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RESEARCH ARTICLES

CASE REPORT

HEART AND HEALTH FOUNDATION OF TURKEY

galenos yayınevi

Editor-in-Chief

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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27
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Administration Office

Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt.
Alsancak / Izmir / Turkey

Phone: + 90 232 464 19 63 / **Fax:** +90 232 464 24 70

e-mail: info@oztekinoto.com | info@tksv.com

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Correspondence

Heart and Health Foundation of Turkey

Address: Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt. Alsancak - İzmir - TÜRKİYE

Phone: +90 232 464 19 63

Fax: +90 232 464 24 70

E-mail: info@tksv.com

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Table of Contents

Volume 11 | Issue 1 | March 2023

Research Articles

Case Report

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Research Article

1

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The Role of Neutrophil-Lymphocyte Ratio and Mean Platelet Volume on the Prognosis of Cardiac Masses

Ali Ahmet Arıkan[1], Burhan Küçük[1], Ahmet Tuğrul Eruyar[2], Aziz Hakkı Civriz[2], Ayşegül Durmaz[3], Oğuz Omay[1], Şadan Yavuz[1], Muhip Kanko[1], Fatih Aydın[4]

[1]Kocaeli University Faculty of Medicine, Department of Cardiovascular Surgery, Kocaeli, Turkey
[2]Kocaeli University Faculty of Medicine, Department of Pathology, Kocaeli, Turkey
[3]Artvin State Hospital, Clinic of Cardiovascular Surgery, Artvin, Turkey
[4]Eskişehir City Hospital, Clinic of Cardiology, Eskişehir, Turkey

Abstract

Objectives: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) are hematological markers used as prognostic markers in cancer and thrombotic diseases. These markers' association with intracardiac masses is unknown. Our goal is to determine the value of NLR, PLR, and MPV as prognostic markers in patients undergoing surgery for intracardiac masses.

Materials and Methods: The study included primary and secondary heart tumors, intracardiac thrombi, and infectious diseases that cause a mass effect in the heart. The pathological examination, location, complications, and mortality are compared with the patients' preoperative characteristics in the heart. The pathological examination, location, complications, and mortality are compared with the patients' preoperative characteristics (NLR, PLR, and MPV).

Results: The surviving patients were followed for 41 (20-75; minimum: 11-maximum: 120) months. NLR was found to be significantly higher in patients undergoing surgery for intracardiac thrombus, pulmonary embolism (PE), or impaired cardiac function (CF) (p=0.031, p=0.021, and p=0.046, respectively). Patients with masses in the left heart chambers and those with postoperative atrial fibrillation had significantly higher MPV values (p=0.001). The expected survival in the

Address for Correspondence: Ali Ahmet Arıkan, Kocaeli University Faculty of Medicine, Department of Cardiovascular Surgery, Kocaeli, Turkey
e-mail: dr_aarikan@hotmail.com **ORCID:** orcid.org/0000-0002-9599-1577
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impaired CF group was significantly lower than in the normal CF group (35.91±13.00 months vs. 109.7±76.92 months, p=0.001).

Conclusion: There was a link between CF impairment and the NLR. The presence or absence of PE, as well as significant differences in NLR between groups of impaired and normal CF, tumors, and thrombus, is thought to be influenced by the patients' clinical condition. The preoperative relationship between the localization of the mass in the left heart and the development of postoperative atrial fibrillation and MPV is remarkable.

Keywords: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, mean platelet volume, intracardiac masses, cardiac tumor, cardiac thrombus

Introduction

Intracardiac masses are uncommon but can cause significant morbidity and mortality. The prevalence of intracardiac tumors ranged between 0.001% and 0.03%[1]. Only 6.4% of patients have their intracardiac thrombi differentiated from tumors during surgery. It has been reported that 15.4% of patients who underwent surgery for an intracardiac tumor had thrombus[2,3].

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory markers used in tumor monitoring, and their relationship with survival has been demonstrated in various tumor types[4,5]. Increased mean platelet volume (MPV) has been linked to hemostatically active platelets and a proclivity to thrombosis. In the presence of atrial fibrillation, it is also linked to stasis, thrombus formation in the heart, and stroke[5,6]. However, there are conflicting findings regarding the role of MPV in thrombotic events[7,8]. The relationship between NLR and PLR with various adverse events has been demonstrated[9-12]. The purpose of this study was to determine the value of prognosticative NLR, PLR, and MPV in predicting the type of mass (thrombi or tumor), the location of the mass, and role in the prediction of complications and mortality in patients who underwent open heart surgery for intracardiac masses. The outcomes of cardiac surgery and their complications are demonstrated.

