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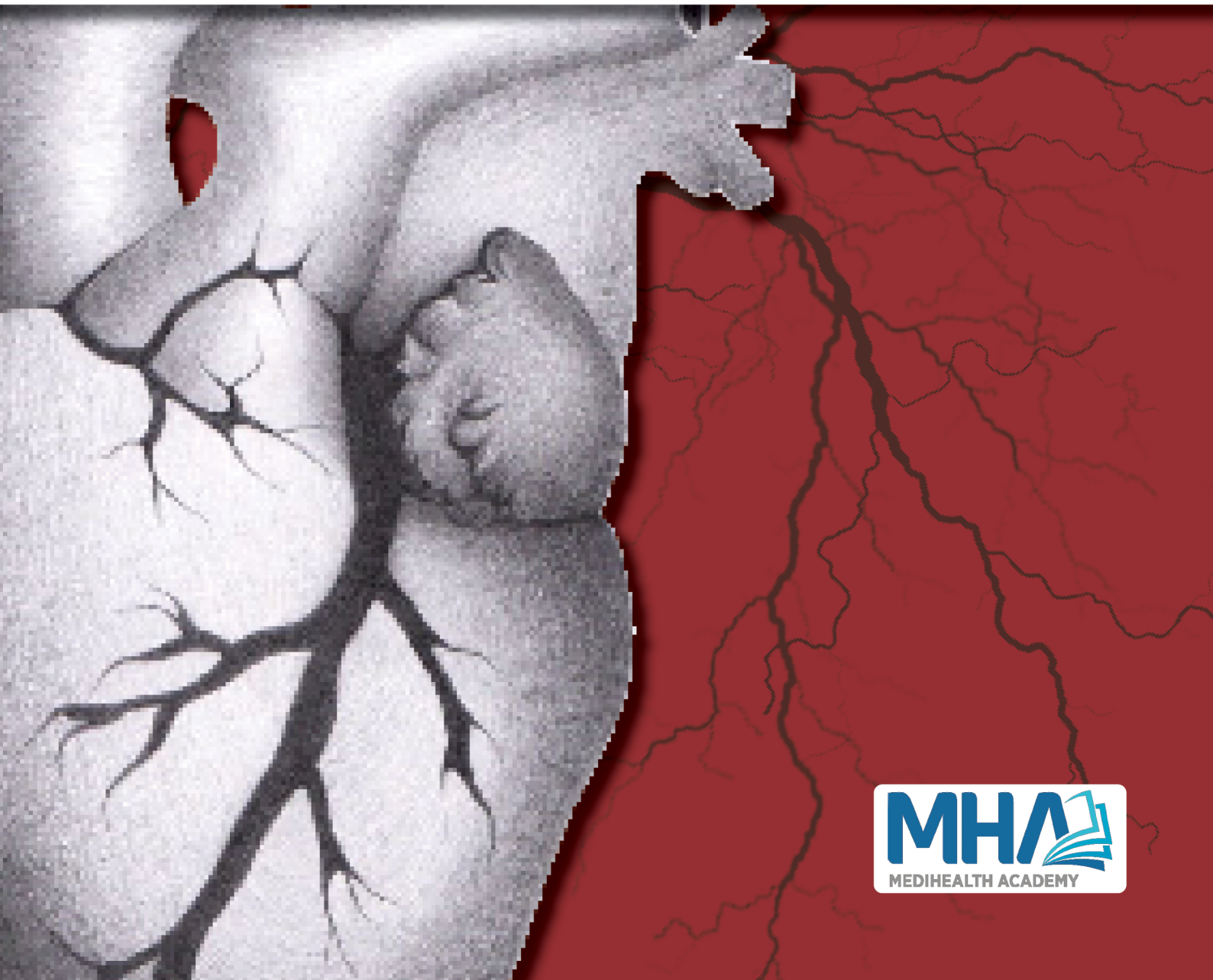

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Dear Colleagues,

I am delighted to welcome you in the first issue of our peer-reviewed academic journal, **Journal of Cardiology & Cardiovascular Surgery**. As editor-in-chief, I am honored to introduce this exciting new journal dedicated to advancing the field of cardiology and cardiovascular surgery. In this first issue, a review of new developments in the field of cardiology, original research, and interesting case reports are included. One of our most important goals is to encourage new research in science and to mediate appropriately the sharing of knowledge and experience among medical professionals, researchers and academics. In this issue, we share with you five articles covering various topics in cardiology and cardiovascular surgery.

The first article of the journal "*Risk factors that may cause congenital cardiac disease*" is an original article including a total of 114 patients and the authors presented the results consistent with literature. The second article "*Interatrial blocks in patients with tavi and their associations with clinic parameters*" is a retrospective study evaluating the association between preprocedural and postprocedural ECG findings and clinical parameters in patients undergoing TAVI. Third article "*Sodium-glucose co-transporter 2 (SGLT2) inhibitors: a brief review*" is a review of sodium-glucose co-transporter-2 inhibitors, which are new antihyperglycemic agents that are mainly used in diabetes mellitus but also have very promising effects on the cardiovascular and renal systems. In the fourth article "*Isolated right ventricular thrombus with the severe chronic obstructive pulmonary disease*", the authors presented an interesting case of isolated right ventricular thrombus confirmed by both echocardiography and MR images. The fifth article "*Cyclosporine induced bradycardia: is it rarely seen?*" is another interesting case presentation highlighting a rare side effect of cyclosporine.

As we embark on this new journey together, I would like to thank the authors, reviewers, editorial team and publisher for their hard work and dedication in bringing this first issue to fruition. We look forward to bringing you the latest developments in cardiology and cardiovascular surgery, and we value your feedback and suggestions. We are also honored to mediate all your contributions to science through our journal.

Sincerely,

Ibrahim Halil Inanc, MD

Editor-in-Chief

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Original Article

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Risk factors related with congenital heart disease: a single center experience

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ABSTRACT

Aims: Many cases of congenital heart disease are multifactorial and result from a combination of genetic predisposition and an as-yet-to-be-determined environmental stimulus. The purpose of the study is to determine the patients who were diagnosed with CHD through echocardiography and to reveal the risk factors that may cause congenital heart anomalies in our center.

Methods: The medical records of pediatric patients applied to our pediatric cardiology clinic between January 2010 –December 2017 were retrospectively reviewed.

Results: 147 cases were diagnosed with CHD. 60 (52.6%) of the cases were female and 54 (47.4) were male. 77 of the 114 patients included in the study were acyanotic (67.5%) and 37 (32.5%) were cyanotic. Seventeen of the acyanotic patients had mixed CHD. The mean maternal gestational age was 28.2±5.78 years. 26 (22.8%) were born preterm. 17 (14.9 %) patients were born with low birth weight (under 2500 g). 8 (7%) patients were LGA (large for gestational age) (birth weight over 4000 g). Average birth weight was 2,98±740,8 gr. Consanguinity was found in the parents of 28 (24.5%) patients. There was a history of CHD in the relatives of 6 (5.2%) patients, siblings of 4 (3.5%) patients, and parents of 5 (4.3%) patients. Chromosomal abnormalities were found in 9 (7.9%) patients.

Conclusion: Our study is a valuable contribution to the existing literature in that it showed that the frequency and distribution of congenital heart diseases have not changed in recent years, and its findings are compatible with the literature findings.

Keywords: Congenital heart disease, risk factors, contemporary clinical practice

INTRODUCTION

The term congenital heart disease (CHD) includes congenital, structural or functional abnormalities in the cardiovascular system that can be identified at birth or later. Congenital heart disease occurs in approximately 0.8% of live births.[1] Many cases of CHD are multifactorial and result from a combination of genetic predisposition and an as-yet-to-be-determined environmental stimulus. Although CHD is one of the most common major congenital anomalies, we have the least information about its causes. There are many risk factors that can cause CHD. Among these, consanguineous marriage, congenital heart disease of the mother, father or one of the family members, the gestational age of the mother, the birth weight of the baby, the diseases the mother had during or before pregnancy (DM, SLE,etc.) the infections the mother had (rubella, mumps, toxoplasmosis,etc, the drugs used by the mother (thalidomide, lithium,etc.) the mother's exposure to radiation during pregnancy, the mother's smoking or alcohol use, the mother's substance abuse (marijuana, heroin, cocaine) and the mother's nutritional status.[2] The purpose of the study is to determine the patients who were diagnosed with CHD through echocardiography and to reveal the risk factors that may cause congenital heart anomalies in our center as contemporary clinical practice.

METHODS

The medical records of pediatric patients applied to our pediatric cardiology clinic between January 2010 – December 2017 were retrospectively reviewed. Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee approved the study (Date: 17.10.2017, Number: 18/07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patent ductus arteriosus (PDA), mitral valve prolapse, physiological peripheral pulmonary stenosis and bicuspid aortic valve disease in preterm newborns were excluded from our study. Transthoracic Echocardiography (TTE) was performed using "Vivid 3 Expert" and "Vivid 7 Pro ECO" devices of General Electric Medical Systems, Chicago, USA and probes of 3, 5, 7 MHz. All measurements were performed by the same pediatric cardiologist. In the measurements, images were taken in subcostal, parasternal long axis, short axis, apical four-chamber, five-chamber, and suprasternal positions, and hemodynamic functions were evaluated with M-mode, 2-dimensional and Doppler echocardiographic examinations. In addition, a tissue Doppler study was performed. American Society of Echocardiography recommendations[3] was taken as a reference for all measurements.

