60.27, p=0.001) is displayed in Figure 2. The mean difference between mean weight and eLBM: 18.26±8.03 (CI 95%: 17.28-19.24, p=0.001) is displayed in Figure 3. In our study, the cut-off value of 42.76 g/m$^{2.7}$, which was the 95th percentile for the control group LVMI value, was taken as the LVH criterion.

Those with obesity and with overweight were found to have a 6.1-fold increased risk of having LVH compared with those without obesity (OR, CI 95%: 2,689-14,226) (Figure 4). Fisher's exact test p-value was 0.001. It was shown that those who did sports had a 0.348-fold increased

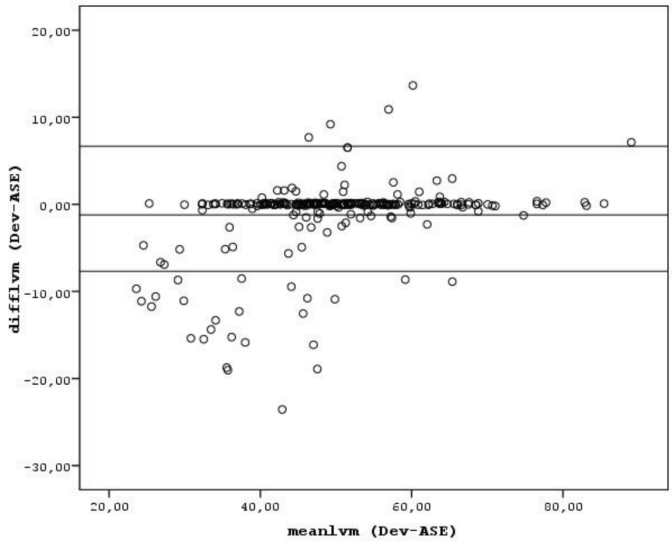

Figure 1. The mean LVM difference between Method I and expLVM

LVM: Left ventricular mass

Table 2. The demographic and echocardiographic data of all groups

	Group 1	Female	Male	Group 2	Female	Male	Group 3	Female	Male
n	89	21	68	87	33	54	84	36	48
	Minimum	Maximum	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum	Mean ± SD
Age (year)	9.33	17.83	13.59±2.01	9	17.5	13.73±2.01	9	16.83	12.43±1.94
Body weight (kg)	25.3	92	52.9±14.27	27.5	90	55.89±12.52	40	144	70.49±16.14
Height (cm)	131	192	164.47±15.67	136	187	163.29±12.19	130	180	157.11±110.02
BSA (m^2)	0.93	2.06	1.49±0.25	0.99	2.03	1.55±0.21	1.28	2.49	1.77±0.2
BMI	14.3	27.54	19.19±2.59	14.21	27.77	20.76±2.99	21.97	48.17	28.25±3.53
w/h	68	114	90.43±11.51	71	118	98.22±13.31	121	217	139.48±15.98
IVS (cm)	0.63	1.25	0.89±0.14	0.61	1.17	0.83±0.12	0.67	1.25	0.9±0.13
LVDd (cm)	3.02	5.39	4.42±0.42	3.03	5.48	4.41±0.47	3.22	5.71	4.45±0.43
LVSd (cm)	1.8	3.56	2.72±0.31	1.94	3.6	2.71±0.34	1	3.67	2.7±0.37
LVPWd (cm)	0.6	1.13	0.84±0.11	0.61	1.09	0.81±0.1	0.67	1.05	0.87±0.11
EF (%)	59.7	80.7	68.48±4.58	60.5	81.3	68.71±4.64	62.2	81.7	69.36±4.69
FS (%)	31.7	49	38.08±3.57	32.5	49.3	38.39±3.89	32.8	50.7	38.81±3.84
LVM (g)	42.6	203	114±37.7	50.6	220	114.28±35.8	60	243	130.81±37.41
LVMI (g/m$^{2.7}$)	12.48	51.54	30.0±8.12	14.8	51.05	30.22±7.21	24.64	61.73	38.19±7.48
Expected LVM	97.3	264.3	178.24±46.92	97.3	296.7	182.08±43.11	76.8	311.6	189.35±43.11
Estimated LBM	19.7	67.5	40.05±11.11	20	63.1	40.47±9.41	24.9	92.4	43.56±10.78
LBM Z-score	-4.56	1.87	-0.27±1.05	-3.43	1.78	-0.83±1.05	-2.78	1.93	-0.57±0.9

BSA: Body surface area, BMI: Body mass index, SD: Standard deviation, LVMI: Left ventricular mass index, LVM: Left ventricular mass, LBM: Lean body mass, LVDd: Left ventricular diastolic diameter, LVSd: Left ventricular systolic diameter, LVPWd: Left ventricular posterior wall diastolic

risk of having LVH compared to those who did not (OR, CI 95%: 0.12-0.942). Fisher's exact test p-value was 0.04.

When we accepted the cut-off value for LVH as 51.0 g/m$^{2.7}$, it was calculated that those with obesity and with overweight had a 5.07-fold increased risk of having LVH compared to those normal.

Discussion

Recently, an increasing number of children have been exposed to cardiovascular diseases such as coronary artery disease, obesity, hypertension, hypercholesterolemia, diabetes those accompanying the obesity due to general, one-sided, fast-food style nutrition, immobile living type, socioeconomic status, increasing stress factors. The number of studies on cardiovascular morbidity and mortality is limited due to the low incidence of cardiovascular events in preadolescents and adolescents.

the study by Twig et al.[4], 86.061 adolescents with a BMI of ≥95th percentile were monitored for an average of 12 years period, after that period, the total cardiovascular death (coronary artery diseases+stroke+sudden death) ratio was reported as 0.2% and the mean death age was reported as 45.2±9.7 years. When a total of 2.298.130

Table 3. The demographic and echocardiographic characteristics of female and male participants

Sex	Female	Male	Total
n	90	170	260
	Mean ± SD	**Mean ± SD**	**p-value**
Age (year)	13.28±1.92	13.25±2.14	0.923
Body weight (kg)	58.92±14.73	59.95±16.99	0.627
Height (cm)	157.74±9.18	163.8±14.9	0.001
BSA (m^2)	1.60±0.23	1.61±0.26	0.796
BMI	23.59±5.02	22.14±4.88	0.026
Percentile	73.16±31.3	65.93±30.15	0.071
W/H	113.21±24.66	106.6±25.54	0.046
IVS (cm)	0.83±0.12	0.904±0.13	0.081
LVDd (cm)	4.29±0.46	4.5±0.41	0.262
LVSd (cm)	2.65±0.3	2.75±0.36	0.15
LVPWd (cm)	0.8±0.098	0.86±0.12	0.017
EF (%)	68.65±3.86	68.94±5.01	0.64
FS (%)	38.11±3.1	38.59±4.07	0.334
LVM (g)	108.38±34.29	125.42±38.16	0.001
LVMI (m)$^{2.7}$	31.58±8.44	33.33±8.47	0.114
Expected LVM	169.08±31.2	190.69±48.74	0.001
Estimated LBM	37.79±7.32	43.2±11.48	0.001
LBM Z-score	-0.84±1.1	-0.41±0.96	0.001

BSA: Body surface area, BMI: Body mass index, W/H: Weight/Height, SD: Standard deviation, IVSD: Interventricular septum diastolic, LVDd: Left ventricular diastolic diameter, LVSd: Left ventricular systolic diameter, LVPWd: Left ventricular posterior wall diastolic, EF: Ejection fraction, FS: Fractional shortening, LVM: Left ventricular mass, LVMI: Left ventricular mass index

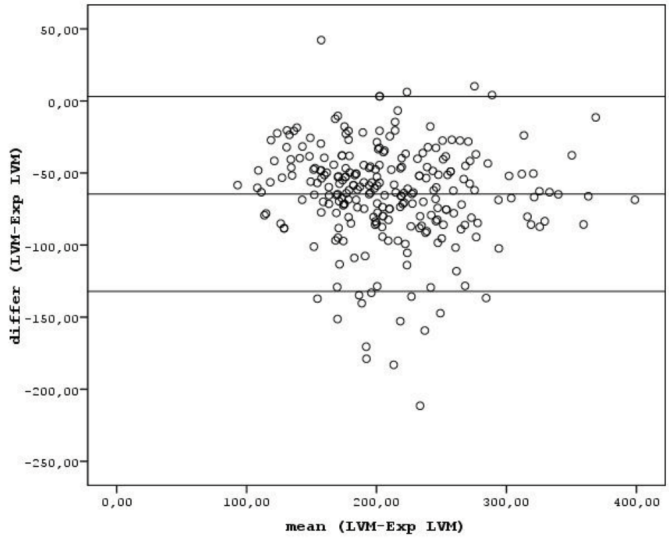

Figure 2. The mean LVM difference between Method I and expLVM

LVM: Left ventricular mass

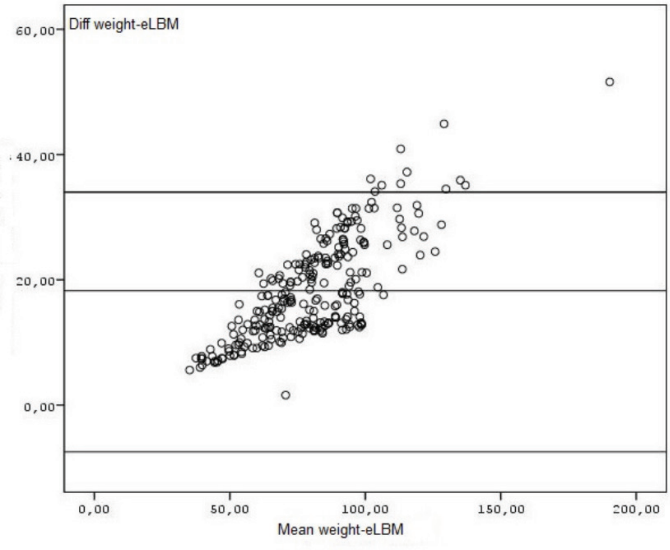

Figure 3. The mean difference between mean weight and eLBM

adolescents were monitored for an average of 18.4-year period, the mean death age was reported as 45.3±9.8 years, whereas the total cardiovascular death ratio was reported as 0.1%. Total cardiovascular deaths were reported as 0.18% for much overweight and obese adolescents.

Although LVMI (LVM/$m^{2.7}$) is also a popular method for normalizing LVM in children, it has an important limitation[5,19]. LVMI increases with decreasing height below about 130-140 cm[2,5]. In several studies, the cut-off value of >38.6 g/$m^{2.7}$ for LVMI, which is the conventionally reported value, is used for the definition of LVH[2,20,21]. In the few studies, the cut-off value of >51.0 g/$m^{2.7}$ for LVMI, which is the conventionally reported value in adults, is used for the definition of LVH[22,23]. In our study, the cut-off value of 42.76 g/$m^{2.7}$, which was the 95th percentile for the control group LVMI value, was taken as the LVH criterion. The 95th percentile cut-off value for LVMI was 46.9 g/$m^{2.7}$ in boys and 45.1 g/$m^{2.7}$ in girls, with the mean values of 33.33±8.44 g/$m^{2.7}$ in boys and 31.58±8.44 g/$m^{2.7}$ in girls. In the studies by Khoury et al.[2], LVH was defined by values above 40 g/$m^{2.7}$ and 45 g/$m^{2.7}$, for girls and boys, respectively[2].

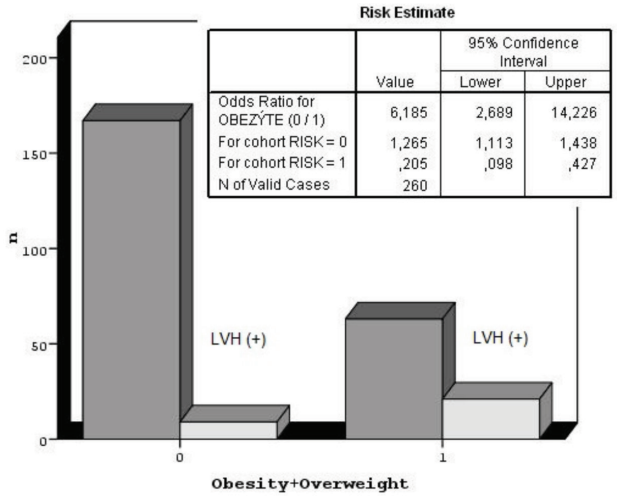

Figure 4. The risk estimation of LVH/Obesity+overweight
LVM: Left ventricular mass

In a study by Hietalampi et al.[24], the gender-specific 90th percentile for LVMI was 34.02 g/$m^{2.7}$ in girls and 37.08 g/$m^{2.7}$ in boys. This study also showed that there was a direct correlation between birth weight and LVM in adolescents, and the level of physical activity was associated with increased LVM and LWPWd. In our study, the gender-specific 90th percentile for LVMI is displayed

Table 4. LVMI percentile values for different groups

Percentiles	Girls (n=90)	Boys (n=170)	Adolescents (n=188)	Preadolescents (n=72)	Group 1 (athlete) (n=89)	Group 2 (control) (n=87)	Group 3 (obesity) (n=84)	Total
5 p	16.22	17.48	16.5	20.28	14.66	16.88	27.48	17.44
10 p	21.35	22.55	20.73	24.02	17.44	21.47	28.98	21.87
25 p	25.77	28.77	26.85	30.22	25.88	24.69	33.16	27.65
50 p	31.1	33.22	31.56	33.9	31.06	29.94	36.71	32.69
75 p	36.87	37.74	37.3	38.08	35.85	35.43	43.04	33.72
90 p	43.06	44.37	43.21	44.41	39.06	39.87	47.18	43.69
95 p	45.16	46.89	45.63	50.17	43.57	42.76	54.47	45.9

LVMI: Left ventricular mass index

Table 5. LVH and LVMI cut-off values

Groups	1 (athlete) (n=89)	2 (control) (n=87)	3 (obesity) (n=84)	Total (n=260)
LVMI cut-off values	LVH	LVH	LVH	LVH
42.6 g/$m^{2.7}$/ n-(%)	5 (5.6%)	3 (3.44%)	21 (25%)	29 (11.15%)
38.6 g/$m^{2.7}$/n-(%)	9 (10.1%)	10 (11.49%)	35 (41.66%)	54 (20.76%)
51.0 g/$m^{2.7}$/n-(%)	1 (1.12%)	1 (1.14%)	6 (7.14%)	8 (3.07%)

LVH: Left ventricular hypertrophy, LVMI: Left ventricular mass index

Table 4. Bartkevičienė[25] reported that LVH was present in 48% of all athletes, in our study incidence of LVH was 5,6%. In a study conducted by Krysztofiak et al.[15] LVM was 113.88 and 93.46 g, in our study 125.42 and 108.38 g, male, and female patients, respectively.

In our study, there was a significant difference between the two groups in terms of LVM and LVMI (p=0.001 and p=0.04, respectively). Furthermore, the 95th percentile cut-off value for LVMI was 50.1 g/m$^{2.7}$ in the preadolescent group and 45.63 g/m$^{2.7}$ in the adolescent group (Table 4).

In the study of Gupta-Malhotra et al.[20] in which they dealt with the pediatric hypertensive patients aged 9-18 years, the risk of LVH was found to be 8.9 times higher in obese compared with normal-weight children. Additionally, in a similar way, also in the study by Kharod et al.[23], it was reported that the risk of LVH in children without hypertension varies between 5.3 and 8.5 depending on whether they are overweight or obese. Cardiovascular adaptation mechanisms that develop in response to exercise are well defined[26]. In the athlete's heart, adaptation to increased hemodynamic load due to physical activity leads to physiological changes in cardiac morphology[27]. In their study, Hietalampi et al.[24], showed that excessive physical activity in healthy adolescents increased LVM, especially the LVPW thickness. This increase in LVM was shown to predict cardiovascular disease, morbidity, and mortality in adults, and subclinical changes caused by cardiovascular disease were shown to start in the childhood age group.

In a study by Castanheira et al.[28]. it was reported that the mean LVM and LVMI of 164 athletes who were involved in federated sports (basketball, swimming, judo, and hockey) for at least five years was 157.3 g and 87.9 g/m^2, respectively; the mean LVMI was 83.8±14.4 g/m^2 in the age group of 14-14.9 years and 91.5±13.2 g/m^2 in the age group of 16-16.9 years. In our study, the mean LVM and LVMI of the athletes were 114 g and 76 g/m^2, respectively.

In a study conducted by Sharma et al.[29], investigating the physiological limits of LVH in high-level athletes, it was reported that there were no female athletes with an LVPWd above 11 mm and only three of the male athletes (0.4% of the total) had an LVPWd above 12 mm. It was reported that LVPWd was increased in athletes compared with controls, it was rarely above 12 mm, and hypertrophic cardiomyopathy should be considered in the presence of LVPWd exceeding 12 mm in boys and 11 mm in girls, and non-dilated left ventricle. While all athletes participated in regional competitions for 4.3±1.5 (1-10) years, 50% of them participated in national competitions during the study period. The mean weekly intense training time was 9.8±3.6 (5-27) hours. In our study, the maximum LVPWd values of the participants in the athlete and control groups were 11.3 mm and 10.9 mm, respectively. In our study, there were no athletes participated in national competitions. The duration of sports engagement was 4.46±2.37 (1-11) years, and the mean weekly training time was 8.08±5.07 (2-24) hours.