Materials and Methods

Patients who were operated on with the diagnosis of an intracardiac mass in our hospital's cardiovascular surgery clinic between 2010 and 2020 were analyzed retrospectively after approval from the Non-Interventional Clinical Research Ethics Committee of Kocaeli University with the number of 2021/03.17; 2021/20; 4/02/2021. Patients were divided into three groups based on their etiology: tumor, thrombus, and infection. The patients' demographic information, laboratory results, echocardiography and radiological examinations, and hospital records were all examined.

NLR, PLR, and MPV values were calculated using data from a preoperative blood test. Complications and mortality in the postoperative period were investigated using follow-up records. Cerebrovascular accident (CVA), acute kidney injury (AKI), atrial fibrillation, and the need for inotropic support for more than 12 h were identified as complications (inotrope group). AKI was determined using the Kidney Disease Improving Global Outcomes classification by examining postoperative blood tests[13,14].

Documented postoperative *de novo* atrial fibrillation was described as an AF. All cases in the CVA, AKI, AF, and inotrope groups were analyzed as a single group called the "overall complications" group. The preoperative cardiac function (CF) of the patient is assessed. Patients with an ejection fraction less than 60%, right ventricular failure,

or the need of positive inotropic support for cardiogenic shock were described as having "impaired CF". Patients with normal cardiac function were classified as having "normal CF". Additionally, the patients were grouped according to the presence or absence of preoperative pulmonary embolism (PE), whether the mass was located in the right or left heart, and whether it was a tumor or thrombus. The resulting mortality and its causes were determined and categorized as 1st month mortality, 1st year mortality, and mortality at the end of the follow-up period.

The study included patients who underwent excision surgery for a mass in the myocardium, a heart cavity, or a heart valve. Patients with intra-pericardial tumors that invade the heart, tumors that only invade the intrathoracic great vessels, patients who have had PE without the presence of an intra-cardiac thrombus, patients with concomitant intra-cardiac thrombus with surgical indication for valvular heart disease, intra-cardiac thrombus secondary to a known arrhythmia or ventricular aneurysm, and patients with vegetation or abscess due to infective endocarditis were excluded.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows, version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to assess the assumption of normality. Numeric variables were presented with a mean, standard deviation, and median (25th-75th percentile). Categorical variables are summarized as counts (percentages). Numeric variable comparisons between groups were performed using independent sample t-tests or Mann-Whitney U tests, as appropriate. The association between two categorical variables was examined by chi-square and Fisher's exact test, if needed. The Kaplan-Meier method was used for survival analysis. All statistical analyses were carried out with 5% significance, and a two-sided p-value of 0.05 was considered statistically significant.

Results

Thirty-five patients (16 women and 19 men) were included in the study. Tumor (n=26), tromus (n=7), and infection (n=2) were found to be the causes of the masses. Due to its small population, the infection group could not be assessed in a statistical analysis as a single group. The patients were followed up for 37.5 (13.7-73) months. The mean follow-up period was 35 (12.75-73.00) months in the tumor group and 24 (0-60) months in the thrombus group. Two cases of hydatid cysts were followed for 42 and 99 months, respectively. The survivors were followed for an average of 41 (20-75; minimum: 11-maximum: 120) months. During the follow-up period, no recurring masses were discovered.

Preoperative Features

The baseline characteristics of all intracardiac masses (tumor and thrombus groups) and the comparison of tumor and thrombus groups are presented in Table 1. The infection group consisted of two men, ages 10 and 58, with hydatid cysts located in the left ventricular wall. A patient with atrial fibrillation and thrombus in the left atrial appendage who was operated on for papillary fibroelastoma was included in the tumor group.

In the tumor group, two patients (one with right atrial leiomyomatosis and one with myxoma in the right atrium) had PE without cardiac shock. Four cases in the thrombus group had massive PE hemodynamic instability and were not candidates for thrombolytic therapy. When the tumor and thrombus groups were compared, the risk of developing PE was found to be higher in the presence of intracardiac thrombus (p=0.011) (Table 1).