Statistical Analysis

The study data were analyzed using SPSS (Statistical Package for the Social Sciences) version 20.0 software (SPSS Inc.). The categorical variables were expressed as frequency and percentage, and continuous variables as mean and standard deviation (SD).

RESULTS

A total of 14,173 patients applied to our clinic between 2010-2017. One hundred and fourteen cases diagnosed with CHD by TTE performed by a pediatric cardiologist were detected. 60 (52.6%) of the cases were female and 54 (47.4) were male. Out of 114 patients, 64 (54.3%) presented with a murmur (detected by the pediatrician in our clinic) while the remaining 50 patients (45.7%) were admitted for other reasons (such as bruising, respiratory distress, routine examination, and positive familial risk factors). 29 patients (25.4%) were diagnosed antenatally. 77 of the 114 patients included in the study were acyanotic (67.5%) and 37 (32.5%) were cyanotic. 17 of the acyanotic patients had mixed CHD. Nineteen of the cyanotic patients were male (51.3%) and 18 were female (48.7%). 42 (54.6%) of the acyanotic patients were female and 35% (45.4%) were male.

The distribution of patients diagnosed with acyanotic, cyantoic, and mixed acyanotic CHD by type is shown on **Table 1**. Ventricular Septal Defect (VSD) was found to be the most common acyanotic anomaly (45 patients; 39.5%). Secundum type Atrial Septal Defect (ASD) was detected in 14 patients (12.2%), and PDA was detected in 12 patients (10.5%). Isolated VSD was also the most common acyanotic anomaly (n=29 patients, 25.4%).The most common mixed acyanotic anomaly was VSD-ASD (7 patients, 6.1%).

Tetralogy of Fallot (TOF) was the most common cyanotic anomaly (10 patients; 8.7%). Tricuspid atresia (TA) was detected in 5 patients (4.3%). Transposition of Great Arteries (TGA) was detected in 6 patients (5.2%), of which 4 were male.

Table 2 shows the risk factors that may be associated with congenital heart disease based on the patient's history. The mean maternal gestational age was 28.2±5.78 years. 88 (77,2%) patients were born at term, and 26 (22.8%) were born preterm. 17 (14,9 %) patients were born with low birth weight (under 2500 g). 8 (7%) patients were LGA (large for gestational age) (birth weight over 4000 g). The average birth weight was 2,982.8±740,87 gr. Consanguinity was found in the parents of 28 (24.5%) patients; and there was first-degree consanguinity in the parents of 18 patients (15.8%), and distant relatives (cousins, and second cousins etc.)in the parents of 10 patients (8.8%). There was a history of CHD in the relatives of 6 (5.2%) patients, siblings of 4 (3.5%) patients, and parents of 5 (4.3%) patients. Chromosomal abnormalities were found in 9 (7.9%) patients; 5 had Down syndrome, 2 had Di George syndrome, 1 Turner syndrome and 1 Edward syndrome. Two of Down syndrome patients had AV septal defect and 2 had VSD. Complicated ASD+VSD+PDA was detected in patients with Edward syndrome. 6 (5.2%) mothers had a history of chronic diabetes mellitus, 2 (1.8%) had a history of blood pressure disease and antihypertensive drug use, 4 (3.5%) had preeclampsia, and 8 (7%) had hypothyroidism with a history of levothyroxine use. Hashimoto's thyroiditis was detected in 5 patients with hypothyroidism. At least 57 (50%) patients had a history of regular folic acid and multivitamin use during pregnancy.

Table. Supposed risk factors for congenital heart disease

Risk factor	
Mean maternal gestational age (year)	28+/-5,8
Low birth weight n (%)	17 (14,9)
Consangiunity between parents n (%)	28 (24,5)
Family history of CHD n (%)	6(5,2)
Regular use of folic acid supplement n (%)	57 (50)
CHD in siblings n (%)	4 (3.5)
Chronic disease in mother (DM) n (%)	6(5,2)
Chromozomal anomaly n (%)	9 (7,9)

DISCUSSION

It is thought that 85-90% of CHD cases are multifactorial (which result from an interaction of genetic and environmental factors). In approximately 8% of cases, a congenital heart anomaly can be associated with a genetic defect; however, in most cases, a genetic etiology cannot be determined.[4]

In our patients there was a slight female preponderance (52,6%). The reason why acyanotic anomalies are more common in girls is the presence of anomalies such as VSD, PDA, ASD in this group, and these data are consistent with the information in the literature.[5] It has been reported that spontaneous septal defect closure is more common in males than females.[6] According to a meta-analysis, the female gender is a risk factor for the presence of CHD in Down Syndrome.[7] On the other hand, there are studies reporting cyanotic anomalies being more frequently detected in males.[2] Biological gender differences in the structure of blood vessels and androgenic hormones may be responsible for gender differences in this regard.[8]

Although the subjects included in the study presented due to reasons such as respiratory distress, cyanosis, familial risk factors or a routine examination, the most common reason for admission was cardiac murmur. 64 (54.3%) patients presented with a murmur. In previous studies, the most common reason for cardiological consultation was also cardiac murmur.[9,10]

Table 1. Distribution of congenital heart diseases in the study population

Isolated Acynotic Defects	N=60	Mixed Acyanotic Defects	N=17	Cyanotic Defects	N=37
VSD	29	VSD+ASD	7	Tetralogy of Fallot	10
Patents ductus arteriosus (PDA)	7	VSD+PDA	4	Transpoistion of great arteries	6
Aort stenosis (AS)	6	VSD+PS	2	Tricuspid atresia	5
Atrioventricular septal defect	5	VSD+ASD+AC	1	Hypoplastic left heart syndrome	4
Aort coarction (AC)	5	VSD+ASD+PDA	1	Hypoplastic right heart syndrome	3
Pulmonary stenosis (PS)	4	VSD+PS	1	Single ventricle	2
ASD	4	ASD+PS	1	Truncus arteriosus	2
				Double outlet right ventricle	2
				Total anomalous pulmonary venous return	2
				Pulmonary atresia	1

Aydogdu et al.[11] showed that VSD was the most common anomaly with a prevalence of 42.9%, and ASD was in the second most common anomaly with a prevalence of 37.5%. In our study, VSD was the most common anomaly (39.5%) followed by ASD (12.2%), a finding which was partially consistent with the literature.[12] The most common cyanotic anomaly was tetralogy of fallot (10 patients; 8.7%); tricuspid atresia was found in 5 (4.3%) patients, and TGA in 6 (5.2%). The fact that 4 of these 6 patients were male is in accordance with literature data indicating that serious and complex heart defects are more common in males.[2]

In our study, consanguinity was found between the parents of 28 (24.5%) patients; It was determined that there was first-degree consanguinity among the parents of 18 patients (15.7%), and distant consanguinity between the parents of 10 patients (8.8%). In a study conducted by Al Mamun et al.[13] on CHD, it was found that 8.85% of children with CHD had a family history of consanguineous marriage between their parents. They found that children who born to consanguineous parents had 2.5 times risk of developing CHD. Having a higher rate of consanguinity, 15.7% of our patients' parents were first-degree relatives. Our data suggest that first-degree consanguineous marriage may be influential in the etiology of CHD.

The recurrence risk for CHD increases two- to threefold when there is a family history.[14] This shows that CHD can be transmitted by Mendelian inheritance.[15] In the literature, it has been shown that having CHD in the family is a risk factor for CHD in subsequent children.[16] In our study, 6 (5.2%) patients had a history of CHD in their relatives, 4 (3.5%) in their siblings, and 5 (4.3%) in their parents.

Congenital heart disease is seen more frequently in some single gene defects and chromosomal abnormalities; for example, approximately 40% of children with Down Syndrome have overt heart disease, 50% of which can be congenital heart diseases such as endocardial cushion defect, VSD, PDA, and TOF.[17] In our study, a chromosomal anomaly was found in 9 (7.9%) patients. Of these patients, 5 had Down syndrome, 2 had Di George syndrome, 1 had Turner syndrome and 1 had Edward syndrome. In a study by Park et al.[18] endocardial cushion defect (43%) was the most common anomaly in patients with Down syndrome, followed by VSD (32%). In a study by Meberg et al.[19] Edwards syndrome was detected 2.1% (58%), in the study of Dorfman et al.[10] 0.5%. In our study, Edwards Syndrome was found at a rate of 0.87%. In Down syndrome patients, there is overexpression of the DSCAM (Down syndrome cell adhesion molecule) gene that creates an imbalance in the epithelial-mesenchymal transformation that leads to a defect in mesenchymal migration and proliferation that causes CHD.[20]

Compared to normal babies born in the same gestational week, low-birth-weight babies are more likely to have ASD, VSD, tetralogy of Fallot, hypoplastic left heart syndrome, pulmonary stenosis, or aortic coarctation.[21,22] In a study performed by Kadivar et al.[9] the mean gestational age was 38 weeks, the mean birth weight was 2812 g, and the number of prematurity was 41 (16.9%). In the study of Aydoğdu et al., the mean birth weight was 2961 g, and 18% of the cases were prematüre.11 In our study, 26 (22.8%) patients were preterm, 17 (14.9%) were low birth weight (under 2500 g), and the mean birth weight was 2.982±740 g. The high rate of low-birth weight and high mean maternal gestational age suggests that these two factors may be influential in the etiology of CHD. Besides comorbidities are also effective risk factors. Maternal diabetes increases the incidence of congenital heart disease. If the mother has insulin-dependent diabetes mellitus, anomalies such as VSD, TOF and great vessel transposition may develop. In the study of Kadivar et al.[9] 9% of patients diagnosed with CHD were born to diabetic mothers. In our study, 6 of the patients (5.2%) had a maternal history of insulin-dependent diabetes mellitus, 2 (1.8%) had a maternal history of hypertension and antihypertensive drug use, and 4 (3.5%) had a maternal history of preeclampsia. Both maternal hypertension and diabetes affect maternal metabolism and cause endothelial dysfunction, which leads to CHD.