Obesity-related LVH reflects the volume and pressure overload, causes different left ventricular geometry adaptations in both children and adults[30]. Childhood obesity is a precursor of increased LVM in adults and is an independent risk factor for subclinical left ventricular dysfunction[31]. In the study by Alkholy et al.[32] on the assessment of LVMI in obese children, the mean BMI was 32.8±4.6 kg/m^2 and the mean LVMI was 56.6±14.1 g/m$^{2.7}$ in the obesity group, while the mean BMI was 18.7±2.9 kg/m^2 and the mean LVMI was 42.7±12.6 g/m$^{2.7}$ in the control group. In our study, the mean BMI was 28.25±4.6 kg/m^2 and the mean LVMI was 38.19±7.48 g/m$^{2.7}$ in the obesity group, while the mean BMI was 20.76±2.99 kg/m^2 and the mean LVMI was 30.22±7.21 g/m$^{2.7}$ in the control group.

In our study, 260 echocardiographically calculated LVMI percentile values were determined for pre-adolescent and adolescent children, girls and boys, and those who were overweight and obese. The cut-off value of 42.76 g/m$^{2.7}$, which was the 95th percentile for the control group LVMI value, was taken as the LVH criterion. It was shown that there was a significant difference between

athlete/obesity and control/obesity groups in terms of LVMI. Those with obesity and with overweight were found to have a 6.1-fold increased risk of having LVH compared with those without obesity. Those who practice sports were found to have a 0.348-fold increased risk of having LVH compared with those who did not. Obesity was found to be a factor affecting LVMI and determining LVH.

Study Limitations

If our study could have had a greater patient population, we would have been able to adopt our findings to the other pediatric populations.

During the study period, most of the participants in the obesity group were followed up endocrinologically at different hospitals. Detailed obesity-related hormonal tests could be performed for all obese participants but not performed for others. The participants in the athlete group were also not the athletes from the same club or team. They were engaged in the same sportive categories (high dynamic, moderate static component) at least.

Conclusion

Recently, obesity and accompanying comorbid diseases in children have gradually increased. In most of these studies, attention is attracted to LVH and its risks. In this study, the LVH risks of children with obesity and overweight, without accompanying comorbid diseases (diabetes, hypertension, dyslipidemia) and who are interested in sports were compared with those of normal healthy children. LVH, the existence of which was investigated in our study, is a critical determinant in cardiovascular diseases, as in obesity, and in diseases that cause significant morbidities such as hypertension and cardiomyopathy. Therefore, it is critical to determine LVH using echocardiography, which can be easily applied in childhood.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Health Sciences Ethics Committee of (The approval number 20.478.486) Manisa Celal Bayar University, Faculty of Medicine, Manisa, Turkey.

Informed Consent: Written informed consent was obtained from participants before the inclusion in the study. The voluntary participation form sign by parents.

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: No financial resources have been used for this article.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(3):110-113

DOI: 10.32596/ejcm.galenos.2022.2021-12-074

Reconstruction of a Prosthetic Vascular Graft Infections in the Femoral Region with Gracilis and Sartorius Muscle Flaps

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Abstract

Objectives: To present early and midterm results of our patients treated using gracilis muscle flap for prosthetic vascular graft (PVG) infections located the femoral region.

Materials and Methods: Eight patients admitted to our clinic between January 2012 and August 2016 and treated using gracilis muscle flap owing to PVG infection in the femoral region were included in the current study. Contents of hospital files of the patients with PVG infection were thoroughly evaluated and recorded. Additionally, routine biochemical tests, Doppler ultrasonography, computed tomography; angiography wound site and blood culture results pertaining to the patients were also evaluated in detail.

Results: In the present study, we treated 8 patients (5 males and 3 females) using gracilis muscle flap. Their average age was 58±8.9 (39-67) years. All the patients showed graft infections spreading to the subcutaneous tissues (Szilagyi grade III). While the prosthetic grafts used in 6 patients were Polytetrafluoroethylene (PTFE), they were Dacron in 2 patients. Moreover, 6 infections occurred in the early period while 2 infections occurred in the late period. The pathogens causing graft infections were identified to be staphylococcus aureus in 3 patients, staphylococcus epidermidis in 1 patient and polymicrobial in 4 patients. Furthermore, while graft occlusion was noted in one of the patients, a 2 cm opening was noticed distal to the skin incision in another patient. There was no loss of limb and mortality in any of the patients we presented here and they were fully recovered.

Conclusion: The present results indicate that gracilis muscle fiber reconstruction in PVG infections is an effective and feasible alternative in order to covering the area exposed to infection and rescuing prosthetic graft material.

Keywords: Prosthetic graft, infection, gracilis, vascular, flap

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Received: 17.12.2021 **Accepted:** 17.08.2022

Cite this article as: Ovalı C, Taştekin T. Reconstruction of a Prosthetic Vascular Graft Infections in the Femoral Region with Gracilis and Sartorius Muscle Flaps. EJCM 2022;10(3):110-113.
DOI: 10.32596/ejcm.galenos.2022.2021-12-074

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Introduction

In patients presenting with peripheral arterial disease, prosthetic grafts have a critical place in cases where medical and endovascular treatments are insufficient[1]. Pringle first reported the use of vein grafts in vascular surgery in 1913[2]. In the last 50 years, the use of grafts has become widespread with the development of surgical techniques and the increase in graft quality. Synthetic grafts such as dacron and polytetrafluoroethylene (PTFE) are widely used in vascular surgery. we also preferred these grafts in our clinic. The widespread use of grafts in vascular surgery has resulted in mortal complications such as graft infection[3]. After prosthetic vascular graft (PVG) infection, patients may continue to be hospitalized for a long time. Operations such as debridement, vacuum-assisted closure (VAC), graft removal, amputation may be needed. The clinical classification of PVG infections was first revealed by Szilagyi et al.[4] (Table 1).

The most common site of graft infection, particularly in overweight patients, is the inguinal region. The patient's skin flora contamination and postoperative wound care difficulties cause it. It shows that the incidence of PVG infection is between 3% and 6%[5]. The most common pathogen in these infections is *Staphylococcus aureus*. Other pathogens include *Staphylococcus epidermidis, Escherichia coli, Pseudomonas, Klebsiella, Proteus, Enterobacter*[5]. In cases where conservative treatments such as antibiotic therapy, debridement, and VAC are insufficient, muscle flaps are one of the most effective methods for fighting an infection. It increases blood supply in the graft area and shortens the recovery period. We present the early and mid-term results of patients we treated with sartorius and gracilis muscle flaps in PVG infections in the femoral region[6].

Table 1. Szilagyi classification in prosthetic graft infections

Grade 1	Infection only in the dermis
Grade 2	No graft involvement, infection in the subcutaneous area
Grade 3	Graft infected

Materials and Methods

Between January 2012 and January 2021, 14 patients treated with muscle flap (gracilis muscle flap in 11 patients, sartorius muscle flap in 3 patients) due to PVG infection in the femoral region in our clinic were included in the study. Additionally, routine biochemical tests, Doppler ultrasonography, computed tomography; angiography wound site and blood culture results about the patients were also evaluated in detail.

Muscle flaps preparation and surgical procedure

First, the periphery of the infected graft and the inguinal region are debrided. The medial circumflex femoral artery, which supplies the gracilis muscle, is preserved. the gracilis muscle is then dissected. The distal gracilis muscle is excised and released. The proximal pedicle was preserved and placed over a prosthetic graft. The same procedure is performed for the sartorius muscle while preserving the superficial femoral artery branch that feeds it.

Results

In this study, we treated 14 patients (9 males and 5 females) using muscle flap. Their average age was 59±8.7 (39-69) years. All the patients showed graft infections spreading to the subcutaneous tissues (Szilagyi grade III). The prosthetic grafts used in 6 patients were PTFE, Dacron was used in 8 patients. Moreover, 11 infections occurred in the early period while 3 infections occurred in the late period. The pathogens causing graft infections were identified to be staphylococcus aureus in 5 patients, staphylococcus epidermidis in 2 patients, and polymicrobial in 7 patients. Furthermore, graft occlusion was noted in a patient, a 2 cm opening was noticed distal to the skin incision in another patient. In two of our patients, the infection continued despite the treatment and graft had to be removed. In one of our patients trans-obturator iliofemoral bypass was performed with a PTFE graft due to the development of critical leg ischemia. There was no loss of limb and mortality in any patient we presented here and they were fully recovered (Table 2).

Discussion

It is critical to attach importance to sterility in operations using PVGs. If the graft is infected, the eradication of the infection is a very difficult process. At the end of this process, post-sespsis mortality, removal of the graft and limb amputation may result. Our first goal in treatment is to start the antithiotherapy appropriate for the wound culture and to clean the wound site by debriding[2,3]. Calligaro et al.[7] achieved 71% success by using debridement, antibiotic and povidone-iodine wound care dressings in patients with prosthetic graft infection and reported a mortality rate of 12% and amputation of 4%.

VAC, which we frequently use in our clinic, is a very effective type of treatment[8]. In particular, we treat many patients with Szilagyi I-II infections through the application of VAC without the need for any other intervention. In the application of negative-pressure wound therapy to patients with Szilagyi III infection, Pinocy et al.[9] reported that the treatment alone was successful in all patients in the study. In the negative pressure wound treatment method, complications that should be considered due to the pressure applied to the arterial system are bleeding and the development of pseudoaneurysm[8]. Although it is unsuccessful in treatment, it can be used to encourage granulation tissue before the muscle flap is applied.

There are many studies advocating the use of muscle flaps for treating patients with Szilagyi III infection[10]. Muscles that can be used as muscle flaps include the sartorius, rectus abdominis, rectus femoralis and gracilis muscles. A pedicled muscle flap provides a favorable environment for vascularization in the infected graft site, increases the oxygen pressure and increases the ability of macrophages to fight infection. The increased blood flow allows antibiotics to be transported more easily to the site of infection.

Creating a gracilis muscle flap is more difficult than creating a sartorius flap. However, there are some advantages of using the gracilis muscle flap[11] (Table 3).

Before being used as a muscle flap, the presence of stenosis or occlusion in the artery feeding this muscle should be evaluated with CT angiography or angiography. Necrosis develops in the muscle flap with blood supply

Table 2. Operational data

	n	%
Previous operation and prosthetic graft used	14	100
Aorta-femoral graft bypass, dacron	4	28.5
Femoro-popliteal graft bypass, dacron	4	28.5
Femoro-popliteal graft bypass, PTFE	6	43
Pathogenic microorganism		
Staf. Aureus	5	36
Staf. Epidemidis	2	14
Polymicrobial	7	50
According to Szilagyi calcification presence of grade III infection	14	100
Treatments before the procedure		
Antibiotic and debridement	14	100
Negative pressure wound therapy	14	100
Use of the gracilis muscle as a graft	11	79
Use of the sartorius muscle as a graft	3	21
Complications	4	28
Graft occlusion	1	7
Wound dehiscence	1	7
Continuation of infection	2	14
Limb loss	0	0
Treatment success	12	85
Mortality	0	0

Table 3. Comparison of gracilis and sartorius muscle flaps

Gracilis muscle flap	Sartorius muscle flap
It is more difficult to prepare.	It is easier to prepare.
The gracilis muscle is supplied by the profunda femoral artery. The profunda femoral artery is more protected from atherosclerosis than the superficial femoral artery. Meanwhile high oxygenation accelerates wound healing.	The sartorius muscle is supplied by the superficial femoral artery. Atherosclerosis can impair the nutrition of the muscle flap.
When used as a flap, it does not reduce extremity movements much.	It causes difficulty in lower extremity flexion movement.

disorder and treatment fails. We believe that these evaluations, which we have done preoperatively in our clinic, are of great importance in the success of treatment.

Conclusion

Because of this study, we see that sartorius and gracilis muscle flap reconstruction is a successful method in eliminating the infection and accelerating wound healing in cases resistant to negative pressure wound treatment with antibiotherapy and debridement after PVG infection.

Ethics

Ethics Committee Approval: Ethics committee approval was not obtained for our study.

Informed Consent: Consent of the patients included in the study was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ovalı C, Taştekin T, Concept: Ovalı C, Taştekin T, Design: Ovalı C, Taştekin T, Data Collection and/or Processing: Ovalı C, Taştekin T, Analysis of Interpretation: Ovalı C, Taştekin T, Literature Search: Ovalı C, Taştekin T, Writing: Ovalı C, Taştekin T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: No financial resources have been used for this article.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(3):114-122

DOI: 10.32596/ejcm.galenos.2022.2022-06-035

Cardiac Implantable Electronic Devices - What We Have Done So Far? A Single-center Experience

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Abstract

Objectives: In this study, we examined the various device treatments that we applied to patients in different scenarios in our clinic and compared the complication rates we encountered with the current literature. This study revised our usual protocols to avoid and treat possible events at an early stage.

Materials and Methods: Between September 2016 and March 2022, 965 consecutive children and adult patients (66.2% men; 66.4±14.0 years) who underwent 1018 cardiac device procedures at our center were analyzed retrospectively. The clinical and electrophysiological characteristics of the study group were evaluated.

Results: The total number of device procedures performed in the electrophysiology laboratory was 1018, including 709 cardiac device implantations, 236 generator replacements, 59 lead revisions, and 14 lead extractions. In the pacemaker group, the study population was older and mostly female [306 patients (48.7% men); 71.1±15.0 years], compared to the implantable cardioverter defibrillators and cardiac resynchronization therapy groups [254 patients (82.2% men); 62.1±13.2 years and 149 patients (75.1% men); 60.1±9.6 years, respectively]. Regarding procedure-related complications, the most common complications were device-related infection (8 patients, 0.8%) and lead-related reintervention (6 patients, 0.6%). Following in order: vascular complications included coronary sinus (6 patients, 0.6%), axillary vein dissection/perforation (3 patients, 0.3%), pneumothorax (4 patients, 0.4%), diaphragmatic stimulation requiring reintervention (2 patients, 0.2%), and cardiac perforation (1 patient, 0.1%) were other complications we encountered. No patient had a device-related hemothorax or brachial plexus injury. The procedure-related mortality rate following the index procedure during the first month was 0.1%.

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Received: 01.06.2022 **Accepted:** 19.08.2022

Cite this article as: Görmel S, Yaşar S. Cardiac Implantable Electronic Devices - What We Have Done So Far? A Single-center Experience. EJCM 2022;10(3):114-122.

DOI: 10.32596/ejcm.galenos.2022.2022-06-035

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Conclusion: In this retrospective study, we present various cardiac implantable electronic device (CIED) procedures performed at our center and their periprocedural results. These data underline the significance of specific methods aimed at reducing CIED complications and improving their management.

Keywords: Electrophysiology, pacemakers, registries

Introduction

In the 21st century, cardiac implantable electronic device (CIED) implantation, consisting of pacemakers (PMs), implantable cardioverter defibrillators (ICD), and cardiac resynchronization therapy (CRT) devices, has become increasingly common worldwide. Nonetheless, there is considerable heterogeneity among countries in PM, ICD, and CRT implantation rates; this is due to epidemiological, social, and socio-economic reasons[1-4].

CIED implantation provides definite clinical benefits; however, one in ten patients receiving device therapy experience various possibly severe complications[5]. To manage and prevent complications, it is necessary to evaluate each patient's indications for CIED implantation, the steps of the implantation procedure, and device function.

As a tertiary center, our hospital is a center where cardiac devices are most frequently implanted. Recently, with increasing interest and confidence in device treatments, especially CRT, the number of patients receiving device treatment in our hospital has increased, and the leading role of our hospital has been consolidated. In this study, we examined the various device treatments we applied to patients in different scenarios in our clinic and compared the complication rates we encountered with the current literature. This study revised our usual protocols to avoid and treat possible events at an early stage.

Materials and Methods

This study was a retrospective analysis, and our population consisted of 965 consecutive children and adult patients (66.2% men; 66.4±14.0 years) who underwent 1018 cardiac device procedures between September 2016 and March 2022 at our center. The clinical and electrophysiological characteristics of the study group were evaluated. There were no exclusion criteria for this study. The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital (approval date: May 26, 2022; approval number: 2022-173) and conformed to the principles of the Declaration of Helsinki.

Statistical Analysis

This was a descriptive study, in which categorical variables were represented as absolute numbers and percentages. Continuous variables are presented as the mean ± standard deviation. Statistical analyses were performed using SPSS for Windows version 26.0 (IBM Corp., Armonk, NY, USA).

Results

The total number of device procedures performed in the electrophysiology laboratory was 1018 that consisted of 709 cardiac device implantations, 236 generator replacements, 59 lead revisions, and 14 lead extractions.