Positron emission tomography was performed in three patients with tumors before surgery (Figure 1).

Three patients in the tumor group were referred to cardiac surgery for metastasis in the heart (one for a testicular tumor with a diagnosis of mature cystic teratoma, one with a previous diagnosis of liposarcoma, and one

Table 1. The baseline characteristics of all intracardiac masses, tumor and thrombus groups and, the comparison of tumor and trombus groups

	All masses (n=35)	Tumor (n=26)	Thrombus (n=7)	Tumor vs thrombus
Age	56.74±15.46	56.54±14.02	64.00±10.45	p>0.05
Female	16 (45.71%)	12 (46.15%)	4 (57.14%)	p>0.05
Male	19 (54.28%)	14 (53.84%)	3 (42.85%)	p>0.05
Impaired CF	8 (22.85%)	4 (15.38%)	4 (57.14%)	**0.042**
CAD requering CABG				p>0.05
Three vessel disease	2 (5.71%)	2 (7.69%)	-	
LAD stenosis	1 (2.85%)	1 (3.84%)	-	
RCA stenosis	1 (2.85%)	-	1 (14.28%)	
Hypertension	19 (54.28%)	13 (50.00%)	5 (71.42%)	p>0.05
Type II diabetes mellitus	9 (25.71%)	7 (26.92%)	2 (28.57%)	p>0.05
CKD	2 (5.71%)	1 (3.84%)	1 (14.28%)	-
PE	6 (17.14%)	2 (7.69%)*	4 (57.14%)**	**0.011**
Pulmonary hypertension	10 (25.57%)	6 (23.07%)	4 (57.14%)	p>0.05
COPD	2 (5.71%)	2 (7.69%)	-	-
CVA	5 (24.28%)	3 (11.53%)***	2 (28.57%)	p>0.05
PAD	2 (5.71%)	1 (3.84%)	1 (14.28%)	-
Anemia	14 (40.00%)	12 (46.15%)	1 (14.28%)	p>0.05
Female	4 (25%)	3 (25.00%)	1 (25.00%)	-
Male	10 (52.63%)	9 (64.28%)	-	-
Hypotiroidism	2 (5.71%)	2 (7.69%)	-	-
Creatinin (mg/dL)	0.79 (0.62-0.99)	0.74 (0.62-0.89)	1.04 (0.62-1.44)	p>0.05
Neutrophyl count (10^3/μL)	4.40 (3.48-5.80)	4.3 (3.32-5.17)	8.3 (5.10-17.90)	**0.001**
Lymphocyte count (10^3/μL)	1.81 (1.41-2.20)	1.75 (1.47-2.20)	1.81 (1.30-2.50)	p>0.05
Hemoglobin (mg/dL)	12.71±1.55	12.44±1.46	13.58±1.61	p>0.05
Hemotocrit (%)	37.97±4.52	37.09±4.18	41.17±4.50	**0.031**
Platelet count (10^3/μL)	234.14±70.51	234.92±66.94	217.57±91.54	p>0.05
MPV (fL)	8.58±1.31	8.78±1.40	8.06±0.86	p>0.05
NLR	2.37 (1.85-3.42)	2.20 (1.84-2.90)	3.81 (3.07-10.00)	**0.021**
PLR	132.44±43.91	132.75±42.61	133.63±57.37	p>0.05

**: One case with leiomyomatosis,and one case with right atrial myxoma*
***: Right vetricular thrombus with acute massive PE with cardiogenic shock and contraindication to systemic thrombolysis*
****: Three cases with left atrial myxoma were presented with CVA*
CABG: Coronary artery bypass grafting, CAD: Coronary arterial disease, CF: Cardiac function, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident, LAD: Left anterior descending artery, MPV: Mean platelet volume, NLR: Neutrophyl to lymphocyte ratio, PAD: Peripheral arterial disease, PE: Pulmonary embolism, PLR: Platelet to lymphocyte ratio, RCA: Right coronary artery

with a history of intra-abdominal leiomyoma) (Figure 2). Two patients in the thrombus group had organized thrombus in the left atrium and a history of cancer (breast and prostate).

NLR, PLR, and MPV are compared among preoperative CF, tumor localization, preoperative PE and AF, overall complications, and the 30-day, one-year, and total mortality groups (Table 2).