It has been shown that folic acid deficiency increases the risk of cardiovascular anomalies in the fetus.[23] Therefore, it is recommended that folic acid supplements be administered to mothers starting one month prior to pregnancy and for two months after the start of pregnancy.[23] In our study, although the mothers of at least 57 (50%) patients regularly used iron, folic acid, and multivitamins during pregnancy, it was determined that many mothers either used folic acid irregularly or did not use it at all.

CONCLUSION

Our study is a valuable contribution to the existing literature in that it showed that the frequency and distribution of congenital heart diseases have not changed in recent years, and its findings are compatible with the literature findings. Families who have a child with a congenital heart anomaly should receive genetic counseling due to a possible cardiac anomaly in the next child; in addition, people who will get married should be informed about CHD, and a good maternal care should be provided before pregnancy.

ETHICAL DECLARATIONS

Ethics Committee Approval: Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee approved the study (Decision No: 18/07 Date: 17.10.2017).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Interatrial blocks in patients with TAVI and their associations with clinic parameters

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ABSTRACT

Aims: The present study attempted to evaluate the prevalence of basal interatrial blocks (IABs), their associations with clinical parameters, and the interatrial conduction in the follow-up after a successful transcatheter aortic valve implantation (TAVI) procedure among patients with severe aortic stenosis.

Methods: We retrospectively evaluated the findings of 90 patients undergoing TAVI in our center. Overall, we considered the presence and grades of IABs and P-wave durations in electrocardiograms (ECG), preoperative echocardiography (ECHO) findings (maximum and mean gradients and left atrium (LA) diameter), valve size and type, and changes in these parameters at sixth month.

Results: Forty-six patients were included in the study which are suitable for the pre-determined inclusion criteria. We found the mean age of the patients to be 74.78±8.66 years. In preoperatively-evaluated ECGs, while we detected partial IABs in 37% of the patients, there were advanced IABs in 6.5%, but 56.5% yielded no interatrial conduction disorder. On the other hand, in postoperatively-evaluated ECGs, while we observed partial IABs in 30.4% of the patients, there were advanced IABs among 21.7% (p=0.017). Nevertheless, we could not conclude any IABs among 47.8% of the patients. Besides, 54.3% of the patients received a self-expandable valve, and a balloon-expandable valve was inserted in 45.7%. In this regard, we detected partial (7 patients) and advanced (2 patients) IABs in the preoperatively-evaluated ECGs of the patients receiving a self-expandable valve. In the postoperative ECGs of these patients, while the partial IAB remained the same in 4 patients (57.1%), it progressed to an advanced IAB in 3 (42.9%). In addition, while the advanced IAB regressed to a partial IAB in one patient, it remained the same for the other patient. In this group, the mean P-wave durations were found to be 118.4±22.67 before the TAVI and 119.6±21.69 after the TAVI (p=0.113). In the preoperative ECGs of 21 patients with a balloon-expandable valve, we detected partial IABs in 10 patients and an advanced IAB in one patient. While a partial IAB developed in five patients (p=0.022), five patients with a partial IAB developed an advanced IAB following the procedure (p=0.022). In this group, we noticed a significant difference between preoperative (127.62±19.4) and postoperative (138.71±32.03) P-wave durations (p=0.038).

Conclusion: In a nutshell, we concluded no significant change in interatrial conduction time of the patients with TAVI compared to the baseline in their sixth-month ECGs. When considered by valve type, we concluded that the development and progression of IABs were significant among those with a balloon-expandable valve. The higher postoperative mean gradient among those with a balloon-expandable valve compared to those with a self-expandable valve may be associated with significantly longer P-wave duration among those with a balloon-expandable valve.

Keywords: TAVI, interatrial block, balloon-expandable valve, P-wave duration

INTRODUCTION

Symptomatic severe aortic stenosis (AS) has become a seminal health problem due to the increased older adult population. AS is now definitely treated with aortic valve replacement (AVR). However, it may be rather challenging to decide on conservative follow-up or surgical treatment in patients at high risk regarding surgery. Occurring particularly among older adults with comorbidities, this situation has led to the improvement of percutaneous intervention techniques with a lower procedure risk than operative techniques.

The percutaneous AVR procedure was first introduced in animal studies in the early 1990s, and Cribier et al.[1] performed the first human application of the procedure in 2002. The procedure, called transcatheter aortic valve implantation (TAVI), may be one of the most exciting developments in interventional cardiology in the last 15 years. Thanks to the promising findings of the research, TAVI has been boosted with significant technological advancements and is now widely adopted worldwide. In many centers, it is adopted as a standard treatment technique for patients with high surgical risk or who cannot be recruited for any operation.

An interatrial block (IAB) is an electrical conduction defect between the right and left atria and is defined as a P-wave duration over 120 milliseconds (ms) in a standard 12-lead surface electrocardiographic (ECG) examination (**Figure 1**).[2]

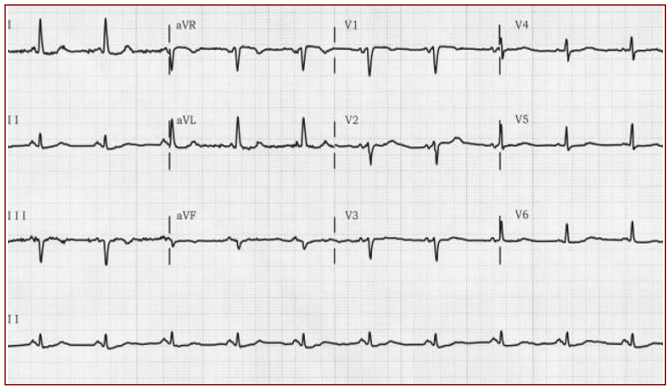

Figure 1. An Example of IAB in ECG

ECG demonstrates the presence of an IAB; the P-wave duration is broad (>110 ms) and bifid. An IAB can be graded as partial or advanced[3,4] ; the distinction is based on P-wave duration and, more apparently, on P-wave morphology. A bifid P-wave (notched P-wave) in leads I, II, III, and aVF is thought to represent a partial IAB.[5] It was previously demonstrated that the negative deflection phase in the P-wave morphology in lead V1 in a partial IAB is less pronounced than in the negative P-wave in left atrial enlargement (LAE).[6] Biphasic P waves (± P-waves) in the inferior leads (II, III, and aVF) of an advanced IAB usually indicate cauda-cranial left atrial activation due to a fixed block in the normal conduction pathway (**Figure 2**).

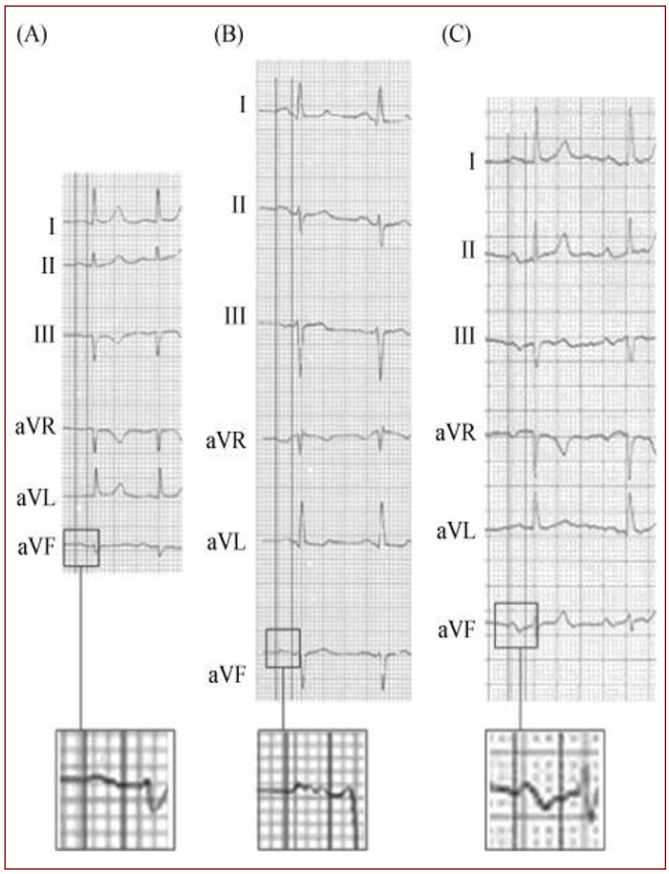

Figure 2. Grading of IABs. (A) normal P-wave, (B) P-wave of a partial IAB, and (C) P-wave of an advanced IAB.