The baseline characteristics of the patients who underwent device implantation are shown in Table 1. In the PM group, the study population was older and mostly female [306 patients (48.7% men); 71.1±15.0 years], in contrast to ICD and CRT groups [254 patients (82.2% men); 62.1±13.2 years and 149 patients (75.1% men); 60.1±9.6 years, respectively]. The ejection fraction of ICD and CRT patients was lower (30.1±11.8 and 23.8±6.3, respectively) as expected, and it was in the normal range for PM patients (58.1±8.5). The number of patients with

sinus rhythm (223; 72.9%) was lower in the PM group compared to ICD and CRT groups (225, 88.6%; 128, 86.0%, respectively). The ratio of patients to who device implantation was applied for non-ischaemic etiology and primary prevention were detected more frequently in the CRT group (62 patients; 41.6%, and 133 patients; 89.3%, respectively) in proportion to the ICD group (59 patients; 23.3% and 195 patients 76.8%, respectively). The ICD group was classified according to the specific cardiomyopathy groups are as follows: of the 254 patients, 12 had hypertrophic obstructive cardiomyopathy (4.7%), 2 had arrhythmogenic right ventricular dysplasia (0.8%), 1 had Brugada syndrome (0.8%), 1 had muscular dystrophy (0.8%), and 1 patient had non-compaction cardiomyopathy (0.8%).

The absolute and proportional numbers of ICD, PM, and CRT device types implanted between 2017 and 2021 are presented in Table 2 and Figure 1. While the number of other devices remained relatively constant, the use of CRTs has increased over the last 5-years.

Complications following the device procedures are shown in Table 3. Regarding procedure-related complications, the most common complication was device-related infection (8 patients, 0.8%) (Figure 2) and lead-related re-intervention (6 patients, 0.6%). Following in order: vascular complications, including coronary sinus dissection/perforation (6 patients, 0.6%) and axillary vein dissection/perforation (3 patients, 0.3%), pneumothorax (4 patients, 0.4%) (Figure 3), diaphragmatic stimulation requiring reintervention (2 patients, 0.2%), and cardiac perforation (1 patient, 0.1%) (Figure 4) were other complications encountered. None of the patients had a device-related hemothorax or brachial plexus injury. The procedure-related mortality rate following the index procedure during the first month was 0.1%.

Considering the iatrogenic causes of atrioventricular (AV) node injuries (26 patients, 2.6%), surgical operations (14 patients, 1.4%), transcatheter aortic valve replacement (TAVR) procedures (self-expandable TAVR, 12 patients, 1.2%; balloon-expandable TAVR, 6 patients, 0.6%), AV node ablation procedures for treating atrial fibrillation (3 patients, 0.3%), and inadvertent AV node impairment during anteroseptal accessory pathway ablation (2 patients, 0.2%) were major indications for

Table 1. The baseline patient characteristics

	PM (N=306)	ICD (N=254)	CRT (N=149)
Age, mean (SD), years	71.1 (+15.0)	62.1 (+13.2)	60.1 (+9.6)
Male gender, N (%)	149 (48.7)	209 (82.2)	112 (75.1)
EF, mean (SD), (%)	58.1 (+8.5)	30.1 (+11.8)	23.8 (+6.3)
QRS duration, mean (SD), ms	N/A	N/A	153.1 (+15.0)
Basal rhythm, N (%)			
-Sinus	223 (72.9)	225 (88.6)	128 (86.0)
-AF	33 (10.8)	24 (9.4)	20 (13.4)
-Unknown	50 (16.3)	5 (2.0)	1 (0.6)
Heart failure type, N (%)			
-Ischeamic	N/A	195 (76.8)	87 (58.4)
-Non-ischeamic	N/A	59 (23.2)	62 (41.6)
Primary & secondary prevention, N (%)			
-Primary prevention	N/A	195 (76.8)	133 (89.3)
-Secondary prevention	N/A	59 (23.2)	16 (10.7)

AV: Atrioventricular, CRT: Cardiac resynchronization therapy device, EF: Ejection fraction, ICD: Implantable cardioverter defibrillator, N/A: Not applicable, PM: Pacemaker

cardiac device implantation. CIED requirements after surgical operations occurring following valve surgeries (valve surgery, totally 12 patients, 1.2%; multiple valve surgery, 8 patients, 0.8%; multiple valve surgery involving tricuspid valve repair or replacement, 6 of 8 patients, 0.6%), congenital heart surgery [ventricular septal defect (VSD) repair, 1 patient, 0.1%], and surgical myectomy (1 patient, 0.1%).

Twelve patients underwent CRT implantation at our institution after indirect percutaneous mitral annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation.

Table 2. Distribution of the number of devices implanted by years

Device type	2017	2018	2019	2020	2021
	N (%)	N (%)	N (%)	N (%)	N (%)
ICD					
- SC	0 (0)	3 (27.2)	66 (83.5)	56 (90.3)	65 (86.7)
- DC	9 (100)	8 (72.8)	13 (16.5)	6 (9.7)	10 (13.3)
- Total	9 (100)	11 (100)	79 (100)	62 (100)	75 (100)
PM					
- SC	7 (13.2)	1 (3.4)	15 (18.1)	11 (17.5)	15 (24.2)
- DC	46 (86.8)	28 (96.6)	68 (91.9)	52 (82.5)	47 (75.8)
- Total	53 (100)	29 (100)	83 (100)	63 (100)	62 (100)
CRT					
- CRT-D	20 (100)	19 (100)	28 (100)	34 (100)	41 (100)
- CRT-P	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Total	20 (100)	19 (100)	28 (100)	34 (100)	41 (100)

CRT: Cardiac resynchronization therapy device, CRT-D: Cardiac resynchronization therapy defibrillators, CRT-P: Cardiac resynchronization therapy pacemakers, DC: Dual chamber device, ICD: Implantable cardioverter defibrillator, PM: Pacemaker, SC: Single chamber device

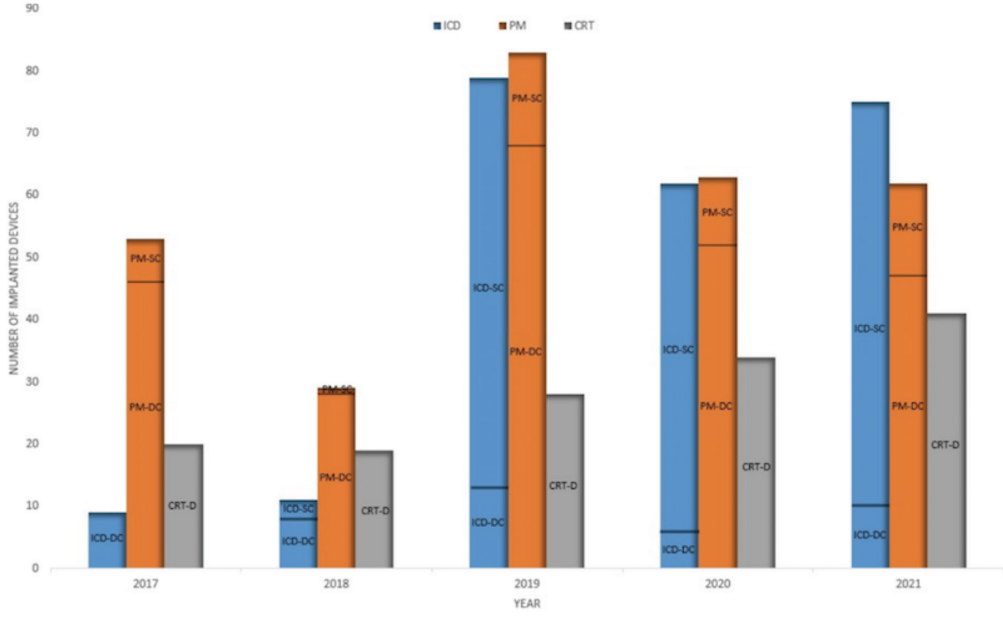

Figure 1. Bar graph showing the types and numbers of cardiac implantable electronic devices by years

Among the 14 lead extraction patients, only one patient had a vascular complication requiring a surgical surgery (Figure 5). The patient was discharged after successful surgery without any disability.

Table 3. Complications of cardiac device procedures

	N (%)
Cardiac device related infection <12 months	7 (0.7)
Cardiac device related infection >12 months	1 (0.1)
Pneumothorax	4 (0.4)
Haemothorax	0 (0)
Coronary sinus dissection/perforation	6 (0.6)
Axillary vein dissection/perforation	3 (0.3)
Diaphragmatic stimulation requiring reintervention	2 (0.2)
Brachial plexus injury	0 (0)
Lead-related reintervention	6 (0.6)
Cardiac perforation	1 (0.1)
Mortality (<30 days)	1 (0.1)

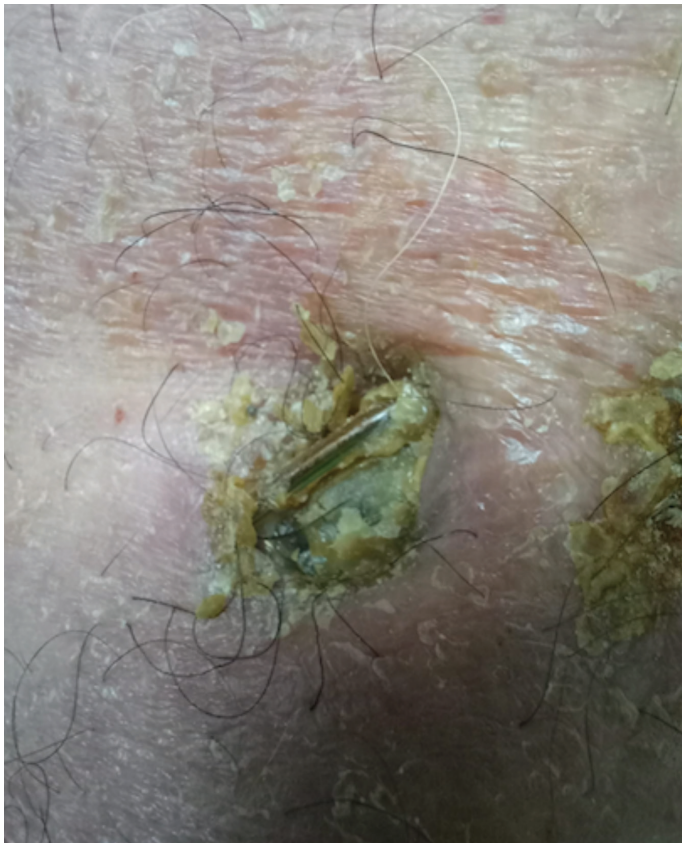

Figure 2. With the seperation of the primary suture line, it is seen that the pacemaker and lead are exposed. Note the infected appearance at the wound site

Discussion

Our national cohort is one of the first registries of CIEDs conducted in Turkey to evaluate CIED patients presenting to our center for device implantation, generator

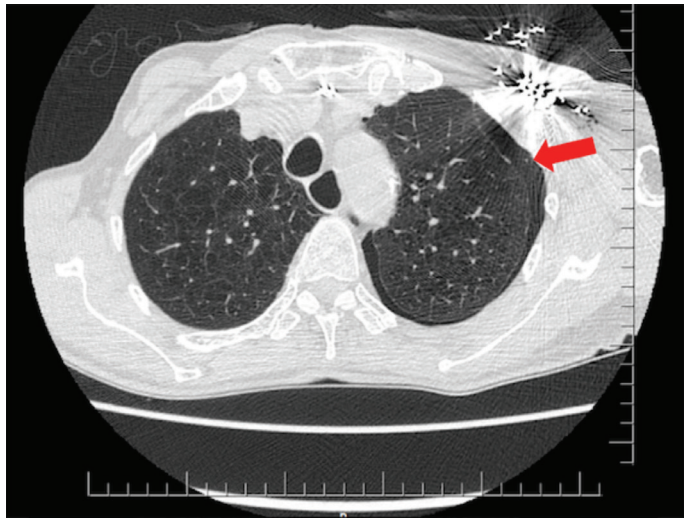

Figure 3. CT scan of the chest (axial view) showing pneumothorax in the left hemithorax after ICD implantation (red arrow)

CT: Computed tomography, ICD: Implantable cardioverter defibrillator

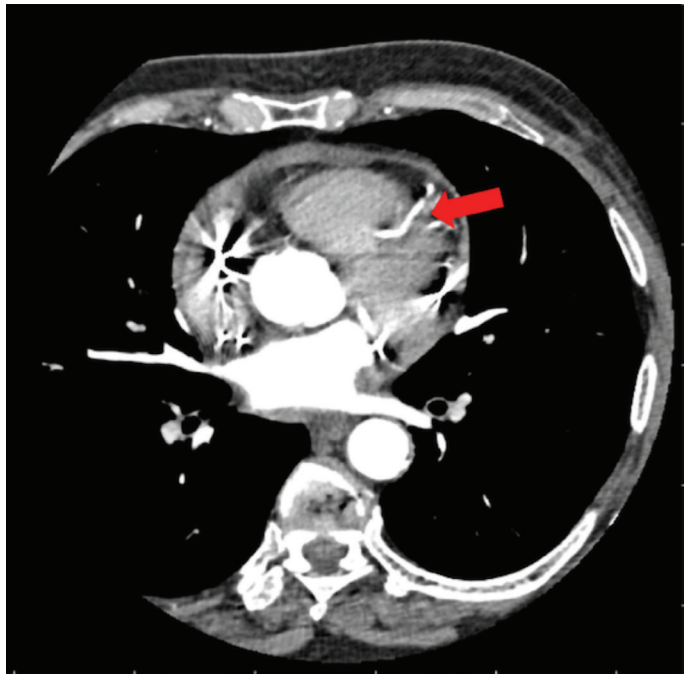

Figure 4. Cardiac CT (axial view) demonstrates a CRT lead that has perforated the right ventricle (red arrow)

CT: Computed tomography, CRT: Cardiac resynchronization therapy

replacement, lead revision, or lead extraction. This article provides key information and first-step guidance on follow-up and treatment for electrophysiologists implanting CIEDs, other cardiologists, and healthcare professionals who follow these patients.

The general descriptive findings from the registry were similar to those in the previously published reports and clinical practice. More male patients than female patients received both ICDs and CRTs compared with patients who received PMs, possibly due to differences in heart failure prevalence and the younger population[6,7]. The reason for the age-related difference between the two groups may be that the device implantation indication in the ICD-CRT groups occurred in the early period due to the primary prevention predominantly, and tachy-brady arrhythmias, as the main indications for device implantation in the PM group, appeared at a later age. AF incidence in the PM group was more prevalent, possibly because the population consisted of a mostly female older population, which is more prone to AF existence. CRT is indicated in patients who have heart failure with reduced EF accompanying AV conduction defects. In this group of patients, degenerative AV node dysfunction may have been a more dominant cause of ischemic etiology. Therefore, CRT device implantation for nonischemic heart failure and/or primary prevention may be seen more often than in the ICD group.

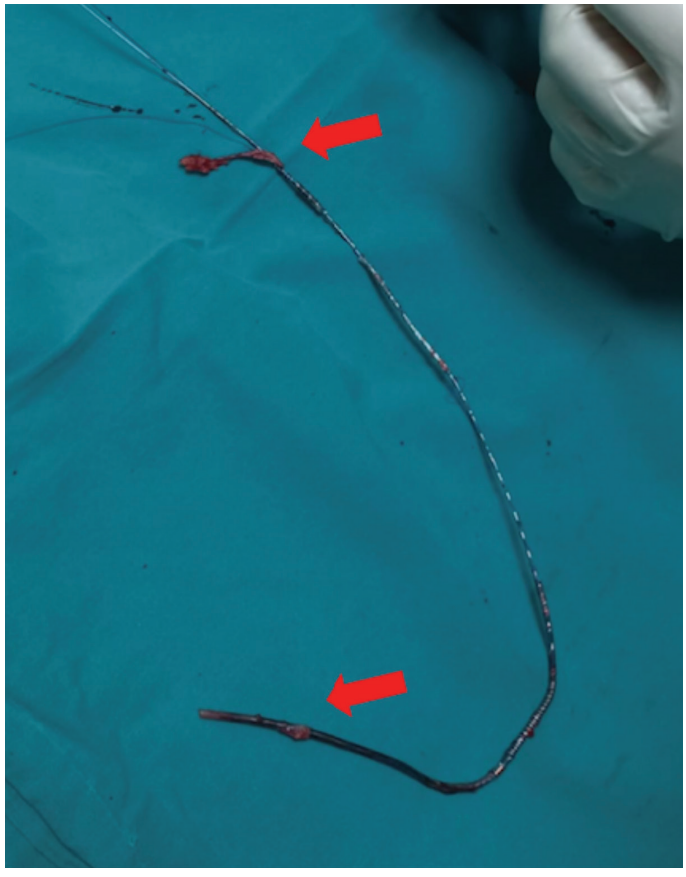

Figure 5. Pieces of tissue detached from the brachiocephalic vein are seen after lead extraction procedure (red arrows)

In our clinic, we have observed an increasing interest in biventricular pacing over time, as is seen worldwide. However, all the CRT devices we implanted were CRT-d due to the reimbursement requirements of the healthcare system, which is exceptionally different in our country.