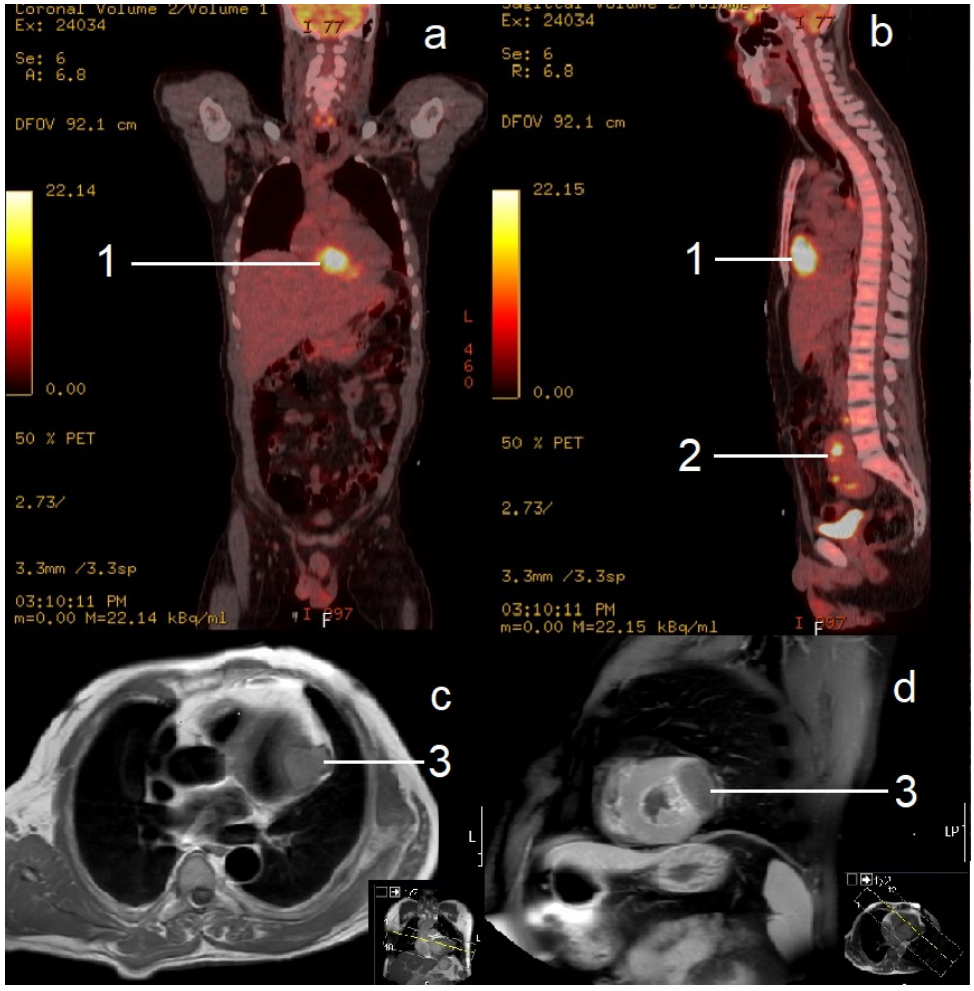

Figure 1. Coronal (a) and sagittal (b) positron emission tomography images of a patient with cardiac (1) and retroperitoneal (2) spread of a testicular tumor. Axial and sagittal magnetic resonance imaging of cardiac cysts (3)

The distribution of the masses according to their location in the heart is given in Table 3.

Postoperative Features

AF developed in 6 (23%) patients in the tumor group and in 1 (14.2%) patient in the thrombus group; AF was not observed in patients operated on for hydatid cyst. AKI developed in 2 (7.6%) patients in the tumor group, and none of the patients required postoperative dialysis. In the tumor group, 1 (3.8%) patient developed postoperative CVA. Eighteen (54.25%) patients were in the inotrope group. The inotrope group consisted of patients in the tumor group (n=13; 50%), in the thrombus group (n=5; 71.4%), and in the infection group (n=1; 50%). There was no significant difference between the tumor and thrombus groups in terms of the inotropic group and overall complications ($p>0.05$). When all complications were examined, no significant difference was found between the tumor and thrombus groups ($p>0.05$).