An IAB may be a primary or causal risk factor for various atrial arrhythmias (particularly atrial fibrillation (AF)) and may also be associated with a variety of other clinical abnormalities, such as thromboembolism, including left atrial dilatation, embolic stroke, mesenteric ischemia.[7]

In their study, Lourdes et al.[8] investigated the preoperative prevalence of IABs and postoperative mortality in TAVI and found that 53% of 1,842 patients did not have interatrial conduction defects, but 31% had a partial IAB and 16% an advanced IAB. In conclusion, the advanced IAB emerged as an indicator of mortality regardless of all causes. A multicenter registry study on the prevalence of IABs, permanent pacemaker insertion, and their relationships with new-onset amnesia and stroke was launched in Spain in 2019 but has not yet been concluded.[9] In this study, we considered the presence and grades of IABs and P-wave duration in electrocardiograms (ECG), pre-procedural echocardiography (ECHO) findings (maximum and mean gradients and left atrium (LA) diameter), valve size and type, and changes in parameters at sixth month. To our knowledge, this is the pioneering study in the literature to address valve types and their effects on interatrial conduction.

METHODS

Sample

The Non-Interventional Researches Ethics Committee of Gaziantep University granted ethical approval to our study (Date: 12/04/2019, Decision No.: 2019/450). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In the study, we retrospectively evaluated the preoperative ECGs of 90 patients undergoing a TAVI and successfully discharged between 2015 and 2020 in the Department of Cardiology of Gaziantep University Sahinbey Training and Research Hospital. However, we excluded 44 patients without archive records, with preoperative and postoperative AF, and without preoperative ECHO data. Then, we retrospectively examined the patients' ECG and ECHO findings at the time of diagnosis, after the procedure at hospitalization, and at the sixth-month follow-up. In the subsequent sections, the patients' demographic characteristics and procedural characteristics are presented.

Preoperative Evaluation

ECG, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), coronary and peripheral angiography, and multislice computed tomography (CT) were routinely performed in all patients with an indication/scheduled for TAVI. We extracted relevant data from the database of our hospital and patient files.

Echocardiographic Evaluation

In this study, the echocardiographic parameters were obtained by a specialist, experienced in the echocardiographic evaluation, by using the GE Healthcare Vivid S6 1-5 MHz transducer in our echocardiography laboratory. In accordance with the latest guidelines of the American Society of Echocardiography (ASE), color tissue Doppler images of the posterior wall (from the parasternal long axis), the septal and lateral walls (from the apical 4-chamber position), and the anterior and inferior walls (from the apical 2-chamber position) were obtained from the patients. Aortic VTI and maximal and mean gradients were taken with CW-Doppler on the aortic valve from the

apical 5-chamber position. Finally, left ventricular outflow tract (LVOT) VTI was taken with PW-Doppler on the LVOT. The LVOT diameter was measured from the parasternal long axis at the junction of the septum of the aortic valve and the anterior leaflet of the mitral valve. Interventricular septum (IVS), posterior wall (PW), left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVSD), and left ventricular ejection fraction (LVEF) were calculated from the MMOD section at the level of the LV papillary muscle. All measurements were performed by considering the mean values of three consecutive cycles. Finally, the aortic valve area was calculated according to the following formula: (LVOT diameter)2×0.785×(LVOT TVI)/(Aortic valve TVI).

Procedural Characteristics

The procedure was performed under fluoroscopy with local anesthesia, as well as general anesthesia in some selected patients. Prior to the procedure, the patients were given 300 mg clopidogrel, 300 mg acetylsalicylic acid, and 2 g cefazolin. Those with chronic renal disease or at high risk of developing contrast-related renal injury were administered intravenous hydration before and after the procedure. The cardiology team applied deep and standard incision and percutaneous intervention to 90 patients. Following balloon predilatation of the native aortic valve, CoreValve/CoreValve Evolut R (CoreValve Revalving Technology, Medtronic, Minneapolis, Minnesota), Edwards SAPIEN 3 or Edwards SAPIEN XT (Edwards Lifesciences, Irvine, California), St. Jude Medical Portico Valve (St. Jude Medical, St. Paul, Minnesota), and Boston Scientific bioprosthetic valve (Boston Scientific, Marlborough, MA) were inserted under burst pacing of the right ventricle. Postdilatation was applied to the cases that were thought to be insufficiently dilated. The team chose the type of intervention, valve model, and other materials based on their preferences and experience.

Statistical Analysis

We tested if the data showed a normal distribution using the Shapiro-Wilk test. While we performed independent pair-wise comparisons of the non-normally distributed data with the Mann-Whitney U test, we utilized the Wilcoxon signed-rank test for comparisons of the related samples. The analysis of the ordered categorical variables at two different times was performed with the McNemar-Bowker test. Moreover, we calculated Spearman's rank correlation coefficients to test the relationships between continuous variables. We performed all statistical analyses on the SPSS 22.0 program and accepted a p-value < 0.05 to be statistically significant.

RESULTS

In this study, we considered the data of 46 patients undergoing TAVI between 2015 and 2020 and satisfying our inclusion criteria. The mean age of the patients, 28 (60.9%) females and 18 (39.1%) males, was found to be 74.78±8.66 years. Their mean left atrium diameter was 41±4.39 mm, while the mean valve size used in the procedures was 26.43±2.69 mm. The mean preoperative and postoperative P-wave durations were calculated to be 122.61±21.52 ms 128.31±28.3 ms. Moreover, the preoperative and postoperative maximum gradients were discovered to be 84±20.35 mm/Hg and 21.5±9.69 mm/Hg, respectively. Finally, the preoperative and postoperative mean gradients were 52.85±13.39 mm/Hg and 11.5±5.78 mm/Hg, respectively (**Table 1**).

Table 1. Descriptive statistics

Parameters	M±SD
Age	74.78±8.66
Valve size (mm)	26.43±2.69
Preoperative P-wave Duration (ms)	122.61±21.52
Preoperative Max. Gradient (mmHg)	84±20.35
Preoperative Mean Gradient (mmHg)	52.85±13.39
Postoperative P-wave Duration (ms)	128.31±28.3
Postoperative Max Gradient (mmHg)	21.5±9.69
Postoperative Mean Gradient (mmHg)	11.5±5.78
LA diameter (mm)	41±4.39

In preoperatively-evaluated ECGs, while we detected partial IABs in 17 patients (37%), there were advanced IABs in 3 patients (6.5%), but 26 patients (56.5%) yielded no interatrial conduction disorder. On the other hand, in postoperatively-evaluated ECGs, while we observed partial IABs in 14 patients (30.4%), there were advanced IABs among 10 patients (21.7%). Nevertheless, we could not conclude any IABs among 22 patients (47.8%). Therefore, the patients did not significantly differ by the presence of an IAB (p=0.017; **Table 2**). The postoperative findings of 26 patients without an IAB in their preoperative evaluation yielded that five patients (19.2%) developed a partial IAB, but 21 (80.8%) did not have any interatrial conduction defects (p=0.017). Given the postoperative findings of 17 patients (37%) with a partial IAB in their preoperative evaluation, we discovered that the partial IAB persisted in 8 patients (47.1%), progressed to an advanced IAB in 8 patients (47.1%), and disappeared in one patient (5.9%) (p=0.017). Finally, the postoperative evaluation of 3 (6.5%) patients with an advanced IAB in their preoperative assessment showed that it regressed to a partial IAB in 1 (33.3%) patient but persisted in the other two (66.6%) (p=0.017).

Table 2. Comparison of IABs in preoperative and postoperative ECGs

Preoperative ECG	Postoperative ECG			p
	No IAB	Partial IAB	Advanced IAB	
	n (%)	n (%)	n (%)	
No IAB	21(80.8)	5(19.2)	0(0)	0.017
Partial IAB	1(5.9)	8(47.1)	8(47.1)	
Advanced IAB	0 (0)	1(33.3)	2(66.7)	

*p < 0.05, ECG: Electrocardiography

The mean postoperative P-wave duration of the patients (128.31±28.3 ms) did not significantly differ from their mean preoperative P-wave duration (122.61±21.52 ms; p=0.095). However, the patients' preoperative maximum and mean gradient values (84±20.35 mm/Hg and 52.85±13.39 mm/Hg) were significantly higher than their postoperative results (21.5±9.69 mm/Hg and 11.5±5.78 mm/Hg, respectively) (p=0.001 for both; **Table 3**).