Device-related infections and lead-related problems were two common urgent complications detected in our study group, consistent with the previous reports (0.3%-4.2% and 1.61%-5.54%, respectively)[8-12]. These complications were associated with high morbidity and substantial financial costs, which caused the device extraction or led to re-intervention[13]. Choosing the most suitable and long-lasting device for the patient and planning the procedure in elective conditions as much as possible will reduce possible lead infections or lead-related problems. In fact, infection rates and lead-related problems were observed at a lower rate in our patients than those in the literature.

Vascular problems, including venous access site complications and coronary sinus complications, emerged as the other common complications encountered in patients treated with CIED at our center, as stated in previous studies[14,15]. Fluoroscopy-guided axillary access was the chosen technique for device implantation in our electrophysiology laboratory because of its convenient calibration and tortuosity compared to subclavian or cephalic access. Coronary sinus dissection and perforation are rare complications in CIED cases. Owing to the low-pressure nature of the cardiac venous system, the conservative approach to venous vascular injuries has generally been successful, and only one patient-required

pericardiocentesis. Since we used the axillary access technique during device implantation at our center, we rarely had pneumothorax complications, and none of the patients developed hemothorax or brachial plexus injury.

Lead-induced right ventricular perforation developed only in a 75-year-old patient 2 weeks after device implantation. In the asymptomatic patient, the incidentally detected perforation on the control chest radiographs consisted of a self-limiting mild pericardial effusion and lead exceeding the cardiac margin. The lead was withdrawn in a controlled and careful fashion in the operating room, and the ventricular lead was re-implanted within 1 week since there were no complications in the follow-up. Considering our patients' advanced age, right ventricular septal (RVS) pacing was preferred for the second time; however, the beneficial effects of RVS pacing compared with right ventricular apical pacing have been shown only in an observational study on the mean risk of perforation[16].

Inadvertent phrenic nerve stimulation (PNS) is common in patients who receive CRT, which has left ventricular (LV) pacing lead[17]. In our population, all PNS procedures except one were moderated using electrical reprogramming, without requiring invasive intervention options for PNS. In the aforementioned patient, the PNS was terminated when the lead was retracted and re-implanted.

The development of iatrogenic AV block after open-heart surgery carries a high risk, especially after multiple valve surgeries involving tricuspid valve repair or replacement, congenital heart surgeries involving VSD, and recurrent surgeries[18]. Our clinic's surgical considerations for device therapy were compatible with those in the previous studies.

The TAVR procedure, which is gradually replacing conventional aortic valve surgeries, can cause transient and sometimes persistent AV block in a target patient group consisting of an elderly patient population, with the massive effect of a bioprosthesis implanted in close proximity to the bundle or left bundle branch within the membranous septum[19]. In a case series of more than 400 patients who underwent TAVR in our clinic, persistent AV block developed in 18 patients, and permanent PMs were implanted in these patients. Consistent with the literature, the rate of development of AV block was higher in patients implanted with a self-expandable valve than in patients implanted with a balloon-expandable valve.

Programmed AV junction ablation in patients AF, by slowing and regularizing the ventricular rate, improves symptoms, quality of life, and cardiac function. In this context, AV node ablation and subsequent PM implantation are appropriate options in cases where drug therapy is insufficient and heart failure cannot be controlled[20]. In our clinic, we performed permanent PM implantation in 3 patients with similar clinical scenarios.

As the risk of developing AV block is higher in the septal pathways, it is necessary to be more careful during the ablation procedure. Cryoablation may be preferred over radiofrequency (RF) ablation to avoid permanent damage[21]. We encountered a persistent AV block complication that required PM implantation after RF ablation[22].

Both CRT and indirect mitral annuloplasty are coronary-based procedures and are indicated for LV systolic function improvement[23]. The presence of CRT lead in the coronary sinus is a contraindication to indirect mitral annuloplasty. Therefore, in the presence of severe functional mitral valve insufficiency, the Carillon mitral contour system (Cardiac Dimensions, Kirkland, WA, USA) was primarily implanted in patients with CRT indications[24]. In this group of patients, we experienced the synergistic effect of the CIED and the Carillon device in the long term.

Infections or lead-related reasons caused us to perform lead extraction in a small portion of our patients. While our lead extraction success rate was better than previous studies established [100% vs. 96.7% (95% CI 96.1%-97.3%)], our all-cause major complication rate was similar to that of low-volume centers [5.8% vs. 4.1% (95% CI 2.7%-6.0%)][25]. Implanting the proper device in

a favorable patient will undoubtedly reduce lead extraction rates.

It is indisputable that device procedures performed at high-volume centers are safer. In this sense, as a high-volume center, we shared the data and experience gained from different CIED procedures applied to different patient groups. We hope that this study will shed light on other multicenter national studies that can be conducted in our country in the future.

Study Limitations

This was a single-center retrospective study in which the epidemiological characteristics of the patients and findings of the device procedures were retrieved from institutional archives. Therefore, the study lacked follow-up data and excluded long-term outcomes.

Conclusion

To the best of our knowledge, this article presents the data on the most comprehensive CIED procedures performed in our country. We investigated patient characteristics, CIED types and requirements for implantation, and peri-procedural results in our study. As a result, our experience as one of the leading centers in our country in terms of the number and diversity of patients was reflected as a low complication rate in our study results.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital (approval date: May 26, 2022; approval number: 2022-173) and conformed to the principles of the Declaration of Helsinki.

Informed Consent: Patient data were collected retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Görmel S, Yaşar S, Concept: Görmel S, Design: Görmel S, Data Collection and/or Processing: Görmel S, Analysis of Interpretation: Yaşar S, Literature Search: Yaşar S, Writing: Görmel S, Yaşar S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: No financial resources have been used for this article.

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E Journal of Cardiovascular Medicine
Research Article
123
EJCM 2022;10(3):123-129
DOI: 10.32596/ejcm.galenos.2022.2022-01-06

Endovascular Treatment of Aorto-iliac Occlusive Disease Using the Kissing Balloon Technique: Mid-term Follow-up

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Abstract

Objectives: This study aimed to present our mid-term experience in the endovascular treatment of aortoiliac occlusive disease using the kissing balloon technique.

Materials and Methods: This two-center, retrospective study included 36 patients (male, n=23; female, n=13; mean age 62.7±9.7 years) with an aortoiliac occlusive disease, who received intervention using the kissing balloon technique between January 2017 and December 2019.

Results: Thirty-six patients with aortoiliac occlusive disease underwent percutaneous intervention. The procedure could not be continued in three patients because of technical failure. Hence, 33 patients were successfully treated using the kissing balloon technique. The technical success rate was 91.6% and the one year patency rate was 83.3%. Of the 33 patients, 3 underwent surgery because of stent occlusion. After 1-year follow-up, in all 30 patients, all the vessels and stents were patent and no re-stenosis, no occlusion and no procedure related morbidity and mortality occurred.

Conclusion: The endovascular treatment of aortoiliac occlusive diseases with kissing balloon technique demonstrated high success and patency rates in appropriate cases. However, in some patients technical failure may occure and the procedure could not be completed. The use of newer recanalization devices, materials or techniques, enrollment of larger cohort and more than 1 year of follow-up may clarify the long-term results of the kissing balloon technique.

Keywords: Endovascular treatment, iliac artery occlusion, kissing balloon technique

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Received: 15.01.2022 **Accepted:** 20.08.2022

Cite this article as: Yılmaz M, Özen A, Yiğit G, Gül M, İşcan Z. Endovascular Treatment of Aorto-iliac Occlusive Disease Using the Kissing Balloon Technique: Mid-term Follow-up. EJCM 2022;10(3):123-129.
DOI: 10.32596/ejcm.galenos.2022.2022-01-06

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Introduction

Atherosclerotic peripheral arterial disease affects 50 million people in the United States and Europe. It is a major challenging disease that can lead to disabling ischemia, limb loss, and reduced quality of life. New interventional modalities, such as percutaneous transluminal angioplasty (PTA) with a drug-eluting balloon or plain balloon angioplasty, stent implantation and atherectomy procedures have been developed for the endovascular treatment of complex arterial occlusive diseases, particularly for extensive lesions of aortoiliac and infrainguinal arteries[1]. Endovascular strategies have become a well-recognized therapeutic alternative to bypass surgery with the aforementioned technical advancements, including the elderly population and patients with chronic total occlusions[2]. The incidence of restenosis in PTA for aortoiliac lesions is high enough not to be ignored, especially for complex lesions[3]. However, paclitaxel-coated balloons (PCBs) were found to be superior to plain balloons in preventing restenosis[4-7]. Furthermore, the durability of endovascular interventions was reported to improve with self-expanding nitinol stents[8]. The term *kissing balloon* was first used by Grüntzig and Hopff[9] to describe the percutaneous treatment of iliac bifurcation stenosis. In 1980, Velasquez et al.[10] published the first report on this technique for distal aorta angioplasty in a patient with Leriche syndrome. Later, several studies have successfully used the kissing balloon technique for treating peripheral artery disease and have taken their place in the literature[11-14]. In this study, we present our mid-term experience in the endovascular treatment of patients with aortoiliac occlusive disease using the kissing balloon technique.

Materials and Methods

Study Population

This two-center, retrospective study was conducted at Ankara Yüksek İhtisas Training and Research Hospital and Aksaray Training and Research Hospital between January 2017 and December 2019. Twenty-seven patients were included from Aksaray Training and Research Hospital, whereas nine patients were from Ankara Yüksek İhtisas Training and Research Hospital. Written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Türkiye Yüksek İhtisas Training and Research Hospital (date: 31.01.2017, approval no. 29620911-929). The study was conducted based on the principles of the Declaration of Helsinki.

In this study, the mid-term results of 36 patients who underwent PTA and stent implantation because of chronic occlusion of iliac arteries were retrospectively analyzed. Eligible patients were those having atherosclerotic diseases of unilateral or bilateral iliac arteries with symptoms varying from moderate intermittent claudication to diffuse pedal ischemia according to the Rutherford classification (classes 2-5)[15] and those who were either ineligible for surgery due to comorbidities or refused open surgery and thus underwent endovascular procedure according to the study protocol. According to the study protocol, all patients were treated using a suitable imaging method [preferably computed tomography (CT) angiography] before the procedure. In addition to the physical examination, color Doppler ultrasonography and CT angiography were performed, when necessary, during the control evaluation after the procedure. Patients who underwent endovascular procedures for chronic total occlusions in iliac arteries but not with the kissing balloon technique and patients who had chronic occlusion lesions in other localizations were excluded from the study.

Patient information was obtained from the hospital archives, outpatient clinical records, image archives of the radiology department, and hospital registry records. Some patients were called for a control visit, and information was obtained by physical examination and radiological examinations. For those who were unable to visit the hospital, other necessary information was obtained by phone call. Patients' demographic, clinical, and procedural data were compiled and analyzed. Demographic data included age, sex, and presence of diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease

(COPD), coronary artery disease, chronic renal failure, obesity, and smoking. Clinical data included the following lesion characteristics: localization, length, and extension (patients classified according to the Trans-Atlantic Inter-Society Consensus (TASC) II classification based on the anatomical characteristics of their lesions). Previous interventions, if present, patency of the procedure, current complaints of the patients, and pre- and post-procedural ankle-brachial index (ABI) were also recorded. Procedural data included the duration of the procedure, technical success of the procedure, any additional procedures, and complications.

Interventions

All percutaneous procedures were performed in a hybrid operating theater under local anesthesia (2% prilocaine), with the patient placed in the supine position on the operating table. In all patients, the first choice for access was either of the femoral arteries. However, in cases where the primary iliac lesion could not be crossed by femoral access, the right axillary artery was used for access. All procedures were initiated by retrograde arterial cannulation using a 6-Fr or 7-Fr introducer sheath (Radifocus Introducer II, Terumo, Europe N.V, Leuven, Belgium). After arterial cannulation, heparin was administered intravenously according to an activated clotting time of 180-200 s. A diagnostic catheter (6.0 Fr, ×150 cm, Boston Scientific, MA, USA) for angiography was delivered retrograde straightforward to the distal aorta from the side of the non-primary lesion. Following the administration of an opaque solution, bilateral iliac and femoral arteries were imaged starting from the distal aorta. The process was continued by deciding on the appropriate size of the balloon and stent according to the initial level and length of the primary iliac lesion. After the imaging procedure, all iliac lesions were crossed by catheter-assisted recanalization with a soft hydrophilic guide wire (0.035" × 150 cm, nitinol guide wire, Terumo) and shapable support catheter (SpeXR, 0.035"×150 cm, Reflow Medical Inc., San Clemente, CA, USA). Subsequently, angioplasty was performed using an appropriate-sized LuminorR PCB catheter (iVascular, S.L.U., Barcelona, Spain) and bailout therapy with appropriate-sized iVolutionR self-expanding nitinol stent (iVascular, S.L.U., Barcelona, Spain) for chronic occlusion lesions (vessel/balloon ratio of 1:1 based on the visual estimate for a total inflation time of 3 min at 6-14 atm) for all patients. Balloons were inflated once. However, when control angiography revealed a residual segmental lesion (>50% stenosis), flow-limiting dissection, or atherosclerotic plaque deformation, a second PCB was performed and dilatation was maintained for a longer period (>3 min). In patients with axillary access, a long, braided introducer sheath (7 Fr, Terumo) was used to continue the procedure. After the procedures, control imaging was performed to check the intra-arterial flow patency, stent configuration, and presence of residual stenosis (Figure 1).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ± standard deviation or median (min.-max.) for continuous variables and in number and frequency for categorical variables. The Shapiro-Wilk test was used to check the normal distribution of continuous variables. Paired-sample t-test was used to analyze and compare ABI values before and after the procedures. The Kaplan-Meier survival analysis was used to test the primary and cumulative patency rates of interventions at and during the follow-up period. The significance level was set at $\alpha=0.05$; $p<0.05$ was considered significant.

Results

Baseline Characteristics

The mean age was 62.7±9.7 years, 23 patients were male, and 13 patients were female. Moreover, 38.9% of the patients had DM; 44.4%, hypertension; 47.2%, hyperlipidemia; 30.6%, COPD; 27.8%, coronary artery disease; and 13.9%, chronic kidney disease. Additionally, 41.7% of the patients were current smokers. Claudication

was the only symptom in 86.1% of the patients, 11.1% had rest pain, and 2.8% had an ischemic wound on one foot. According to the TASC II classification, 5 (13.8%) patients were included in TASC A, 9 patients in TASC B (25%), 15 patients in TASC C (41.6%), 7 (19.4%) patients in TASC D.