Thirty-day mortality occurred in a case of left atrial myxoma and postoperative acute respiratory distress syndrome despite the use of veno-venous extracorporeal membrane oxygenation in the tumor group and in two patients in the thrombus group who presented with massive PE and impaired CF. Mortality between 30 days and 1 year was noted to be the result of ventricular fibrillation in one patient operated on for myxoma.

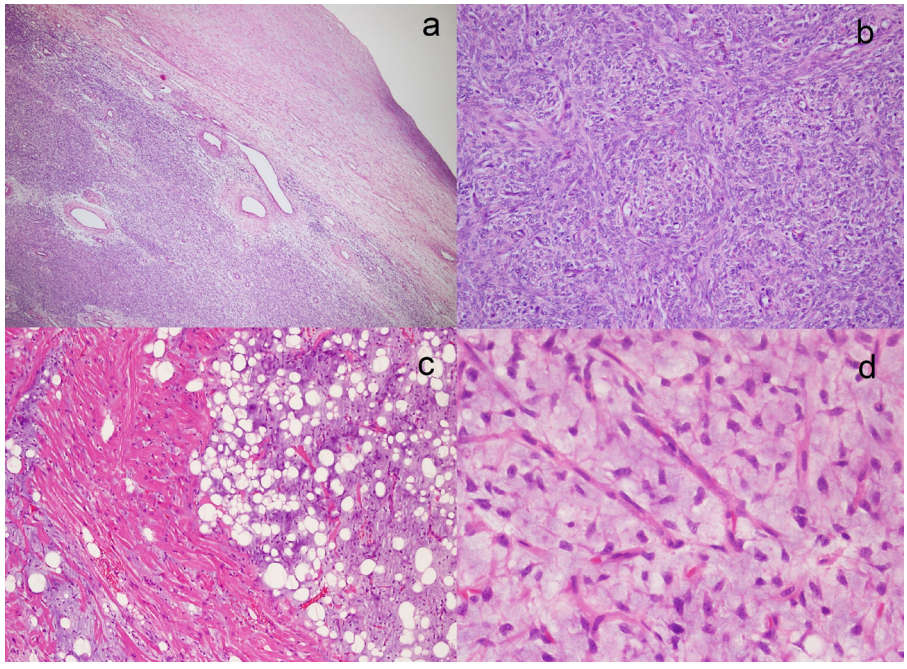

Figure 2. Histological image of intracardiac leiomyoma metastasis (a, b): Cells forming spindle-shaped, intersecting fascicles with indistinct borders are observed. Tumor-forming cells consist of eosinophilic cytoplasm, cigar-shaped nuclei (with tapering ends), and small nucleoli. Atypical mitosis, pleomorphism, and necrosis are not observed in the cells.
Histological image of cardiac liposarcoma metastasis (c, d): lipoblasts with monotonous nuclei, with signet ring cell morphology in places, in a myxoid matrix with a prominent plexiform vasculature between muscle fibers, showing an infiltrative growth pattern. Lipoblasts with indistinct, monotonous nuclei and indistinct cell borders are found in various areas of the tumor within the plexiform vessel framework

Table 2. Compairson of NLR, PLR, MPV among preoperative features and outcomes

	MPV (fL)	p-value	NLR	p-value	PLR	p-value
All mases (n=35)	8.58±1.31	-	2.37 (1.85-3.42)	-	132.44±43.91	-
Impaired CF (n=27)	8.5±1.36	p>0.05	2.18 (1.8-3.07)	**0.046**	136.01±42.98	p>0.05
Normal CF (n=8)	8.88±1.13		3.38 (2.13-9.73)		120.38±47.83	
Preoperative PE (n=6)	8.05±0.94	p>0.05	3.56 (2.38-14.78)	**0.031**	127.54±47.27	p>0.05
Without PE (n=29)	8.69±1.36		2.18 (1.80-3.23)		133.45±44.00	
Right heart (n=12)	7.75±1.00	**0.006**	2.10 (1.80-3.07)	p>0.05	135.99±51.35	p>0.05
Left heart (n=23)	9.01±1.26		2.92 (2.01-7.66)		130.58±40.63	
Postoperative AF (n=7)	9.66±1.44	**0.022**	2.45 (1.54-4.17)	p>0.05	127.41±60.28	p>0.05
Without AF (n=28)	8.31±1.15		2.30 (1.86-3.36)		133.66±40.16	
All complications (n=24)	8.83±1.36	p>0.05	2.44 (1.86-3.44)	p>0.05	134.01±49.05	P>0.005
No complications (n=11)	8.04±1.04		2.18 (1.80-3.38)		129.00±31.67	
30 days mortality (n= 3)	8.02±1.07	p>0.05	3.32 (1.86-29.13)	p>0.05	119.58±51.42	p>0.05
30 days survival (n=32)	8.64±1.33		2.30 (1.82-3.41)		133.64±43.89	
One year mortality (n=4)	8.34±1.08	p>0.05	3.38 (2.22-22.70)	p>0.05	130.82±47.62	p>0.05
One year survival (n=31)	8.61±1.35		2.23 (1.80-3.38)		132.65±44.25	
Overall mortality (n=8)	8.27±1.27	p>0.05	3.00 (1.90-7.57)	p>0.05	135.88±48.51	p>0.05
Overall survival (n=27)	8.68±1.33		2.23 (1.80-3.38)		131.42±43.4	