Table 3. Preoperative and postoperative electrocardiographic and echocardiographic parameters

Parameters	Patients n (46)	
Preoperative P-wave Duration (ms)	122.61±21.52	p=0.095
Postoperative P-wave Duration (ms)	128.31±28.3	
Preoperative Max. Gradient	84±20.35	p=0.001
Postoperative Max. Gradient	21.5±9.69	
Preoperative Mean Gradient	52.85±13.39	p=0.001
Preoperative Mean Gradient	11.5±5.78	

*p < 0.05, ms: millisecond

While 25 patients (54.3%) received a self-expandable valve, it was the balloon-expandable valve in 21 patients (45.7%). The preoperative ECG findings of 25 patients with a self-expandable valve showed that 16 had no IAB, 7 had a partial IAB, and 2 had an advanced IAB. Regarding their postoperative ECG findings, we discovered that 16 patients still had no IAB. While the partial IAB was protected in 4 (57.1%) of 7 patients, it progressed to an advanced IAB in 3 patients (42.9%). Finally, the advanced IAB regressed to a partial IAB in one patient but was protected in the other.

The preoperative ECG findings of 21 patients with a balloon-expandable valve showed that ten patients had no IAB, ten patients had a partial IAB, and one had an advanced IAB. The postoperative ECG findings of these patients demonstrated that five patients still had no IAB, while the other five developed a partial IAB (p=0.022). The partial IAB of 4 patients (40%) remained the same, disappeared in 1 (10%), and progressed to an advanced IAB in 5 patients (50%) (p=0.022). The advanced IAB remained the same in one patient (**Table 4**).

Table 4. Distribution of preoperative and postoperative IABs by valve type

	Postoperative ECG			p
	No IAB	Partial IAB	Advanced IAB	
	n(%)	n(%)	n(%)	
Self-expandable	Preoperative ECG			0.317
No IAB	16(100)	0(0)	0(0)	
Partial IAB	0(0)	4(57.1)	3(42.9)	
Advanced IAB	0(0)	1(50)	1(50)	
Balloon-expandable	Preoperative ECG			0.022
No IAB	5(50)	5(50)	0(0)	
Partial IAB	1(10)	4(40)	5(50)	
Advanced IAB	0(0)	0(0)	1(100)	

p < 0.05, ECG: Electrocardiography

We discovered no significant difference between the mean preoperative (118.4±22.67 ms) and postoperative (119.6±21.69 ms) P-wave durations of 25 patients with a self-expandable valve (p=0.113). Nevertheless, we concluded a significant difference between the mean preoperative (127.62±19.4 ms) and postoperative (138.71±32.03 ms) P-wave durations of 21 patients with a balloon-expandable valve (p=0.038). There were no significant differences between the patients with self- and balloon-expandable valves by preoperative and postoperative maximum gradients (82.56± 22.35 mm/Hg vs. 85.71± 18.07 mm/Hg and 19.2±5.97 mm/Hg vs. 24.24±12.41 mm/Hg, respectively; p=0.174). It was also the case between the patient groups by mean gradients (52.76±13.6 mm/Hg vs. 52.95±13.47 mm/Hg and 9.92±3.86 mm/Hg vs. 13.38±7.1 mm/Hg, respectively; p=0.068) (**Table 5**).

Table 5. Comparison of P-wave durations and gradients by valve type

Variables	Self-expandable (n=25)	Balon-expandable (n=21)	p
Preoperative P-wave Duration (ms)	118.4±22.67	127.62±19.4	0.113
Postoperative P-wave Duration (ms)	119.6±21.69	138.71±32.03	0.038
Preoperative Max. Gradient (mmHg)	82.56±22.35	85.71±18.07	0.439
Postoperative Max. Gradient (mmHg)	19.2±5.97	24.24±12.41	0.174
Preoperative Mean Gradient (mmHg)	52.76±13.6	52.95±13.47	0.833
Postoperative Mean Gradient (mmHg)	9.92±3.86	13.38±7.1	0.068

p < 0.05, ECG: Electrocardiography

DISCUSSION

An IAB may be associated with a variety of other clinical abnormalities for various atrial arrhythmias (particularly AF), such as thromboembolism, including prior stroke and mesenteric ischemia. Unfortunately, scholarly efforts, as well as physicians, are still deprived of sufficient data to hinder and treat IABs. The questions of if there are factors predicting arrhythmias in patients with an IAB and whether anticoagulants should be started before arrhythmia remain covered. IABs deserve more scholarly attention; thus, further research is highly needed to reach a consensus on appropriate management strategies. An IAB is an anomaly prevalently detected in the general population and among older adults undergoing a TAVI and can be quickly diagnosed with the help of ECGs. Previously, it was found to be associated with significant endpoints such as AF, ischemic stroke, and mesenteric embolism. Carrillo-Loza et al.[10] showed it to have a robust predictive property in predicting recurrent stroke in strokes of unknown origin.

Left atrial dilatation causes disturbances in impulse conduction in the atrium, where P-wave duration is prolonged, and AF develops in advanced cases. Escobar-Robledo et al. demonstrated that an advanced IAB is linked with an elevated risk of stroke in patients with heart failure. O'Neal et al.[11] revealed that the incidence rate of ischemic stroke among patients with an advanced IAB is twice that of those without.

In their study, Cotter et al.[12] evaluated the incidence of AF in patients with loop recorder implantation to assess for unexplained stroke. They found the incidence of AF to be 25.5% and concluded IABs to be significantly more prevalent in patients with AF compared to those without. In another study, Cotter et al.[13] evaluated younger patients (< 55 years) with cryptogenic stroke and found that young patients with unexplained stroke had more prolonged P-wave durations and a higher prevalence of IABs.

In a study by Enriquez et al.[14] the presence of an IAB was found to be the highest risk factor for AF after atrial flutter ablation.

Çinier et al.[15] proposed IABs are prevalent in patients with STEMI and associated with the presence of diffuse coronary artery disease and new onset of AF. In our study, we focused on the presence of preoperative and postoperative (sixth month) IABs, their grades, and their associations with TAVI-related factors among older adults with TAVI procedure.

We first considered the data of 90 patients undergoing TAVI between 2015-2020 and included the data of 46 who met our inclusion criteria. We excluded 25 patients with AF in their preoperative ECGs, 10 patients without the follow-up ECG findings, and 11 patients with AF rhythm in the sixth-month follow-up.

Due to the high prevalence of IABs reported in previous research on their epidemiology, the presence of IABs has sometimes been called a "pandemic." In a study with older adults with sinus rhythm, the prevalence of IABs was found to be 49% in patients aged > 65 years. In our study, the mean age of the patients was 74.78±8.66 years, and 43.5% had an IAB. We found that the presence of an IAB increased to 51.5% following the TAVI procedure. Particularly, the development of an advanced IAB increased among the patients. While present in three patients before the procedure, it was observed in ten patients after the procedure. Besides,

despite prolonged P-wave duration after the TAVI, it was not statistically significant. When comparing the patients with self- and balloon-expandable valves, the P-wave durations of those in the latter group were prolonged after the procedure. In addition, postoperative mean gradients were found to be higher in patients with a balloon-expandable valve than the others. There were no significant differences in the development of an IAB before and after the procedure and its transition from partial to advanced in patients with a self-expandable valve, but we discovered that while a partial IAB developed in half of the patients with a balloon-expandable valve who initially did not have interatrial conduction defects, the initial partial IAB in the other half progressed to an advanced IAB. The postoperative mean gradient was found to be higher among those with a balloon-expandable valve compared to the patients with a self-expandable valve. In general, we considered that increased left ventricular diastolic pressure may be reflected in the left atrium, contributing to the development of an IAB.

The small sample size and the single-center, retrospective design may be counted among the limitations of our study. However, it should be noted that we were able to reach the data of a significant number of patients in our country and that it is a pioneering study on this subject.

CONCLUSION

Overall, IABs are prevalent in patients with severe aortic stenosis scheduled for a TAVI. We concluded no significant change in the interatrial conduction time in the sixth-month ECG findings of patients undergoing a TAVI compared to their baseline findings. Considering the patients by valve type, we discovered that the development and progression of an IAB were significant in those with a balloon-expandable valve. Finally, we think that the higher postoperative mean gradients in the patients with a balloon-expandable valve compared to the others may be related to the significantly longer P-wave duration in these patients..

ETHICAL DECLARATIONS

Ethics Committee Approval: The Non-Interventional Researches Ethics Committee of Gaziantep University granted ethical approval to our study (Date: 12/04/2019, Decision No: 2019/450).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Sodium-glucose co-transporter 2 (SGLT2) inhibitors=a brief review

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ABSTRACT

Sodium-glucose co-transporter-2 inhibitors are novel antihyperglycemic agents which have crucial effects on the heart and kidneys beyond their glucose-lowering features. Their main clinical benefits have been reported in individuals with type 2 diabetes mellitus, chronic kidney disease, heart failure, and proteinuria. However, adverse reactions (euglycemic ketoacidosis, kidney dysfunction, genital and urinary tract infections, hypovolemia, etc) remain to be the main object of the debate regarding their use. The recruited data have encouraged clinicians to use those medicines in individuals who fit the indications for use.