Operative Findings

The mean intervention time was 76.7±8.7 min. A total of 36 patients received interventions for aortoiliac occlusive disease. Three patients with additional femoro-popliteal lesions located on the ipsilateral side of the iliac occlusive lesion received interventions simultaneously. Retrograde sub-intimal aortic dissection developed in two patients due to the failure of pass the iliac lesion to reach the aortic lumen during the guide-wire and catheter manipulation, after which the procedure was terminated. In one patient, the procedure was terminated because the iliac lesion could not be crossed at all. Moreover, in four patients, the procedure was continued from the right axillary access because of failure via the femoral access so that the procedure could be completed. In total, 33 patients were successfully treated by this technique, with a success rate of 91.6%. Moreover, six patients developed procedure-related complications. The procedure was terminated in two patients who developed retrograde aortic dissection, and who underwent open surgery immediately after the intervention under elective conditions. Two patients developed a hematoma in the groin, and another patient had femoral artery pseudoaneurysm; these complications

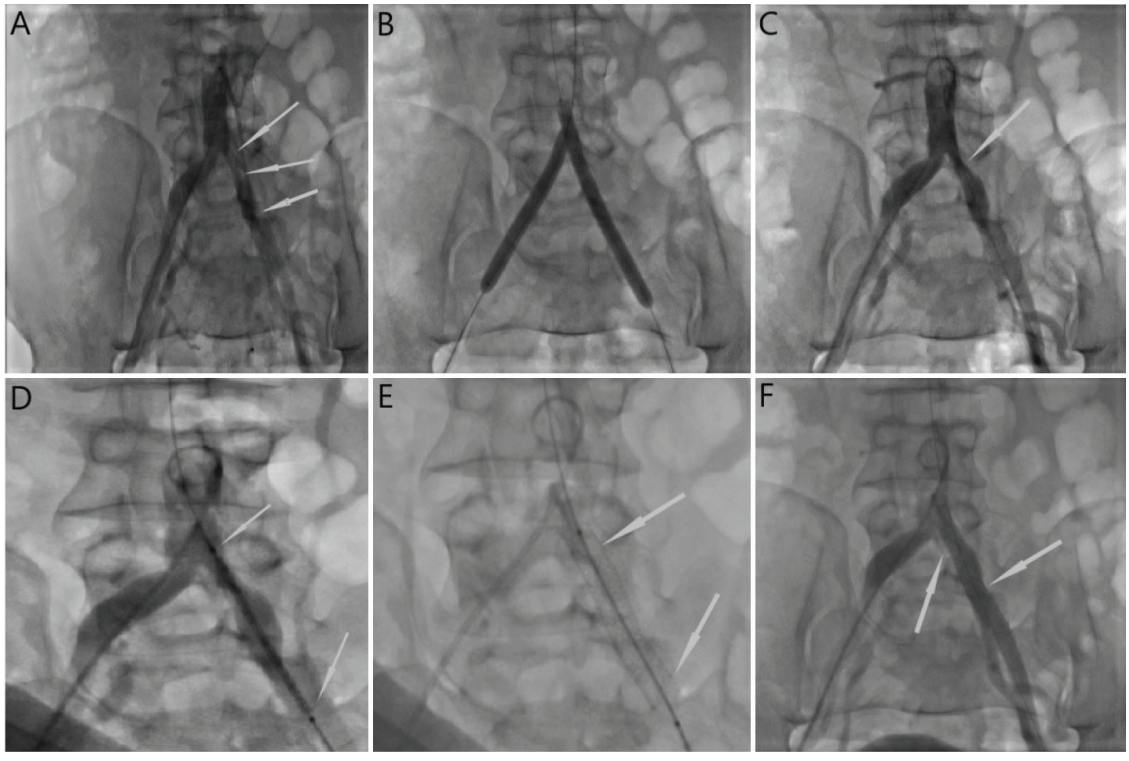

Figure 1. Angiographic images of a 61-year-old man presented with claudication in left leg caused by aorta-iliac occlusive disease in left common iliac artery. This patient intervened with kissing balloon technique and serial images show whole procedure step by step. **(A)** Angiographic imaging shows a diffuse atherosclerotic plaque begins from initial level of iliac bifurcation and extends to left external iliac artery (arrows). **(B)** After catheter supported recanalization of occlusive segment, kissing balloon dilatation was performed with paclitaxel coated balloons (7x100 mm for left, 7x120 mm for right iliac arteries). **(C)** After balloon dilatation, control imaging shows a successful recanalization with residual stenosis (arrow). **(D)** Image shows assessment of true localization of an 8x80 mm self-expandable nitinol stent before deployment. Stent's proximal and distal markers are visible (arrows). **(E)** Control imaging shows successfully deployment of the stent (arrows). **(F)** After all the procedure control imaging shows successfully treatment of occlusive segment and stent configuration and arterial lumen patency seems to be excellent

resolved spontaneously without surgery. In one patient, acute severe ischemia was observed in the treated extremity because of procedure-related debris embolism, and then urgent open surgery was performed.

Other Findings and Follow-up

Approximately 12 h after the procedure, one patient underwent urgent open surgery because of severe ischemia and leg pain. Left aorto-femoro-popliteal bypass surgery was performed in the same session via the retroperitoneal approach. Intraoperative exploration of the aorta revealed a plaque shift and debris embolism that occluded the iliac artery lumen, which required intervention. The patient was discharged on postoperative day 7 and recovered completely. In one patient, open surgery was performed under elective conditions after 1 month because of sub-acute stent occlusion. In one patient, open surgery was performed after 6 months under elective conditions due to chronic re-occlusion of the stent that was previously inserted before the procedure. After 1 year, all stents were patent, and no misconfiguration, residual stenosis, and occlusion occurred in any of the 30 patients. Although all patients were preoperatively symptomatic and had claudication, 76.7% of them were asymptomatic and 23.3% had mild symptoms at the end of the follow-up period. ABI values were improved significantly in the treated extremity during the post-procedural period ($p<0.001$).

Discussion

Both PTA and stenting are commonly used endovascular interventions for iliac artery occlusive disease. A stenotic or occlusive lesions of the iliac artery can be successfully treated with PTA alone. If PTA alone is technically unsuccessful, additional stent placement is indicated (provisional stenting). Alternatively, a stent could be placed primarily to treat iliac artery stenosis or occlusion (primary stenting). However, which endovascular treatment strategy is superior for stenotic and occlusive lesions of the iliac arteries is barely known given the limited evidence available[16]. The availability of endovascular stents has significantly increased the number of aortoiliac lesions that may be treated percutaneous by providing a larger acute gain in luminal diameter, scaffolding the lumen to prevent embolization of debris and enhancing long-term patency compared with balloon angioplasty alone. For common iliac bifurcation lesions, kissing balloon expandable stents have become the preferred option[17,18]. The TASC II document describes characteristic lesion morphology for ideal (type A) and unfavorable (type D) iliac lesions for endovascular therapy[19]. Surgical and percutaneous treatments of TASC II type B and C lesions have been compared in a nonrandomized observational study[20]. No difference was found in limb salvage or patient survival at 5 years, but vessel patency was reduced in limbs with poor runoff and those treated with stents compared with surgery. Other trials comparing surgery with percutaneous intervention for iliac occlusive diseases include a randomized comparison of balloon angioplasty with surgery for 157 iliac lesions, which found no difference in the 3-year cumulative rate for death, amputation, or revascularization failure[21]. Another randomized controlled trial of surgery versus angioplasty in 102 patients with severe claudication and limb-threatening ischemia demonstrated no difference at 1 year for angioplasty or surgery[22]. On the basis of these and other trial data, current recommendations favor endovascular procedures for TASC II A and B lesions and selected C lesions. Generally, patients with TASC II D lesions will be considered candidates for surgery, but with newer technologies (reentry devices and covered stent grafts) these patients are being increasingly considered for endovascular therapy on a case-by-case basis[23]. However, in a systematic review, twenty-one studies presented 1,390 patients. Rutherford classification 1/2/3 was the indication in 76.2% of patients, and 48.4% of the lesions were classified as Trans-Atlantic Inter-Society Consensus C or D. The technical success rate was 98.7%, and the complication rate was 10.8%. The clinical improvement at 30 days was achieved in 89.9%. Primary patency at 12, 24, and 60 months was 89.3%, 78.6%, and 69.0%, respectively[24].

We successfully treated 33 patients using the kissing balloon technique. We also used catheter-supported recanalization and primary-stenting techniques to complete the procedure. The main problem appears to be the recanalization process in patients with TASC II D lesions with procedural options and material settings that we used. Excimer laser-assisted recanalization is one of the most frequently used methods for the recanalization of chronic total occlusions. Although this technique was used in many studies in the 1990s and early 2000s[25-28] and achieved early successful results, it is no longer used nowadays, as it was found to have high restenosis rates due to severe vascular inflammation in long-term follow-up compared with other recanalization techniques in later studies[29]. In a series of 48 patients, published in 1999, all stents were placed successfully, and no major complications occurred. In this study, primary stenting was used in addition to the kissing balloon technique similar to our study, but excimer laser-assisted recanalization was used as the recanalization method of chronic total aortoiliac occlusive lesions. All patients experienced symptomatic improvement, and the 2-year patency rate was 87%[13].

Conclusion

The early and mid-term results of this study revealed that the kissing balloon technique is a successful treatment option for aortoiliac lesions. However, patients with TASC II D group lesions demonstrated poor outcomes, which may be due to the ineffective recanalization method employed. In this group, better results may be obtained using more effective recanalization methods in addition to the kissing balloon technique.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Türkiye Yüksek İhtisas Training and Research Hospital (date: 31.01.2017, approval no. 29620911-929).

Informed Consent: Written informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yılmaz M, Özen A, Yiğit G, Gül M, İşcan Z, Concept: İşcan Z, Design: Yılmaz M, Data Collection and/or Processing: Yılmaz M, Yiğit G, Analysis of Interpretation: Gül M, Literature Search: Yılmaz M, Özen A, Writing: Yılmaz M, Özen A, Yiğit G.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: No financial resources have been used for this article.

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Research Article

E Journal of Cardiovascular Medicine

EJCM 2022;10(3):130-136

DOI: 10.32596/ejcm.galenos.2022.2022-04-027

Acute Effects of Blood Sugar Regulation on Endothelial Functions in Patients with Diabetes

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Abstract

Objectives: Coronary artery disease (CAD) due to atherosclerosis is an important and common cause of mortality and morbidity in patients with diabetes mellitus (DM) and prediabetes. Endothelial dysfunction is a possible reason for the increased atherosclerosis in patients with diabetes. Previous studies have shown that hyperglycemia deteriorates endothelial functions, but there are not many studies have been conducted to investigate the acute effect of blood sugar regulation on impaired endothelial functions in patients with diabetes. So in this study, we evaluated the acute effect of blood sugar regulation with insulin infusion on endothelial functions in patients with diabetes.

Materials and Methods: Forty-four patients with diabetes who were planned to start insulin infusion and 20 healthy individuals of similar age and gender were included in this study. Flow-mediated dilatation (FMD) method was used to evaluate endothelial functions. FMD values before and after insulin infusion in patients with diabetes were calculated and compared with those in the patient population and the healthy control group.

Results: The mean age of the patients was 54.9±13.6 years and 54.5% were female. When the hyperglycemic and the normoglycemic periods were compared among themselves, FMD measured in the normoglycemic period was found to be significantly higher (6.13±3.11 vs 10.89±3.65, $p<0.001$). The FMD value in the group with diabetes was found to be significantly lower than that in the control group, even after treatment (10.89±3.65 vs 12.84±1.86, $p<0.006$).

Conclusion: In type 2 patients with DM, endothelial functions are impaired during periods of hyperglycemia. Although endothelial functions improved in the acute period after blood sugar regulation, endothelial functions still continue to be

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Received: 02.05.2022 **Accepted:** 20.08.2022

Cite this article as: Mammadov G, Şimşek E, Yıldırım Şimşir I, Yağmur B, Soydaş Çınar C. Acute Effects of Blood Sugar Regulation on Endothelial Functions in Patients with Diabetes. EJCM 2022;10(3):130-136.
DOI: 10.32596/ejcm.galenos.2022.2022-04-027

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impaired compared with the healthy control group. Patients with diabetes may be at higher risk of vascular events during hyperglycemic periods than in normoglycemic periods.

Keywords: Diabetes, hyperglycemia, endothelial dysfunction, flow-mediated dilation

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases[1]. Coronary artery disease (CAD) due to atherosclerosis is an important and common cause of mortality and morbidity in patients with DM and prediabetic. It is considered that increased atherosclerosis in patients with diabetes develops on the basis of endothelial dysfunction[2-5]. Oxidative stress caused by hyperglycemia, increased free oxygen radicals, decreased nitric oxide (NO) synthesis, increased endothelin 1 production and hyperglycemia-related metabolic products (3-deoxyglucosone, amadori products, methylglyoxal) are important causes of endothelial dysfunction in patients with DM[6-9].

Flow-mediated vasodilation (FMD) test is a widely used non-invasive method for evaluating endothelial functions. During this test syfingomanometer cuff is inflated on the forearm for 5 min to stop arterial flow and cause ischemia. After the deployment of the cuff, hyperemia and increased shear stress will trigger the healthy endothelium to release vasodilator factors, especially NO. Basal and after ischemia brachial arter diameters are measured using ultrasound probe and an increase in the brachial arter diameter more than 10% is expected in people with healthy endothelial[10,11]. It has been shown that acute hyperglycemia with intravenous glucose in healthy individuals leads to deterioration in endothelial functions. Endothelial function is impaired in the chronic period in patients with diabetes[12-16]. However, comparison of endothelial functions between hyperglycemic and normoglycemic periods in patients with DM has not been investigated before.

This study is designed to test the hypothesis that acute worsening of endothelial functions may occur in acute hyperglycemic periods in patients with DM by comparing endothelial functions before and after insulin infusion therapy.

Materials and Methods

Between September 2018 and October 2019, patients with type 2 DM who were planned to start an intravenous (i.v.) insulin infusion by an endocrinologist at the study center were evaluated 44 patients aged between 18 and 75 years, who signed the informed consent, were included in the study. Patients with pregnancy, ketoacidosis, malignancy and had low left ventricular ejection fraction (LVEF <40%) were excluded from the study. In the hyperglycemic period, echocardiography and FMD evaluation was performed before insulin infusion then control FMD evaluation was performed immediately after blood glucose levels were taken under control (blood glucose <180 mg/dL) and insulin infusion was discontinued. The medical history of the patients, routine laboratory tests and the other medications were recorded.

The control group was formed by 20 volunteers of similar age and gender to the patient group, who signed the informed consent, and did not have any known history of cardiovascular (CV) disease.

Flow-mediated Vasodilation

For the brachial ultrasonographic evaluation, a 4.5-12 MHz Linear ultrasound probe (Vivid E9 4D Cardiovascular ultrasound system, Model 11L-D GE Healthcare, Chicago, USA) was used in the high resolution mode (>10 Mhz), and the brachial artery was imaged longitudinally from 5-10 cm proximal to the antecubital pit. After measuring the basal diameter of the brachial artery, the sphygmomanometer cuff was inflated to 220 mmHg,

then the cuff was deflated 5 min later. After occlusion, the measurement was made 1 min after the cuff air was released and at the end of diastole. FMD was obtained by calculating the ratio of arterial diameter change to basal artery diameter as a percentage (%).

Statistical Analysis

The normal distribution of the variables was determined by the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean (mean) and standard deviation, while non-normally distributed continuous variables were expressed as median and minimum-maximum, while categorical variables were expressed as percentage and number of cases. Continuous variables from the hyperglycemic and normoglycemic period measurements before insulin infusion were compared with the paired t-test used in the evaluation of repetitive measurements, and categorical variables were compared with the McNemar test. In comparing the control group and the DM patient group, t-test or Mann-Whitney U test was used according to the normal distribution pattern for continuous variables, while chi-square or Fisher's Exact test was used for categorical variables. A p-value of <0.05 was considered statistically significant. Ege University Faculty of Medicine Clinical Research Ethics Committee approval was obtained for the study (decision no: 18-6/43). All comparisons were made using SPSS (Statistical Package for Social Sciences) v25 (IBM, Armonk, NY, USA) statistical package program.

Results

Forty-four patients who met the inclusion criteria and 20 healthy volunteers of similar age and gender were included in the study. The mean age of the patient group was 54.9±13.6 years and 54.5% were female. All the patients included in the study were diagnosed with type 2 DM. 63.6% of the patients had hypertension, 38.6% hyperlipidemia, 13.6% chronic renal failure, 13.6% CAD and 6.8% cerebrovascular disease. None of the patients had been diagnosed with heart failure and the mean LVEF was 60.8%±4.5% (Table 1). Left ventricular diastolic dysfunction was present in 82% of the patients. When insulin infusion was started, the blood glucose level of all patients was above 300 mg/dL and the mean was 384±76 mg/dL. While the mean HbA1c value of the patients was 11.04±2.31%, the duration of DM including the time from the first diagnosis to the study was 12.6±9.4 years. FMD values were found as 6.13%±3.11 in the first measurement. The patients received insulin infusions for 3 days. After the blood glucose level decreased below 180 mg/dL, insulin infusion was stopped and FMD measurement was repeated in normoglycemic period. The mean blood glucose at the time of control FMD measurement was 151±27 mg/dL. The mean FMD value after glycemic control in patients was calculated as 10.89±3.65%, and this value was found to be significantly lower than the hyperglycemic period (p<0.001) (Table 2, Figure 1).

The mean age of the healthy volunteers taken as the control group was similar to that of the patient group (52.6±8.6 vs 54.9±13.6 years, p=0.52). Since it has been reported that there may be changes in FMD according to gender, the female gender distribution was also found to be similar (54.5% vs 50%, p=0.736). While no additional CV disease was found in the control group, LVEF values were similar to the DM group (62.3%±3.0 vs 60.9±4.5%,

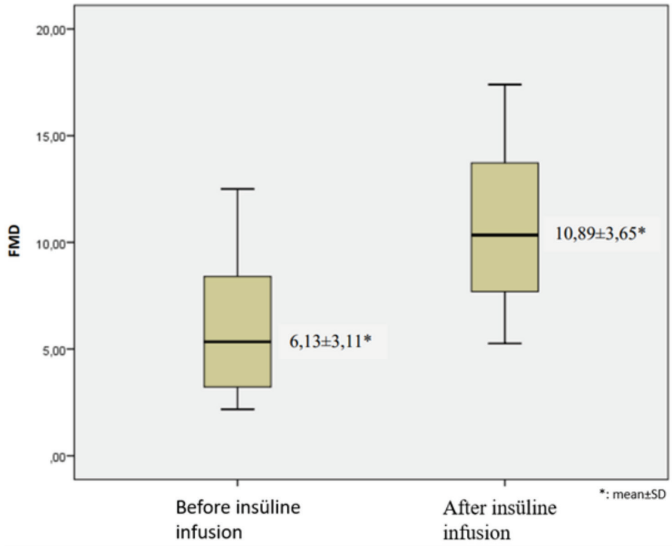

Figure 1. Flow mediated diameter change before and after insulin infusion

p=0.376). On the resting electrocardiography (ECG), the heart rate was higher in the patient group (83.7±10.3 vs 73.2±5.04, p=0.001). FMD measurement in the healthy group was 12.84%±1.86%. Both hyperglycemic and normoglycemic measurements obtained in the patient group were found to be significantly lower than those in the control group (p=0.001 and p=0.006) (Table 2, Figure 2).

Discussion

The current study shows that the FMD value in the hyperglycemic period in patients with DM is significantly lower than that the healthy control group, and a significant improvement was achieved immediately after blood glucose-level regulation, however normoglisemic FMD values were still significantly lower than healthy volunteers. Decreased endothelium-dependent vascular

Table 1. Comparison of the main characteristics of the patient-control group

	Patient group (n=44)	Control group (n=20)	p-value
Age (year) (mean ± SD)	54.9±13.6	52.6±8.6	0.52
Female gender [% (n)]	54.5 (24)	50 (10)	0.736
BMI (kg/m^2) (mean ± SD)	30.5±6.25	26.4±3.3	0.001*
Heart rate (beat/minute) (mean ± SD)	83.7±10.3	73.2±5.04	0.001*
NYHA I [% (n)]	59.1 (26)	100 (20)	0.001*
NYHA II [% (n)]	40.9 (18)	0 (0)	
LVEF (%) (mean ± SD)	60.9±4.5	62.3±3	0.376
Hypertension [% (n)]	63.6 (28)	0	
Hyperlipidemia [% (n)]	38.6 (17)	0	
CAD [% (n)]	13.6 (6)	0	
CRF [% (n)]	13.6 (6)	0	
CVE [% (n)]	6.8 (3)	0	
HbA1c (%) (mean ± SD)	11.04±2.31	NA	
Smoking [% (n)]	79.5 (35)	55 (11)	0.043*
Insulin usage [% (n)]	61.4 (27)	NA	
ACEI/ARB [% (n)]	54.5 (24)		
OAD [% (n)]	52.3 (23)	NA	
Beta Blocker [% (n)]	34.1 (15)		
Statin [% (n)]	29.5 (13)		
ASA [% (n)]	25 (11)		
CCB [% (n)]	9.1 (4)		
Nitrate [% (n)]	6.8 (3)		

BMI: Body mass index, CAD: Coronary artery disease, CRF: Chronic renal failure, CVE: Cerebrovascular event, HbA1c: Hemoglobin A1c

Table 2. FMD comparison (before infusion, after infusion, control group)

	Before insulin infusion	After insulin infusion	Control group	p1	p2	p3
Brachial artery basal diameter (mm) (mean ± SD)	34.86±5.43	34.70±5.74	36.25±3.93	0.57	0.08	0.07
Brachial artery diameter after hyperemia (mm) (mean ± SD)	36.98±5.71	38.41±6.02	40.9±4.44	0.001*	0.15	0.13
FMD (%) (mean ± SD)	6.13±3.11	10.89±3.65	12.84±1.86	0.001*	0.001*	0.006*

p1: Before and after insulin infusion, p2: Before insulin infusion and control group, p3: After insulin infusion and control group, SD: Standard deviation, FMD: Flow mediated vasodilation

response in patients with type 2 DM is one of the earliest markers of atherosclerosis[17-19]. It has been shown that FMD is an independent predictor of CV events in patients with stable CAD, heart failure, and peripheral artery disease. Additionally, FMD was correlated with the Framingham risk score in asymptomatic individuals who underwent community screening[20-22]. Hyperglycemia in patients with diabetes could cause endothelial dysfunction by causing increased secretion of biochemicals such as AGEs, ROS, RNS, 3-deoxyglucosone, amadori products, diacylglycerol and methylglyoxal[23-26]. Tan et al.[27] evaluated FMD in 170 type 2 patients with DM and 86 healthy control groups and found that FMD was worse in patients with DM than in the healthy control and these results were consistent with AGE levels. They also showed that the fasting blood glucose values of the patient group were higher than those of the healthy group as expected, but this and many similar studies did not consider the blood glucose levels of the patients during FMD measurement. On the other hand current study showed that FMD is impaired in patients with diabetes, regardless of their glycemic status however blood glucose levels during FMD measurement affected the results and endothelial functions were worse in the hyperglycemic period than in the normoglycemic periods.

Previous studies with a small patient population shown that acute hyperglycemia causes endothelial dysfunction in healthy and diabetic persons[28-31]. Kawano et al.[32] showed a decrease in FMD in 17 normal glucose tolerance (NGT), 24 impaired glucose tolerance (IGT), 17 patients with DM at the 1st hour after the oral glucose tolerance test (OGTT). FMD in the group with NGT and IGT was increased at the 2nd hour after OGTT. However, FMD was still decreased in the DM group[32]. In contrast to the acute glycemic stress created in the OGTT, the current study evaluates the effect of relatively acute (within 3 days) regulation of chronic hyperglycemia in patients with diabetes on endothelial functions in order to more accurately represent real life. In parallel to Kawano et al.'s[32] study, significant changes were observed in FMD values in the normo- and hyperglycemic periods in this study.

Insulin hormone is secreted in response to glucose and macronutrient intake and suppresses ROS production and activation of inflammatory mechanisms. Thus, insulin is thought to have anti-inflammatory effects, while glucose has pro-inflammatory. Insulin induces endothelium-derived NO-mediated vasorelaxation in isolated rat skeletal muscle arteries. Insulin has a stimulating effect on basal blood flow[33]. It is difficult to evaluate whether the improvement in endothelial functions between the hyper- and normoglycemic periods is solely due to glycemic control or the insulin infusion in the current study. However, in a study with Goto-Kakizaki mice

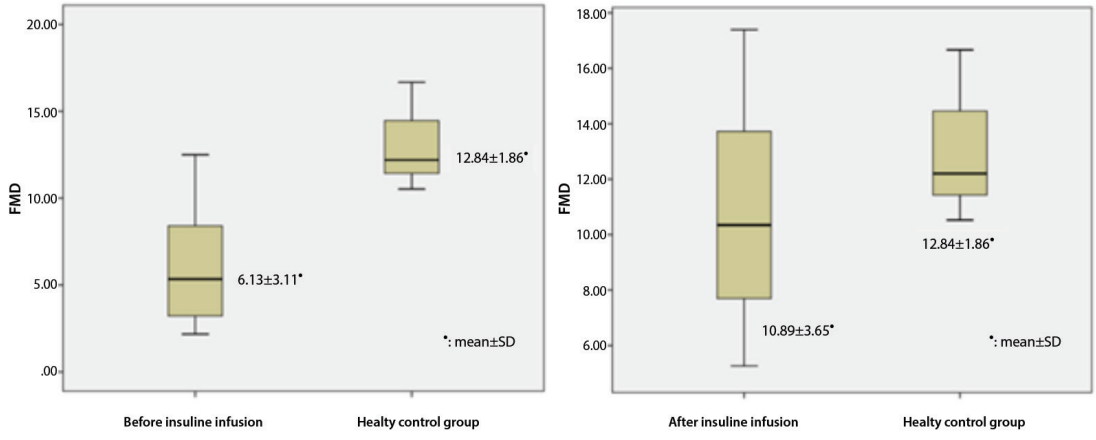

Figure 2. Flow-mediated dilatation of the healthy control group and patient group before and after insulin infusion
FMD: Flow-mediated vasodilation, SD: Standard deviation

(non-obese diabetic mouse model), monocyte adhesion was increased, which is an early step of atherosclerosis, in the aortic endothelium after glucose infusion, while after the administration of octreotide (which inhibits insulin secretion) adhesion response did not change[34,35]. This suggests that insulin levels are unimportant in the increased endothelial monocyte adhesion during hyperglisemia. According to those studies, changes in the endothelial functions in this study should be due to the control of hyperglisemia not the insulin infusion alone.

In the hyperglycemic period, endothelial dysfunction and increased atherosclerosis markers such as impaired FMD as shown in the current study or increased monocyte adhesion shown in other studies suggest that hyperglycemia may be associated with poor outcomes. In an observational clinical study, an inverse relationship was found between LVEF values measured at hospital discharge and glucose levels at admission in 500 patients who had first anterior myocardial infarction and underwent reperfusion therapy, and this results continued even after correction was performed for HbA1c levels. Such studies support the hypothesis that hyperglycemia should not only be the only risk marker but also it should be a risk factor associated with poor outcomes[36].

The results of this study support the hypothesis that hyperglycemia impairs endothelial functions, in line with other studies in the literature. However, the present study was also unique for showing that acute control of glucose levels could improve decreased endothelial functions.

Study Limitations

The main limitation of the study was the lack of long-term follow-up of the patients in terms of clinical outcomes. Another limitation was the small patient population. The duration of diabetes of the patients is not homogeneous, although it should not have a significant effect on results because two different conditions (normo and hyperglisemic conditions) of every patient were compared between each other.

Conclusion

In type 2 patients with DM, endothelial functions are worse during hyperglycemia compared to the normoglycemic period. Endothelial functions are worse in both the normo- and hyperglycemic periods in patients with diabetes compared in the healthy control group. This suggests that patients with diabetes should be at additional CV risk during acute hyperglycemic periods.

Ethics

Ethics Committee Approval: Ege University Faculty of Medicine Clinical Research Ethics Committee approval was obtained for the study (decision no: 18-6/43).

Informed Consent: Written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mammadov G, Şimşek E, Yıldırım Şimşir I, Concept: Şimşek E, Soydaş Çınar C, Design: Mammadov G, Yıldırım Şimşir I, Data Collection and/or Processing: Mammadov G, Yıldırım Şimşir I, Analysis of Interpretation: Şimşek E, Yağmur B, Literature Search: Mammadov G, Soydaş Çınar C, Writing: Mammadov G.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: No financial resources have been used for this article.

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E Journal of Cardiovascular Medicine
EJCM ejcvsmed.com

Research Article

137

EJCM 2022;10(3):137-143

DOI: 10.32596/ejcm.galenos.2022.2022-08-045

The Association Between Coronary Instent Restenosis and Eosinophil/Monocyte Ratio

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Abstract

Objectives: Although the incidence of coronary artery restenosis has decreased with the use of novel oral antiplatelet drugs and the use of new generation drug-eluting stents, it is a major problem that we encounter in daily practice due to the prolonged human lifespan and increasing numbers of percutaneous interventions. In this study, we investigated the association between instent restenosis, which is also an inflammatory process, and eosinophil/monocyte ratio (EMR), which is one of the new inflammatory indexes.

Materials and Methods: A total of 207 patients admitted with the acute coronary syndrome and underwent coronary angiography between June 2020 and June 2022 were analyzed retrospectively. The patients were divided into three groups: those with stent implantation and culprit lesion with stent restenosis (Group A), those with stent implantation and culprit lesion with the non-stent lesion (Group B), and patients without a stent and no critical lesion (Group C). Demographic characteristics, clinical presentations, comorbidities, hematological and biochemical parameters of the patients were evaluated.

Results: EMR was found to be statistically significantly lower in Group A compared in Group B (0.16±0.10 vs 0.40±0.9, p=0.041). There was also a statistically significant difference between the groups in terms of neutrophil (p=0.046) and high-density lipoprotein levels (p=0.010). Additionally, glucose levels at the time of admission were found to be significantly higher in Group A than in Group B (196.53±99.04 vs 159.57±84.31, p=0.048) and Group C (196.53±99.04 vs 140.41±89.66, p=0.001). There was no difference in terms of the levels of white blood cells, lymphocyte, monocyte, eosinophil, platelet, hemoglobin, total cholesterol, low-density lipoprotein, and triglyceride.

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Received: 24.08.2022 **Accepted:** 30.08.2022

Cite this article as: Şabanoğlu C, Polat E, Yüce Eİ. The Association Between Coronary Instent Restenosis and Eosinophil/Monocyte Ratio. EJCM 2022;10(3):137-143.
DOI: 10.32596/ejcm.galenos.2022.2022-08-045

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Conclusion: Since a significant relationship has been shown between the instent restenosis of the culprit lesion and low EMR, EMR can be used as a simple tool to aid in the diagnosis of suspected restenosis in patients with stent implantation presenting with the acute coronary syndrome.

Keywords: Instent restenosis, eosinophil/monocyte ratio, EMR, acute coronary syndrome, admission blood glucose

Introduction

Coronary instent restenosis (ISR) is defined as the narrowing of the implanted stent in the lesion in the epicardial coronary artery[1]. Currently, the use of bare metal stents has been replaced by drug-eluting stents, and the development of a new generation drug-eluting stents, the incidence of ISR has decreased, but its incidence is still between 5 and 30%[1-3].

In the pathophysiology of ISR, elastic recoil in the early period, arterial remodeling, and neointimal hyperplasia appear to play a role in the long term. Additionally, incomplete coverage of the lesion, stent implantation in incorrect localization, stent fracture, and allergic reaction to nickel and molybdenum may also cause ISR[3-8].

As to pathophysiological mechanisms, arterial remodeling is one of the late-period mechanisms of ISR and is a negative arterial remodeling seen after balloon angioplasty. Although the exact mechanism of arterial negative remodeling is not known, there is partial improvement in this negative deformation after stent implantation[4,5].

Another mechanism involved in the formation of ISR is neointimal hyperplasia. There is mechanical structural destruction of the endothelium due to trauma caused by balloon inflation and trauma during stent implantation[4,5]. This destruction induces platelet adhesion, platelet activation, and cytokine release. The cytokine release stimulates the migration of smooth muscle cells to the intima and neointimal hyperplasia begins. The neointimal hyperplasia causes the late ISR formation in the long term[4,5].

A mononuclear cell-rich inflammation was also observed during mechanical damage to the endothelium during stent implantation. It is thought that the cells that create the inflammatory response here play a part in instent restenosis[4,5].

Considering the research on inflammatory markers in ISR, in which the inflammatory process also plays a role in its formation, a significant relationship was observed between the neutrophil/lymphocyte ratio and ISR[9]. Similarly, a significant correlation was observed between C-reactive protein (CRP) and stent restenosis[10].

Eosinophil/monocyte ratio (EMR) is one of the inflammatory markers that has been increasingly used. It has been suggested to be associated with ischemic cerebral events, decompensated heart failure, and acute ischemic coronary disease, prognosis, and survey[11-13]. There are very few studies investigating the association between EMR and ISR. In this study, we evaluated the relationship of EMR with ISR in patients with the acute coronary syndrome.

Materials and Methods

Study Design and Settings

The study was designed retrospectively. Patients who underwent coronary angiography with acute coronary syndrome between June 2020 and June 2022 were included. The ethics committee approval of this study was obtained from Gaziantep İslam Science and Technology University Coordinatorship of Local Ethics Committee (date: 07.06.2022, approval no: 125.17.14). In the study, data were obtained from hospital system records, cardiology clinical records, coronary angiography, and archive records.

Selection of the Participants

Three different groups were defined in this study. The first group (Group A), was the patients with acute coronary syndrome whose culprit lesion was instent restenosis, the second group (Group B) comprised those with the acute coronary syndrome who had a stent but whose culprit lesion was not instent restenosis, and the third group (Group C) was the patients with the acute coronary syndrome who did not have a significant lesion in their coronary arteries. The sample size was calculated using G-Power 3.1 and it was observed that a minimum of 69 patients should be included in each group. The patients were examined from 2022 to 2020, and the examination was terminated when there were 69 consecutive patients. Patients having both stent restenosis and critical lesions in the non-stent implanted vessels were excluded from the study. Additionally, patients with high CRP and erythrocyte sedimentation rate levels and those given antibiotics during hospitalization were excluded from the study.

Measurements and Outcomes

Instent restenosis was defined as angiographically ≥50% of stenosis within the stent implanted segment or inside a 5-mm segment distal or proximal to the stent[14]. Following the guideline, patients were grouped as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP)[15].

The complete blood count and the admission blood glucose were taken in the emergency room. The lipid profiles of the patients at hospitalization were examined.

Statistical Analysis

The SPSS 25.0 package program was used for data analysis in this study. Descriptive data on the demographic characteristics of the participants are given in the frequency tables. When the data of the study were analyzed in terms of normality assumptions, Kolmogorov-Smirnov values were determined as $p>0.05$. Additionally, the ANOVA test, one of the parametric tests, was applied to determine whether there was a significant difference between the laboratory data and the groups. In case of a significant difference between the groups, the LSD test, one of the post-hoc tests was used to determine between which groups the significance was. $P<0.05$ was considered statistically significant.

Results

The study included 207 patients, with 69 patients in each group. While the male gender dominated the study in Group A (n=46, 66.7%), and Group B (n=50, 72.5%), it was observed that females were more common in Group C (n=39, 58.5%) (Table 1). As a clinical presentation, NSTEMI was observed more frequently in Group A (n=30, 43.5%), UAP in Group B (n=34, 49.3%) and NSTEMI in Group C (n=44, 63.8%) (Table 1).

The prevalence of diabetes mellitus was 47.8% (n=33) in Group A, 31.9% (n=22) in Group B, and 23.2% (n=16) in Group C. Hypertension was present in 76.8% (n=53) patients in Group A, 91.3% (n=63) patients in Group B, and 42% (n=29) patients in Group C. The frequency of hyperlipidemia was 43.5% (n=30) in Group A, 55.1% (n=38) in Group B, and 14.5% (n=10) in Group C (Table 1).