Keywords: Sodium-glucose co-transporter, diabetes mellitus, heart failure, kidney disease

INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, also called gliflozines or flozines, are blood glucose-lowering agents that act on SGLT-2 proteins expressed on the surface of various organ cells, especially in the proximal renal tubules. Dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin are FDA-approved SGLT-2 inhibitors for the treatment of adult patients with type 2 diabetes mellitus (DM) to improve glycemic control in addition to diet and exercise.[1]

In March 2013, canagliflozin was approved by the FDA as the first SGLT-2 inhibitor in type 2 DM treatment that does not induce hypoglycemia and promotes weight loss by losing 300 to 400 kcal/day.[2] It also reduces the risk of cardiovascular (CV) adverse events in patients with type 2 DM with underlying CV disease and reduces the risk of developing end-stage renal disease (ESRD), CV mortality and hospitalization for heart failure in patients with type 2 DM with diabetic nephropathy and albuminuria.[3]

Dapagliflozin was the second SGLT2 inhibitor that received FDA approval in 2014. It is indicated in adult patients with type 2 DM to lower high blood glucose in adjunct to diet and exercise. Additionally, it demonstrates beneficial features; minimizing the hospitalization attributed to heart failure in type 2 DM patients with underlying CV disease or various CV risk factors, reducing the risk of CV mortality and hospitalization in adult patients with heart failure with decreased ejection fraction with New York Heart Association (NYHA) classification II-IV.[4,5] It has also an indication of use to reduce the risk of decline of estimated glomerular filtration rate (eGFR), ESRD, CV mortality, and hospitalization due to heart failure in chronic kidney disease (CKD) patients.[4,5]

In August 2014, empagliflozin became the third SGLT inhibitor to receive approval from the FDA.[6] It achieved similar use of indications with dapagliflozin. Recent evidence has extended the indications of the use of SGLT2 inhibitors to patients with HF, with and without T2D, finding that SGLT-2 inhibitors (particularly dapagliflozin and empagliflozin) are effective therapeutic agents for the treatment and prevention of HF.[7] Finally, in 2017, ertugliflozin received approval from the FDA in order to use for adult patients with type 2 DM to improve higher blood glucose in addition to diet and exercise.[8]

Distribution of SGLT2 Proteins and Their Effects

Sodium-dependent glucose cotransporters (or sodium-glucose-linked transporters, SGLT) are a family of glucose transporters encoded by the SLC5A1 gene family and found in the intestinal mucosa (enterocytes) of the small intestine (SGLT1) and in the proximal tubule of the nephron (SGLT2). To date, 10 additional members of the human SLC5A protein family have been described.[9,10] The distribution of all types of SGLT2 proteins in the body is given in **Table 1**.[11-13]

Table 1. SGLT2 transmembrane proteins are being expressed widely in the body

Protein	Co-transporting	Tissue/Organ
SGLT1	Glucose/Galactose	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2	Glucose	Kidney, brain, liver, thyroid, muscle, heart
SGLT3	Glucose	Intestine, testis, uterus, lung, brain, thyroid
SGLT4	Glucose, Mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas
SGLT5	Glucose, Galactose	Kidney
SGLT6	D-chiro inositol	brain, kidney, intestine

Adopted from the references 13. SGLT; sodium-glucose co-transporter-2

The Na^+/K^+-ATPase on the basolateral membrane of proximal tubule cells induces ATP molecules to move three sodium ions out of the cell and two potassium ions into the cell. This movement creates a downward sodium ion gradient from the outside to the inside of the proximal tubule cell.

The SGLT transmembrane proteins use the energy of this downward sodium ion gradient established by the ATPase pump to transport glucose across the apical membrane against an upward glucose gradient. These co-transporters are also referred to as secondary active transport. Members of the GLUT family of glucose uniporters then transport glucose across the basolateral membrane into the peritubular capillaries. Because sodium and glucose move across the membrane in the same direction, SGLT1 and SGLT2 are called symporters. GLT2, located in the S1 segment, is a low-affinity, high-capacity transporter that reabsorbs up to 90% of filtered glucose (**Table 2**).[13] SGLT1, located in the S3 segment, is a high-affinity, low-capacity transporter that reabsorbs the remaining 10%.[14,15] Of course, sodium can be consumed, so the sodium-hydrogen antiporter first brings sodium into the cell. Therefore, glucose is actually moved by pushing protons out of the cell, with sodium as an intermediary. SGLT-2 inhibitors suppress renal glucose reabsorption and thereby increase urinary glucose excretion by lowering the renal threshold for glucose excretion.[14] Hyperglycemia is thereby ameliorated. However, SGLT-2 inhibitors inhibit the reabsorption of only ~30-50% of the glucose filtered into the proximal tubules. The answer to why they are unable to inhibit 90% of glucose reabsorption in humans is unclear.[16,17]

Table 2. The comparison of SGLT1 and SGLT2

	SGLT1	SGLT2
Localization	Intestine, proximal convoluted tubule (segment 3)	proximal convoluted tubule (segment 1,2)
Capacity	Low	High
Affinity	High	Low
Contribution to glucose reabsorption	10%	90%
Mutation/deficiency	Glucose and galactose malabsorption	familial renal glucosuria
Symptoms in case of illness	Diarrhea, glucosuria	glucosuria
Clinical course	Death if glucose and galactose are not restricted	benign
Inhibitors	Phlorizin	SGLT2 inhibitors

Adopted from the references 13, SGLT-2; Sodium-glucose co-transporter-2

Inhibition of SGLT-2-dependent glucose and sodium reabsorption leads to an increase in distal tubular sodium load. This not only inhibits the activity of the renin-angiotensin-aldosterone system, but also ameliorates failed tubuloglomerular feedback mechanisms, which include lowering intraglomerular renal pressure, promoting tubuloglomerular feedback, downregulating sympathetic activity, and reducing cardiac preload and afterload.[17,18]

Introduction of SGLT2 inhibitors and Management

SGLT2 inhibitors are effective at any stage of type 2 DM because of their unique, insulin-independent mechanism of action. Data support their use as add-on therapy to any other antidiabetic agent and as monotherapy in patients who cannot tolerate metformin. However, the degree of renal dysfunction and the possible development of side effects may limit its use. Patients of younger age, with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m2 (renal function unimpaired), with established cardiovascular disease, without frequent genitourinary tract infections, overweight or obese, or with hypertension (moderate to high blood pressure) are likely to generally receive the greatest benefit from these drugs. Lower doses are recommended at the start of treatment with SGLT2 inhibitors. Consideration of concomitant therapies is also important to minimize the risk of adverse effects. The daily insulin dose should be reduced by 20% in patients with an HbA1c of less than 8.5% to avoid insulin withdrawal and minimize the risk of euglycemic diabetic ketoacidosis.[19,20] A brief overview of initiating treatment with SGLT2 inhibitors is provided in **Table 3**.

Table 3. Available forms of SGLT2 inhibitors and Their Dosages in Adults

Canagliflozin[21,22]

- 100 mg and 300 mg tablets for oral use.
- eGFR ≥60 ml/min/1.73 m2= 100-300 mg once daily
- eGFR ≥30 and < 60 ml/min/1.73 m2= 100 mg once daily
- eGFR <30 ml/min/1.73 m2= Initiating therapy with canagliflozin is not advised in patients with an eGFR of less than 30. Although 100 mg once daily may be administered in subjects with albuminuria >300 mg daily if already in use. This may further decrease ESRD risk, cardiovascular mortality, and hospitalization for heart failure and reduce the rise in serum creatinine in this subset of patients. Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

Dapagliflozin[4]

- 5 mg and 10 mg tablets for oral use
- eGFR ≥45 ml/min/1.73 m2= 5-10 mg once daily
- eGFR ≥25 and < 45 ml/min/1.73 m2= 5 mg once daily
- eGFR <30 ml/min/1.73 m2= Initiating medication in patients with eGFR less than 25 is not advised, but therapy may be continued to decrease the risk of declining eGFR, ESRD, cardiovascular mortality, and hospitalization for heart failure. Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

Empagliflozin[5]

- 10 mg and 25 mg tablets for oral use
- eGFR ≥45 ml/min/1.73 m2= 10-25 mg once daily
- eGFR <30 ml/min/1.73 m2= Initiating therapy with empagliflozin is not advised in patients with an eGFR of less than 30 ml/min/1.73 m2. However, therapy may be continued to decrease the risk of declining eGFR, ESRD, cardiovascular mortality, and hospitalization for heart failure. Empagliflozin is not advised in individuals with a diagnosis of type 1 DM as it increases the risk of diabetic ketoacidosis (DKA). Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

Ertugliflozin[23]

- 5 mg and 15 mg tablets for oral use
- eGFR ≥45 ml/min/1.73 m2= 5-15 mg once daily
- eGFR < ml/min/1.73 m2= Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m2. It should be discontinued when eGFR is persistently less than 30 mL/min/1.73 m2 or CrCl is persistently less than 30 mL/min. It should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as there is no clinical data to support effectiveness in these patients. Ertugliflozin is not advised in individuals with a diagnosis of type 1 DM as it increases the risk of diabetic ketoacidosis (DKA). Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

eGFR; estimated glomerular filtration rate, ESRD; end-stage renal disease, DM; diabetes mellitus, DKA; diabetic ketoacidosis, CrCl; creatinine clearence

Adverse Reactions

Genital infections are probably the most common adverse effect of gliflozines. In clinical trials, fungal infections, urinary tract infections, and osmotic diuresis occurred more frequently in patients receiving gliflozines (**Table 4**). Because they can increase the absorption of ketone bodies from proximal tubule cells, they can specifically cause euglycemic DKA (DKA in which blood glucose is not elevated).[24] The perioperative period has been reported to be a particularly high risk for ketoacidosis. Therefore, consideration may be given to discontinuing SGLT2 inhibitors before surgery.[25]

Table 4. Common Adverse Reactions Reported in the Patients under SGLT-2 inhibitors[4,5,23,26]

Canagliflozin
• Genital mycotic infections in females (10.6% - 11.6%) • Urinary tract infections (4.4% - 5.9%) • Increased urination (4.6% - 5.1%) • Genital mycotic infections in males (3.8% - 4.2%) • Thirst (2.4% - 2.8%) • Constipation (1.8% - 2.4%) • Nausea (2.1% - 2.3%) • Vulvovaginal pruritus (1.6% - 3.2%)
Dapagliflozin[23]
• Genital mycotic infections in females (6.9% - 8.4%) • Nasopharyngitis (6.3% - 6.8%) • Urinary tract infections (4.3% - 5.7%) • Back pain (3.1% - 4.2%) • Nausea (2.5 - 2.8%) • Genital mycotic infections in males (2.7% - 2.8%) • Influenza (2.3% - 2.7%) • Dyslipidemia (2.1% - 2.5%) • Constipation (1.9% - 2.2%) • Discomfort during urination (1.6% - 2.1%) • Pain in extremities (1.7% - 2%)
Empagliflozin
• Urinary tract infection (7.6% - 9.3%) • Genital mycotic infections in females (5.4% - 6.4%) • Genital mycotic infections in males (1.6% - 3.1%) • Upper respiratory tract infection (3.1% - 4%) • Increased urination (3.2% - 3.4%) • Dyslipidemia (2.9% - 3.9%) • Arthralgia (2.3% - 2.4%) • Nausea (1.1% - 2.3%)
Ertugliflozin
• Genital mycotic infections in females (9.1% - 12.2%) • Urinary tract infection (4% - 4.1%) • Genital mycotic infections in males (3.7% - 4.2%) • Headache (2.9% - 3.5%) • Vaginal pruritus (2.4% - 2.8%) • Increased urination (2.4% - 2.7%) • Nasopharyngitis (2% - 2.5%) • Back pain (1.7% - 2.5%) • Decrease in weight (1.2% - 2.4%) • Thirst (1.4% - 2.7%)

Monitoring SGLT2 Inhibitor Users

Volume status is the most important consideration before initiation of SGLT-2 inhibitors because all patients can be hypovolemic at any age. Symptomatic hypotension and a transient increase in serum creatinine may be observed. Therefore, renal function and blood pressure should be routinely checked after initiation of SGLT-2 inhibitors. Individuals diagnosed with renal impairment receiving a loop diuretic and elderly patients on SGLT-2 inhibitor therapy should be monitored more closely because of a higher risk of complications related to volume depletion. A complete blood count, a metabolic panel including blood glucose, a lipid panel, and renal function tests should be routinely performed because changes in serum creatinine, eGFR, hematocrit, hemoglobin, low-density lipoprotein (LDL) cholesterol, serum bicarbonate, serum phosphate, and potassium may occur to varying degrees after initiation of treatment with an SGLT2 inhibitor.[27,28]

Treatment with SGLT2 inhibitors may cause necrotizing fasciitis of the perineum, also known as "Fournier's gangrene". If perineal necrotizing fasciitis is suspected, appropriate treatment with broad-spectrum antibiotics and, if necessary, surgical debridement should be initiated, and SGLT-2 inhibitors must be discontinued, other treatment options of therapeutic regimens for glycemic control should be used, and blood glucose levels should be monitored after the switch.[28,29]

Canagliflozin and ertugliflozin have been associated with lower limb amputations, so patients with peripheral vascular disease, history of amputation, neuropathy, high HbA1C at baseline, and diabetic foot ulcers should be closely monitored; infection or ulceration must be treated immediately. Lower extremity infections, gangrene, and foot ulcers are the common factor in the causes of amputations.[28]

CONCLUSION

SGLT2 inhibitors are promising new therapeutic options for the treatment of type 2 DM. Reabsorption of filtered glucose, mainly in the proximal renal tubules, is inhibited by their use. This results in glucose excretion in the urine and correction of diabetes-related hyperglycemia. In addition to their effect in ameliorating hyperglycemia, SGLT2 inhibitors offer potential benefits by lowering weight and blood pressure. One SGLT2 inhibitor, empagliflozin, has also been shown to have benefits on renal disease progression, cardiovascular and all-cause mortality, and hospitalization for heart failure. Adverse effects such as hypoglycemia and volume-dependent events necessitate re-monitoring after taking SGLT2 inhibitors. The elderly, patients receiving diuretics, previous orthostatic hypotension, blood pressure lability, or previous syncope are the main factors for the development of adverse reactions.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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Case Report

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Isolated right ventricular thrombus with the severe chronic obstructive pulmonary disease-case report

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ABSTRACT

Immunosuppressive patients experience various side effects from their treatment. Cyclosporine is a commonly prescribed immunomodulatory agent with increasing clinical applications. Although nephropathy is the most common documented side effect, it can cause several cardiac side effects. This report presents a rare side effect of cyclosporine; bradycardia attacks in an immunosuppressed patient.

Keywords: Cyclosporine, cardiovascular toxicity, bradycardia, arrhythmia, syncope

INTRODUCTION

Right ventricular thrombus (RVT) is a life-threatening disorder that is rare and likely underdiagnosed. Multiple risk factors have been found, including younger age, prior bleeding events, congestive heart failure, malignancy, syncopal episodes, transient systolic blood pressure greater than 100 mmHg, and arterial oxygen saturation lower than 90%.[1] Isolated RVT is extremely rare, and it is constantly associated with pulmonary embolism (PE), deep vein thrombosis or right ventricular (RV) infarction.[1,2] We reported a case of isolated RVT with severe chronic obstructive pulmonary disease (COPD).

CASE REPORT

An 80-year-old male patient presented to our emergency department with dyspnea, oxygen saturation of 74%, tachypnoea,and tachycardia. Medical history was positive for chronic obstructive pulmonary disease, Alzheimer's, diabetes mellitus, and atherosclerotic heart disease. The patient did not use his medication and oxygen treatment regularly. An examination of his lungs revealed wheezing and prolonged expiratory sound. The heart beat was regular, and the S1 and S2 were normal. There were no S3, S4, or murmurs. The electrocardiogram (ECG) showed T wave inversion in the anterior (V1-V5) and inferior leads(D2-D3-AVF), the previous ECG was similar. Thoracic computed tomography (CT) was negative for pulmonary embolism and abnormal masses. We applied routine transthoracic echocardiography (TTE) for assessment of cardiac function and there was a 1.5×2.8 cm mass between right ventricular trabeculae. There was also right ventricular dilatation, 2+ tricuspid regurgitation (TR), and tricuspid annular plane systolic excursion (TAPSE) measured 8 mm. We performed cardiac MRI to clarify the diagnosis. A nodular lesion in the right ventricle with a hypointense presentation and no enhancement on late gadolinium enhancement imaging was discovered using cardiac MRI. Apixaban medication was initiated and the patient was followed up under medication.

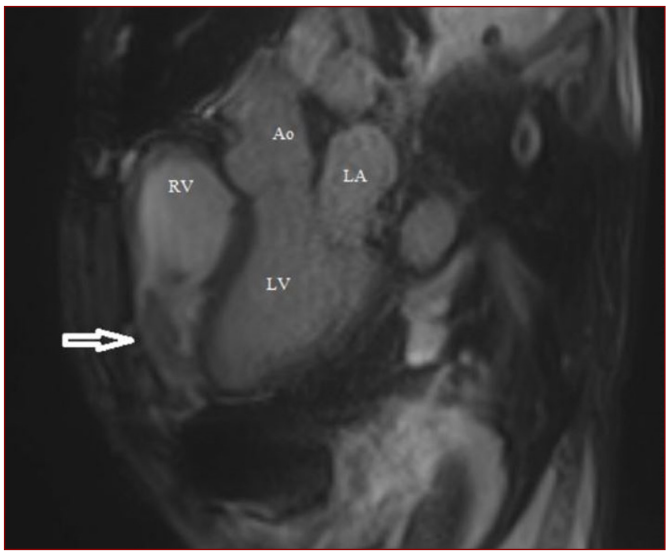

Figure 1: Cardiac MRI image of thrombus

DISCUSSION

Isolated RVT is extremely rare, even though the incidence of right ventricular thrombus is unknown, it has been associated with nephrotic syndrome, RV infarction, and particularly PE in the litarature.[1-4] To the best of our knowledge, this is the first reported case isolated RV thrombus within severe chronic obstructive pulmonary disease.

Cor pulmonale is a clinical condition in which a pressure overload affects the right side of the heart, particularly RV, causing variations in RV function and structure. Pulmonary

hypertension, RV dilatation, and RV longitudinal strain reduction associated with severe COPD in our case may have brought about thrombus formation.[5]

RV thrombus would be identified by TTE, transesophagial echocardiography, and cardiac magnetic resonance imaging. Despite the fact that TTE is the preferred method in clinical practice, diagnosing RV thrombus is not diagnosed as easy as in LV thrombus. Newer studies suggest that CMR is the most specific technique for cardiac thrombi.[6,7] Although cardiac MRI is more expensive than TTE, it may be employed in the differential diagnosis of cardiac mass or when high-mortality diseases such as RVT are suspected.[8]

CONCLUSION

Right ventricular remodeling is common during progress of COPD as well as obstructive and amphiteomatous changes in the pulmonary system. Imaging should be part of the routine examination in patients with COPD to detect thrombus/mass that may affect mortality, as well as assessment for elevated pulmonary pressure.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Cyclosporine induced bradycardia: is it rarely seen?