As laboratory parameters, there was a statistically significant difference between the groups in terms of EMR (p=0.048). The Post hoc test revealed a statistically significant difference between Group A and Group B (p=0.041) (Table 2).

There was also a statistically significant difference in terms of blood glucose values at the time of admission (p=0.001). After the Post hoc test was performed, a statistically significant difference was shown between Group A and Group B (p=0.048), and between Group A and Group C (p=0.001) (Table 2).

There was a statistically significant difference between the groups in terms of neutrophil values (p=0.046). According to the Post hoc test, a statistically significant difference was observed between Group A and Group C (p=0.047) (Table 2).

Table 1. Distribution of demographic and clinical data of the patients

		ISR + Group A		Had a stent without ISR Group B		Do not have a significant lesion Group C	
Variable		**n**	**%**	**n**	**%**	**n**	**%**
Gender	Male	46	66.7	50	72.5	30	43.5
	Female	23	33.3	19	27.5	39	58.5
Clinical presentation	STEMI	19	27.5	14	20.3	25	36.2
	NSTEMI	30	43.5	21	30.4	44	63.8
	UAP	20	29.0	34	49.3	0	0.0
DM	No	36	52.2	47	68.1	53	76.8
	Yes	33	47.8	22	31.9	16	23.2
HT	No	16	23.2	6	8.7	40	58.0
	Yes	53	76.8	63	91.3	29	42.0
HL	No	39	56.5	31	44.9	59	85.5
	Yes	30	43.5	38	55.1	10	14.5
CAD	No	0	0.0	4	5.8	69	100.0
		69	100.0	65	94.2	0	0.0

Group A; was the patients with acute coronary syndrome whose culprit lesion was instent restenosis
Group B; was the patients with acute coronary syndrome who had a stent but whose culprit lesion was not instent restenosis
Group C; was the patients with acute coronary syndrome who do not have a significant lesion in their coronary arteries
STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction, UAP: Unstable angina pectoris, DM: Diabetes Mellitus, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease

Table 2. Comparison of laboratory findings by groups

	ISR + Group A Mean ± SD n=69	Had a stent without ISR Group B Mean ± SD n=69	C- Do not have a significant lesion Group C Mean ± SD n=69	p	Post-hoc
EMR	0.16±0.10	0.40±0.9	0.32±0.34	**0.048**	1-2
Glucose (mg/dL)	196.53±99.04	159.57±84.31	140.41±89.66	**0.001**	1-2.3
WBC (10^9/L)	10.22±3.26	9.74±3.19	8.98±2.92	**0.068**	
Lymphocyte (10^9/L)	2.21±1.36	2.4±1.44	2.03±0.88	**0.223**	
Monocyte (10^9/L)	0.66±0.28	0.65±0.31	0.66±0.30	**0.990**	
Eosinophil (10^9/L)	0.15±0.14	0.22±0.37	0.17±0.15	**0.284**	
Neutrophil (10^9/L)	7.14±2.88	6.32±2.24	6.08±2.71	**0.046**	1-3
Platelet (10^3u/L)	274.87±84.85	264.57±84.16	260.04±71.19	**0.540**	
Hemoglobin (g/dL)	13.62±1.88	13.91±2.01	13.94±1.86	**0.556**	
Total cholesterol (mg/dL)	185.88±55.64	184.08±49.38	193.07±39.92	**0.520**	
LDL (mg/dL)	117.51±45.36	112.91±41.49	113.68±35.98	**0.780**	
Triglyceride (mg/dL)	137.82±88.83	166.67±102.44	168.37±99.75	**0.119**	
HDL (mg/dL)	41.54±8.44	40.06±10.35	51.26±37.91	**0.010**	3-1.2

ANOVA test, post-hoc: LSD test applied. p<0.05 statistically significant.
EMR: Eosinophil/monocyte ratio, WBC: White blood cell, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

High-density lipoprotein (HDL) value showed a statistically significant difference between the groups (p=0.010). According to the post-hoc test, a statistically significant difference was observed between Group C and Group A (p=0.014) and between Group C and Group B (p=0.039) (Table 2).

Among the groups, white blood cell (WBC) (p=0.068), lymphocyte (p=0.223), monocyte (p=0.990), eosinophil (p=0.284), platelet (p=0.540), hemoglobin (p=0.556), total cholesterol (p=0.520), low-density lipoprotein (LDL) (p=0.780), triglyceride (p=0.119) values did not show a statistically significant differences (Table 2).

Discussion

In our study, one of the main findings was that the EMR was found to be significantly lower in patients with previous stent implantation presenting acute coronary syndrome, with the culprit lesion stent restenosis, compared with those without stent restenosis. Additionally, the admission blood glucose values of the patients were found to be significantly higher in those with stent restenosis as the culprit lesion. The neutrophil count was found to be higher in the patients with stent restenosis than in patients without critical lesions. In patients without critical lesions, HDL values were found to be higher than in those with critical lesions.

Although the stent restenosis rates have decreased with the use of new generation drug-eluting stents and new oral antiplatelets, it is still a major problem in daily practice. Although in the previous studies, ISR was mostly presented with non-MI conditions, the frequency of presentation with acute MI conditions has increased in recent studies[16-19]. Since patients with stable angina pectoris were excluded from our study, we can only state a frequency among acute coronary syndrome groups. As a result, NSTEMI was seen the most frequent in the group with ISR. Our findings are consistent with a recent ISR and acute coronary syndrome study[19].

Inflammation is thought to play a part in the formation of stent restenosis[4]. There are many studies on neutrophils, lymphocytes, and monocytes that play a role in this inflammation. The number of studies on eosinophils, which is a cell whose role in inflammation is unclear, is few. It is thought that eosinophils may cause acute coronary syndrome by releasing proinflammatory and proanticoagulant proteins[20]. Additionally, it has been suggested that eosinophil count and eosinophil/lymphocyte ratio (ELR) are inflammatory markers that can be used in risk assessment in coronary artery disease[21]. Bilik et al.[22] reported that ELR was found to be significantly higher in patients with stent restenosis in their study.

It is thought that monocytes cause stent restenosis via macrophages[23]. It is thought that macrophages produce foam cells from oxidized LDL and the formed foam cells cause inflammatory factor release and lead to stent restenosis[24]. It has been reported that high monocyte counts play a role in plaque progression, and a high ratio of monocyte to HDL (MHR) can be used as an indicator of inflammation[25,26]. In the study by Chen et al.[27] it was observed that the count of monocytes and ratio of monocytes to HDL (MHR) in patients with stent restenosis was higher than in those without stent restenosis.

EMR is a recently used inflammatory marker obtained by dividing the eosinophils by the monocytes. It has been observed that a low EMR value is associated with poor prognosis in acute ischemic stroke events[11]. When we reviewed the cardiac studies on EMR, Chen et al.[12] showed that low EMR is associated with poor prognosis in patients with decompensated heart failure. Additionally, Deng et al.[13] showed that patients with STEMI with low EMR had poor prognosis and mortality in the 1-month and long term. In our study, the EMR of patients presenting with acute coronary syndrome due to stent restenosis in patients with had a stent was found to be significantly lower than compared the other groups.

Studies have shown that neutrophil, one of the cells involved in inflammation, also increase coronary ischemia and infarction, especially in post-intervention reperfusion[28,29]. In our study, the neutrophil count was found to be significantly higher in patients with instent

restenosis than in patients without significant coronary stenosis.

It has been shown that stress-induced hyperglycemia increases cardiovascular events in both diabetic and non-diabetic patients in the short and long term and increases major adverse cardiovascular and cerebrovascular events in patients with STEMI[30,31]. It has been reported that the high-admission glucose level at the time of admission is associated with in-hospital adverse events and length of stay in the hospital in NSTEMI[32]. When we examine the glucose studies for stent restenosis, researchers have shown that HbA1c and fasting glucose are among the values predicting stent restenosis[33]. In our study, the admission blood glucose level was significantly different. In patients with ISR, admission blood glucose was found to be higher than the group without the stent with the culprit lesion and the group without coronary lesion. Since our study was retrospective and patients presenting with acute coronary syndrome were not routinely tested for HbA1c, we could not comment on fasting glucose and HbA1c.

One of the risk factors for coronary artery disease is dyslipidemia. The relationship between high LDL levels and low HDL levels and coronary artery disease is known[34]. Yanık et al.[35], when examining patients with and without stent restenosis, showed that there is a relationship between low HDL cholesterol and stent restenosis. In our study, when ISR was compared with patients without significant coronary lesions, low HDL was observed in the ISR group.

Study Limitations

Our study has several limitations. First, the study was designed as retrospective. Another limitation is whether the previously implanted stent was drug-eluting or bare metal in patients stents. Additionally, it is not known whether the patients had a history of allergic disease or an infectious disease at the time of stenting. Finally, it is recommended to use of optical coherence tomography and intravascular ultrasound for stent restenosis and typing, but only coronary angiography has been used for stent restenosis because to the lack of these devices.

Conclusion

In our study, a low EMR was observed in an acute coronary syndrome patient who had a stent, in those with instent restenosis of the culprit lesion. The high glucose level at the time of presentation accompanying these findings is proof of how closely stent restenosis is associated with inflammation and impaired metabolic process.

Ethics

Ethics Committee Approval: Ethics committee approval of this study was obtained from Gaziantep İslam Science and Technology University Coordinatorship of Local Ethics Committee (date: 07.06.2022, decision no: 125.17.14)

Informed Consent: No written informed consent form was obtained from patients because the study was retrospective.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: Şabanoğlu C, Polat E, Design: Şabanoğlu C, Polat E, Yüce Eİ, Data Collection and/or Processing: Polat E, Yüce Eİ, Analysis and/or Interpretation: Şabanoğlu C, Polat E. Literature Search: Şabanoğlu C, Polat E, Yüce Eİ, Writing: Şabanoğlu C, Polat E, Yüce Eİ.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

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Case Report

E Journal of Cardiovascular Medicine

EJCM 2022;10(3):144-147

DOI: 10.32596/ejcm.galenos.2022.2022-07-042

Successful Surgical Management of Aortopulmonary Window and Supravalvular and Valvular Aortic Stenosis in Five Years Old Child

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Abstract

The aortopulmonary window (APW) is a rare congenital abnormality referring to communication between the main pulmonary artery and ascending aorta. To avoid irreversible pulmonary vascular disease, this type of congenital abnormalities should be repaired whenever it is diagnosed. The recommended timing for the surgery, in common practice, is three months of age. In older patients, the outcome is determined by pulmonary vascular resistance at the time of surgical repair. In this report, we present our five years old patient who underwent a valvular and supravalvular aortic surgery and concomitantly closure of APW successfully.

Keywords: Aortopulmonary window, supravalvular aortic stenosis, aortic valvular stenosis, pulmonary hypertension

Introduction

The aortopulmonary window is a rare cardiac anomaly representing 0.2%-0.6% of all congenital heart diseases[1]. Since these types of congenital abnormalities occur between the ascending aorta and the common pulmonary artery, they may cause pulmonary arterial hypertension in a short while if they are not closed by surgical or transcatheter techniques[2,3]. The pathophysiology and clinical manifestations of APW in general are quite similar to those of patients with patent ductus arteriosus. Even if

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Received: 26.07.2022 **Accepted:** 20.08.2022

Cite this article as: Dayanır OB, Oto Ö. Successful Surgical Management of Aortopulmonary Window and Supravalvular and Valvular Aortic Stenosis in Five Years Old Child. EJCM 2022;10(3):144-147.

DOI: 10.32596/ejcm.galenos.2022.2022-07-042

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arterial pulmonary hypertension is manifests and elevated pulmonary vascular resistance has occurred, the closure of APW has still been recommended with acceptable long-term results[4]. Since the patient had been closely followed up with severe valvular and supravalvular aortic stenosis, the timing of the operation was delayed due to the possible need of mechanical aortic valve replacement (AVR). Although pre-operative computed tomography (CT) angiography showed an APW, it was not confirmed at any pre-op echocardiography. Here we report a case of successfully surgical closure of APW concomitantly with aortic root and supravalvular aortic stenosis enlargement and mechanical AVR in a five-year old boy.

Case Report

A five-year-old male child with echocardiographic diagnosis of supravalvular and valvular aortic stenosis at birth was admitted to the hospital with mild short of breath on exertion. CT angiography revealed enlargement of the pulmonary artery at the conus level and a large APW and increased diameters of pulmonary veins with enlarged left atrium and left ventricle enlarged significantly (Figure 1). Pre-operative echocardiography showed a supravalvular aortic stenosis with a peak gradient of 65 mmHg, first-degree aortic regurgitation, mild mitral regurgitation and 50 mmHg peak gradient of valvular aortic stenosis, with no confirmation of APW.

The patient underwent aortic open heart surgery with standard technique. When vertical standard pericardiotomy was performed, a large APW was observed when (Figure 2). At this very moment, inoperability was discussed due to the large APW and pulmonary artery. For a scientific decision making, pulmonary artery pressure was measured directly with a diagnostic line. Pulmonary arterial peak pressure was measured as 55 mgHg while simultaneous arterial pressure was 105 mmHg. An aortotomy was performed and selective antegrade cold blood cardioplegia was applied to the right and left coronary ostium. On these measurements, the patient was accepted as being operable, and the operation was carried out. After the cross-clamping of the aorta, bicaval cannulation and dual venting was applied (one to left atrium via patent foramen ovale, a second one to pulmonary artery) to provide a completely clear, bloodless exposure. Selective coronary antegrade cold blood cardioplegia was applied for myocardial protection. The APW, which measured approximately 2.0-2.5 cm, was observed between the ascending aorta and the pulmonary artery. An oblique aortotomy extended into the non-coronary sinus of the valsalva to the aortic annulus to perform Nick's aortic root enlargement with a bovine pericardial patch. A 19 size Medtronic mechanical bileaflet valve was replaced after the root enlargement. Before the enlargement of the supravalvular segment of the aorta, a separate round pericardial patch was tailored to

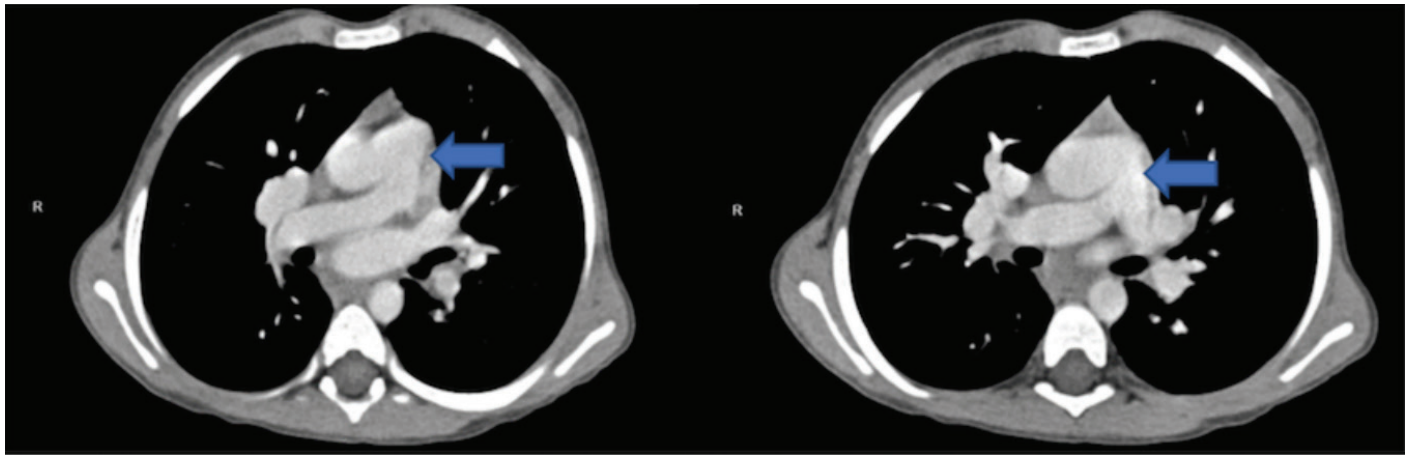

Figure 1. Aortopulmonary window CT angiography image from two different sections marked with a blue arrow
CT: Computed tomography

2 cm diameter and the APW was closed with 5-0 prolene and the continuous running suture technique.

The patient was separated from the extracorporeal circulation without positive inotropic support, and was followed an uneventful post-operative course with extubation at the 4th hour postoperatively.

Post-operative echocardiography confirmed no residual shunt and no supravalvular gradient with normal mechanical aortic valve functions and surprisingly normal pulmonary artery pressure. The patient was discharged from the hospital on the fourth post-operative day with no symptoms.

Discussion

Aortopulmonary window

The aortopulmonary window is a developmental anomaly of the conotruncal septum and has an incidence of 0.2%-0.6% among all congenital heart diseases. It is an extremely rare cardiac[1,5]. Should be repaired when diagnosed, preferably before three months of age. Survival in APW depends on the defect size and the pulmonary arterial hypertension. The ideal timing for repair of APW is before the development of irreversible pulmonary arterial hypertension[1]. Cases where APW is not treated at the ideal time may result in heart failure and death at an advanced age. Early closure is often the best treatment to ensure patient survival[6]. In this case, APW was not noticed and could not be treated at the ideal time, although the patient was able to survive until late childhood. Postoperative management of pulmonary hypertension and its long-term course are the most important factors affecting the decision to surgical treatment in patients past infancy[1]. Other literature has demonstrated favorable early and long-term outcomes after surgical correction, regardless of age or pulmonary vascular resistance[2,4]. We decided to repair the defect based on preoperative pulmonary artery pressure measurement. The surgery was uneventful and the post-operative recovery was successful. In the surgical treatment of multiple anomalies, APW closure is important because it reduces pulmonary artery pressure. The aortic stenosis and APW observed in our patient are examples of this situation.

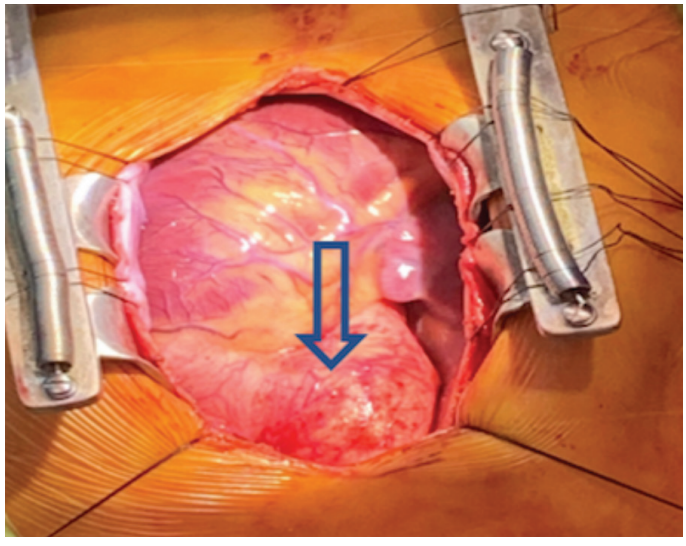

Figure 2. Blue arrow points to the connection between the aorta and the pulmonary artery

Our report strongly supports the need for surgical repair as soon as the diagnosis is made, regardless of the patient's age. Additionally, APW repair contributed positively to the postoperative course in the patient who required surgery due to aortic stenosis.

The reason for lack of confirmation of APW at pre-operative echocardiography seems to be high turbulence due to supravalvular aortic stenosis, which possibly shadowed the large APW flow.

Conclusion

The aortopulmonary window can be treated surgically in early years of childhood. Surgical risk and indications of operation need to be carefully considered regardless of the patient's age. Pulmonary hypertension is the most important parameter affecting the operation decision, postoperative course, and long-term results. Accompanying aortic stenosis with APW may be misleading on echocardiographic examination. Therefore, CT angiography is a useful method in the diagnosis phase. Additionally, APW repair contributed positively to the

postoperative course in the patient who required surgery due to aortic stenosis.

Ethics

Informed Consent: The informed consent was obtained for the article.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.B.D., K.Y., Ş.P., M.K., Ö.O., Design: O.B.D., K.Y., Ş.P., M.K., Ö.O., Data Collection and/or Processing: O.B.D., K.Y., Ş.P., M.K., Ö.O., Analysis and/or Interpretation: O.B.D., K.Y., Ş.P., M.K., Ö.O., Literature Search: O.B.D., K.Y., Ş.P., M.K., Ö.O., Writing: O.B.D., K.Y., Ş.P., M.K., Ö.O.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

E Journal of Cardiovascular Medicine

EJCM 2022;10(3):148-152

DOI: 10.32596/ejcm.galenos.2022.2022-07-043

Benign Outcomes in Two Heart Transplant Patients with COVID-19 Pneumonia

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Abstract

We report here two consecutive coronavirus disease-2019 (COVID-19) pneumonia in our post-heart transplant patients 13 years and 15 years after the transplantation during the pandemic. COVID-19 pneumonia were confirmed clinically and by thorax computed tomography in both of the cases. Due to severe symptoms and the high-risk condition of the patients, they were immediately admitted to the hospital and standard COVID-19 treatment protocol with oral favipravir and low molecular weight heparin were applied to both patients. None of them was needed to transfer to intensive care unit and responded immediately to medical treatment and observed in regular COVID-19 ward. No alterations in their immunosuppressive therapy was applied during their stay in the hospital and none of them had cytokine storm during their stay in the hospital. Echocardiography of both patients showed normal left and right ventricular functions with no myocardial depression or sign of pulmonary hypertension. Patients were discharged at fifth and tenth days of diagnosis, respectively, with COVID-19 negative polymerase chain reaction and asymptomatic status.

Keywords: Heart transplant, COVID-19 pneumonia, immunosuppression

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Received: 26.06.2022 **Accepted:** 20.08.2022

***This article was presented in its first form at the 17th International Congress of Update in Cardiology and Cardiovascular Surgery.**

Cite this article as: Dayanır OB, Oto Ö. Benign Outcomes in Two Heart Transplant Patients with COVID-19 Pneumonia. EJCM 2022;10(3):148-152.

DOI: 10.32596/ejcm.galenos.2022.2022-07-043

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Introduction

We report here two consecutive coronavirus disease-2019 (COVID-19) pneumonia in our post-heart transplant patients 13 years and 15 years after the transplantation during the pandemic. COVID-19 pneumonia was confirmed clinically and by thorax computed tomography (CT) in both the cases. Because of severe symptoms and the high-risk condition of the patients, they were immediately admitted to the hospital and the standard COVID-19 treatment protocol with oral favipravir and low-molecular-weight heparin were applied to both patients. None of them needed to be transferred to an intensive care unit and all responded immediately to medical treatment and were observed in regular COVID-19 ward. No alterations in their immunosuppressive therapy were applied during their stay in the hospital and none of them had a cytokine storm during their stay in the hospital. Echocardiography (ECHO) of both patients showed normal left and right ventricular functions with no myocardial depression or sign of pulmonary hypertension. Patients were discharged in the fifth and tenth days of diagnosis, respectively, with COVID-19-negative polymerase chain reaction (PCR) and asymptomatic status.

Case Reports

Case 1

A 66-year-old female patient (L.G.) who had orthotopic heart transplantation due to ischemic heart failure in 2009 was admitted to the hospital with the complaints of sluggish feeling, nausea and tiredness on December 7, 2020, with the suspicion of rejection.

On physical examination, body surface temperature was 36.7 °C, peripheral oxygen saturation was 98%, and respiratory rate was 16 breaths per minute. Routine laboratory tests revealed no abnormality as well as no sign of chronic rejection with left ventricular ejection fraction (LVEF) of 60% in transthoracic ECHO that was performed to evaluate allograft functions.

Cardiac rejection, which could be associated with tiredness and sluggish feeling, was therefore excluded (Table 1).

Despite that, the reverse transcriptase-PCR (RT-PCR) test result of the nasopharyngeal swab sample taken on December 07 for 2019-nCoV was positive. Thorax CT showed subpleural reticular density increases in the middle lobe of the right lung and bilateral lung lower lobes and peripheral ground-glass opacities in the lower lobe of the left lung (Figure 1). The patient was diagnosed with

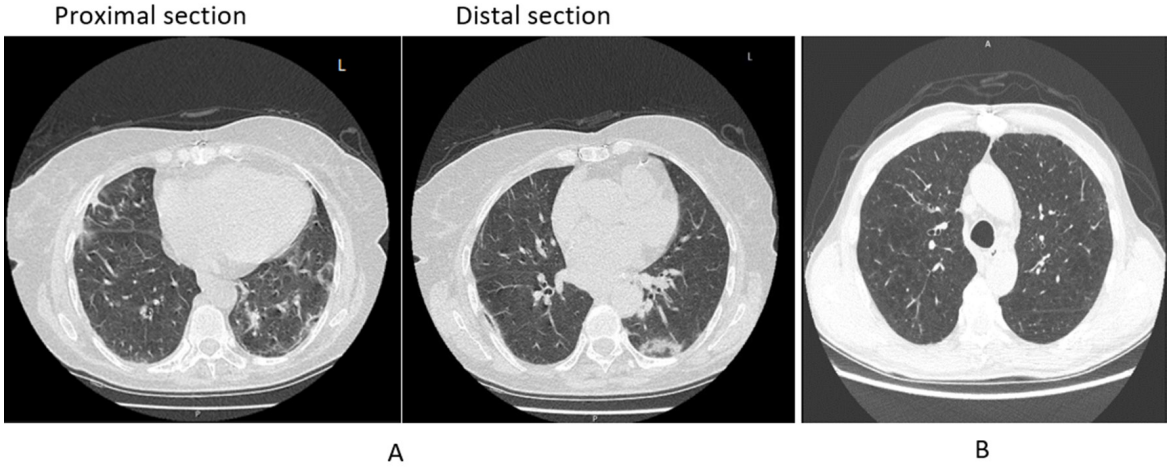

Figure 1. A: Case 1, Two different cross-sectional views of the ground glass areas, especially seen in the left lung, B: Case 2, Emphysema and bronchial enlargement was observed in thorax CT.

CT: Computed tomography

COVID-19 pneumonia by a pneumonologist on call and was immediately transferred to the COVID ward of the same hospital (Dokuz Eylül University Hospital/İzmir, Turkey).

She was already on Tacrolimus 2.5 mg once a day and mycophenolate mofetil 0.5 g twice a day with very strictly controlled Tacrolimus plasma level (12.3 ng/mL) with no additional risk factors like diabetes mellitus, pulmonary hypertension, or heart failure apart from being an New York Heart Association class-0, asymptomatic heart transplant case. Additionally, she was not vaccinated before hospitalization since the corona vaccination program has not started at that time in Turkey.

She was put on favipravir 1600 mg b.d. continued with 600 mg once a day and 4 mg of enoxaparin s.c. once a day for thrombosis prophylaxis as well as supportive vitamin treatment and diet. Since there was been no desaturation, tachypnea, fever, or any other sign of clinical deterioration for five days during her hospital stay, she was considered as convenient for "home follow-up" and was discharged. On the seventh day of her outpatient clinic examination, she has negative RT-PCR test with no complaints of tiredness or sluggish feeling.

Case 2

A 60-year-old male patient (A.S.) who received a heart transplant due to hypertrophic cardiomyopathy in 2009 was admitted to the hospital with complaints of cough, feeling cold and chills on September 28, 2021. On physical examination, body surface temperature was 37 °C, peripheral oxygen saturation was 96%, and respiratory rate was 18 breaths per minute. Routine laboratory tests revealed signs of acute infection with CRP 75.6 mg/L, ferritin 334 ng/mL, LDH 216 U/L, D-Dimer 332 Âµg / mL with no sign of rejection on ECHO with 60% LVEF.

The RT-PCR test result was positive on September 28, 2021, and no specific findings related to COVID-19 pneumonia but chronic emphysema and bronchial enlargement were observed in Thorax CT (Figure 1B).

The patient was already on Tacrolimus 2.5 mg once a day and mycophenolate mofetil 1 g twice a day. Before admission, the last tacrolimus plasma level was found to be 15.54 ng/mL. He had only controlled hypertension with carvedilol 12.5 mg once a day as a risk factor for COVID-19, besides immunosuppressive treatment for heart transplantation.

He had prior regular vaccination with 3 doses of CoronaVac (Sinovac) and the last dose was approximately 2 months before the onset of the symptoms.

The patient, who was considered to have mild pneumonia, was followed up in the Pandemic Service because he was using immunosuppressive therapy. 1600 mg twice daily on the first day and each day 600 mg twice daily for favipravir treatment was initiated. This treatment was applied for five days.

During this period, 60 mg enoxaparin was administered subcutaneously once a day for thrombosis prophylaxis. There was no desaturation, tachypnea, or fever during his hospital stay. The patient, who showed no clinical progression for nine days, was considered suitable for home follow-up and was discharged (Table 2).

Discussion

These cases showed us that heart transplant recipients may have similar clinical presentation and progression to non-transplant patients. Additionally, in these cases, the use of immunosuppression drugs is not an aggravating

Table 1. Laboratory blood test results

LAB	WBC	CPR	Ferritin	LDH	D-Dimer	EF	EKG
Case 1	5x1000/uL	1.1 mg/L	630.8 ng/mL	166 U/L	0.2 ug/mL	60%	Sinus
Case 2	5.29x10³/uL	334 ng/mL	1.1 mg/L	216 U/L	332 ug/mL	60%	Sinus

Leukocytes (WBC) (normal value 4-10.3 x 1000/µL), CRP: C-reactive protein (normal value 0.2-5 mg/L), ferritin 630.8 ng/mL (normal value 11-306.8 ng/mL), LDH: Lactate dehydrogenase 166 U/L (normal value 125-221 U/ L), D-Dimer 0.2 ug/mL (normal value 0-0.55 ug/mL), EF: Ejection fraction, EKG: Electrocardiography

Table 2. Clinical characteristics of heart transplant patients with COVID-19 pneumonia

Clinical information	Explanation	Explanation
Case 1		**Case 2**
Personal information	Female, 66 years old	Male, 60 years old
Complaint	Weakness nausea and fatigue	Cough and chill
Comorbidities	Hypertension	Hypertension
Medical history	MI in 2000 CABG in 2003, heart tx in 2009	HCM in 2006, heart tx in 2007
Immunosupression	Mycophenolate mofetil 2x500 mg, Tacrolimus 1x2.5 mg	Mycophenolate mofetil 2x1000 mg, Tacrolimus 1x5 mg
Physical examination	Fever: 36.7, SatO2: 98, RR: 16	Fever: 7, SatO2: 96, RR: 18
RT-PCR	Nasopharyngeal swab positive	Nasopharyngeal swab positive
Thorax CT	Ground-glass opacities in the lower lobe of the left lung	No specific findings
Treatment	Favirpravir 2x1600 mg first day, after each day 2x600 mg oral, Enoxaparin 1x40 mg for five days	Favirpravir 2x1600 mg first day, after each day 2x600 mg oral, Enoxaparin 1x60 mg for five days

Prognosis: Clinical well-being is expressed as no desaturation, no fever, and no respiratory[2]
COVID-19: Coronavirus disease-2019, RT-PCR: Reverse transcriptase-polymerase chain reaction, CT: Computed tomography

factor for the clinical course. In China, COVID-19 pneumonia was detected in two different heart transplant recipients. These cases may represent of COVID-19 in heart transplant recipients and suggest that presentations and prognosis appear to be similar to those observed in non-transplant patients. But they also associated radiological resolution with clinical well-being and the regression of radiological lesions in the lung was accepted as one of the healing criteria[2]. In this regard, further quantitative criteria are needed as indicators of positive response for the treatment of COVID-19 pneumonia and more epidemiological studies would be useful for associating COVID-19 with organ transplant patients.

The list of heart transplantation patients in Dokuz Eylül University (DEU) between the years of 1998- 2015 can be seen in Table 3.

Conclusion

The resulting studies show that the spectrum of the disease caused by the new type of coronavirus (2019-nCoV, SARS-CoV-2) is variable from the common cold to Severe Acute Respiratory Syndrome (SARS). Advanced age, immunosuppression (transplantation, immunosuppressive drug users), cardiovascular disease, hypertension is among the serious risk factors in COVID-19 pneumonia[3]. In this

Table 3. List of heart transplantation patients in the DEU

Name-surname with initials	Year of transplantation
F. S.	1998
R. T.	1999
C. S.	2000
E. S.	2002
S. D.	2003
O. Ü.	2004
A. Y.	2004
H. Y.	2005
S. G.	2006
H. S.	2006
A. S.	2007
E. G.	2007
H. A. A.	2007
M. A.	2007
N. Y.	2007
F. C.	2007
N. K.	2008
A. D.	2008
S. A.	2008
F. S.	2008
A. S.	2008
L. G.	2009
B. Y.	2009
I. A.	2009
A. G.	2010
S. K.	2010
M. İ.	2011

Table 3. Continued

Name-surname with initials	Year of transplantation
A. S.	2011
M. B.	2011
Z. S.	2012
R. B.	2012
M. Ö.	2013
Y. E.	2015

article, we report a heart transplant recipient we detected with COVID-19 pneumonia.

Immunosuppression in heart transplant patients may be a favorable factor during COVID pneumonia. The absence of potential risks of immunosuppression in our cases seems to be another positive predictive factor. Hypertension and immunosuppression were observed in both cases. However, in the second case, the German vaccine may be effective in a milder course of lung disease. In this article, we emphasized a relatively mild clinical course of COVID pneumonia in heart transplant patients under immunosuppression therapy.

Ethics

Informed Consent: The informed consent was obtained for the article.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.B.D., O.K., Ö.O., Design: O.B.D., O.K., Ö.O., Data Collection and/or Processing: O.B.D., O.K., Ö.O., Analysis and/or Interpretation: O.B.D., O.K., Ö.O., Literature Search: O.B.D., O.K., Ö.O., Writing: O.B.D., O.K., Ö.O.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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