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ABSTRACT

Immunosuppressive patients experience various side effects from their treatment. Cyclosporine is a commonly prescribed immunomodulatory agent with increasing clinical applications. Although nephropathy is the most common documented side effect, it can cause several cardiac side effects. This report presents a rare side effect of cyclosporine; bradycardia attacks in an immunosuppressed patient.

Keywords: Cyclosporine, cardiovascular toxicity, bradycardia, arrhythmia, syncope

INTRODUCTION

Cyclosporine is a commonly prescribed immunomodulatory agent with increasing clinical applications. The principal application is following solid organ transplantation and certain autoimmune diseases.[1] It has been linked to nephropathy, gingival hyperplasia, and increased hair growth. This report presents a rare side effect of cyclosporine; bradycardia attacks in an immunosuppressed patient.

CASE

A 61-year-old male patient (body weight: 78 kg, height: 1.77 cm) with a history of steroid-resistant immune thrombocytopenic purpura was admitted to the emergency department with syncope. He had no complaints, such as angina, palpitation, or dyspnea. Total loss of consciousness occurred as a sudden and short duration while he was walking, with no prodrome. The patient spontaneously recovered. His past medical history remarks three splenectomy operations, two of which being accessory spleen in 1982, 2015, and 2017. He denied using illicit drugs, mad honey, alcohol, or cigarettes. Before admission, 80 mg methylprednisolone and 50 mg cyclosporine PO were started three weeks ago. Cyclosporine dosage was up-titrated to 100 mg during the first week. He experienced syncope on the second day after the new dose adjustment. During the initial evaluation, blood pressure (BP) was 95/50 mmHg, and heart rate (HR) was 50 bpm. In the initial ECG, sinus bradycardia was detected (PR: 160 ms, HR:50/min, QTc: 402 ms) (**Figure 1**). No abnormality was detected in cardiac and neurologic examination besides the bradycardia. There was no pathology detected in biochemical and hematological parameters. Computed tomography and diffusion magnetic resonance imaging excluded a cerebrovascular incident, trauma, or internal hemorrhage. Transthoracic echocardiography demonstrated a minimal mitral regurgitation with an ejection fraction of 55%. Multiple sinus pauses were revealed in the cardiac telemetry. (**Figure 2**) After intravenous fluid resuscitation and 0.5 mg atropine, BP was increased to 110/60 mmHg, and HR increased to 75 bpm. (**Figure 3**) After a thorough investigation, the adverse drug reaction probability scale (ADR) was calculated as six, and the bradycardia was deemed related to medicine. Although the cyclosporine blood level was calculated as 275 ng/ml, which was in the normal range, the medicine was stopped. Following discharge, 24-hour ambulatory ECG demonstrated a mean HR of 76 bpm, minimum HR of 60 bpm, and a mean QTc of 422 ms, without any significant bradyarrhythmia, and symptoms regressed. The 6th-month follow-up was uneventful.

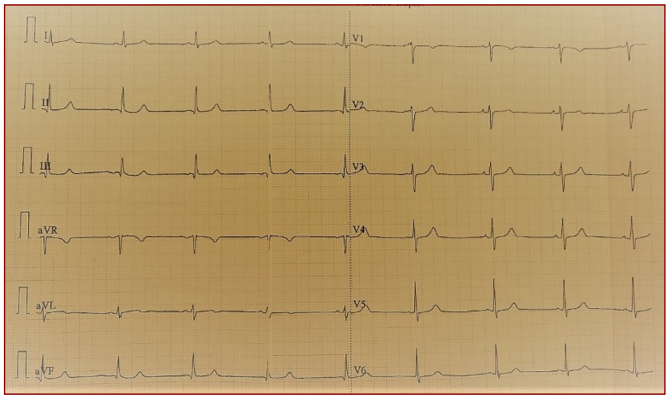

Figure 1. Initial electrocardiography in emergency room demonstrated bradycardia.

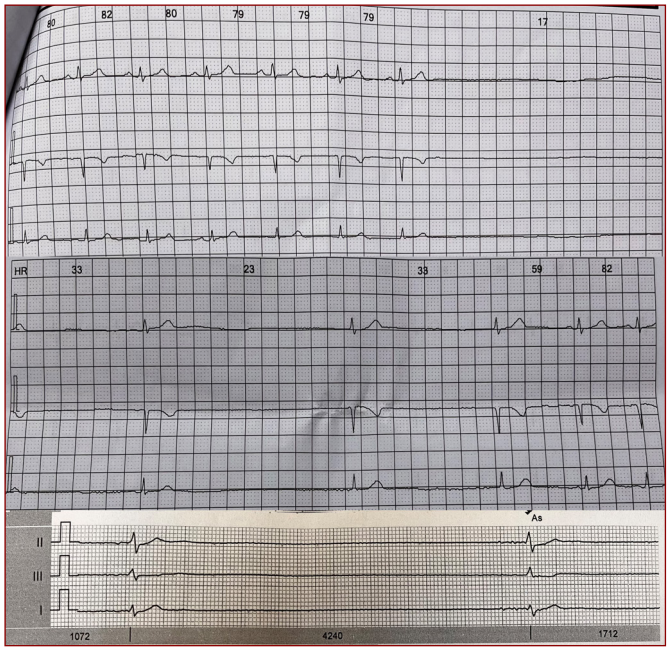

Figure 2: Telemetry records demonstrated multiple sinus pauses.

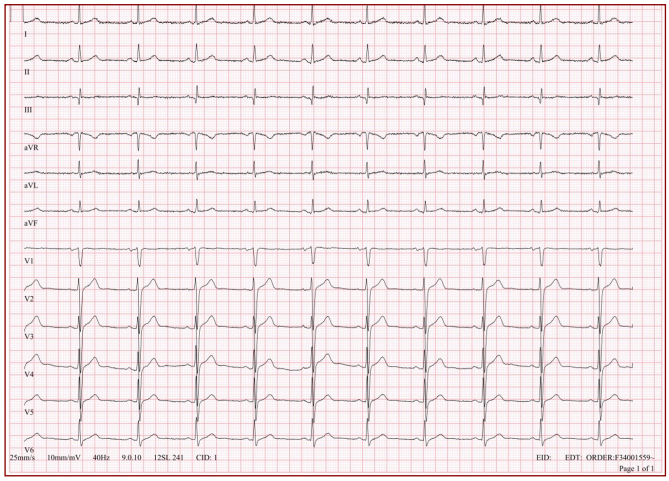

Figure 3: Electrocardiography after the treatment.

DISCUSSION

Cyclosporine is an immunosuppressant drug widely used in transplantation to prevent rejection and treat autoimmune disorders and acts by selective inhibition of the interleukin-2-driven proliferation of activated T-lymphocytes.[2] Nephrotoxicity is the most important; gingival hyperplasia and increased hair growth are clinical side effects. Cardiovascular adverse effects include hypertension and bradycardia after transplantation.[3,4]

In our case, we observed bradycardia attacks caused by the medication. The patient had no structural/arrhythmogenic heart disease and no drug interactions. We used the ADR[5] to assess whether the cause of bradycardia was Cyclosporine. The scale is used to help standardize casualty for all adverse drug reactions, not only for some specific drug classes. We calculated the score as six, the possible ADR in our case.

Moreover, we also performed a search on the Federal Drug Administration Adverse Event Reporting System (FAERS) database.[6] This database is mainly based on individual reports from healthcare professionals or ordinary people who are not healthcare professionals. Although there is a bias possibility due to this mixed nature, it is widely used worldwide and constitutes the most significant side effect database. According to the FAERS database search, only 26 cases were linked to Cyclosporine alone. However, after all of the cases were analyzed, only two of them could be the cause of the bradycardia. As a result, it is safe to say that it is rarely seen.

As our case developed, Cyclosporine induced bradycardia. There are two different mechanisms considered in this setting. The first theory suggests that the drug can suppress nodal automaticity leading to sinus exit block.[7] The following less likely theory suggests bradycardia resulted from the medication's parasympathomimetic activity.[8] The bradycardia side effect was determined as dose-dependent,[4,9] which is consistent with our case. Moreover, steroids, verapamil, diltiazem, and ketoconazole can alter the blood concentration of cyclosporine. Therefore, drug interactions must be considered in every individual, especially when any side effect is encountered. In autoimmune diseases, cyclosporine is used at lower doses compared to post-transplant, and the concentration of cyclosporine in our patient was in the therapeutic range. Even in the therapeutic range, the possibility of side effects, as in our case, should be kept in mind, albeit rarely.

CONCLUSION

Immunosuppressive patients experience various side effects from their treatment. Cardiovascular side effects of their treatment are one of the weighty considerations that can be mistaken. Drug-induced bradycardia must be considered in all patients using cyclosporine in their treatment.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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