AF: Atrial fibrillation, CF: Cardiac function, MPV: Mean platelet volume, NLR: Neutrophyl to lymphocyte ratio, PLR: Platelet to lymphocyte ratio

Table 3. Localisation of the masses

	Myxoma	Thrombus	Other tumors	PFE	Hydatid cyst
Aortic valve	-	-	-	3	-
Right atrium	2	5*	1**	-	-
Right ventricle	-	-	1***	-	-
Left atrium	17	1	-	-	-
Left ventricle	-	-	-	-	2†††
Right atrium and VCI	-	1	1†	-	-
Interatrial septum compressing VCI	-	-	1††	-	-

**: One with extension on interartrial septum and patent foramen ovale, one with extension on VCI, one with extension on right ventricle*
***: Rosai Dorfmann disease (Sinus histiositosis)*
****: Fibrin and exudate in a patient with testis tumor*
†: Intravascular leiomyoma
††: Metastasis of myxoid liposarkoma
†††: One of the cases was treated with ventriculoplasty (Dor procedure)
PFE: Papillary fibroelastoma, VCI: Vena cava inferior

Table 4. Relation of localisation, cardiac function and mass type with postoperative outcomes

	n, (%)	AF n, (%)	All complications n, (%)	30 days mortality n, (%)	One year mortality n, (%)	Overall mortality n, (%)
Left heart	23, (65.7%)	6, (26.1%)	15, (65.2%)	1, (4.3%)	2, (8.7%)	3, (13%)
Right heart	12, (34.3%)	1, (8.3%)	9, (75%)	2, (16.7%)	2, (16.7%)	5, (41.7%)
Impaired CF	8, (22.9%)	1, (12.5%)	6, (25%)	2, (25%)	**3, (37.5%)***	**6, (75%)****
Normal CF	27	6, (22.2%)	18, (66.7%)	1, (3.7%)	**1, (3.7%)***	**2, (7.4%)****
Tumor	7 (21.2%)	6, (23.1%)	19, (73.1%)	1, (3.8%)	2, (7.7%)	5, (19.2%)
Thrombus	26 (78.8)	1, (14.3%)	5, (71.4%)	2, (28.6%)	2 (28.6%)	3, (42.9%)

Involvement of the left heart and right; impaired and normal CF, tumor and trombus are compared with the prescence or abscence of AF, overall complications, 30 days mortality, one year mortality, and overall mortality. All of the comparisons had a p>0.05, excepting 1 year mortality and overall mortality between CF groups
**: p=0.030*
***: p<0.001*
AF: Atrial fibrillation, CF: Cardiac function

After 1 year, mortality occurred in patients operated on the right atrial thrombus (at 14 months), Rosai Dorfmann disease (at 42 months), left atrial myxoma and CABG (at 48 months), and leiomyomatosis (at 77 months) due to non-cardiac causes. At the end of the whole follow-up period, mortality was observed in 8 cases (22.8%). The relationship between complications and mortality among the groups of localization, type, complications, and CF of the masses is presented in Table 4.

In the Kaplan-Meier survival analysis, the 1-month survival of the 35 patients examined in the study was 91.4±0.47%. The 12-month survival was 88±0.54%, and the 60-month survival was 73.8±0.09%.

In the impaired CF group, 1-month survival was 75%, 12-month survival was 62.5%, and 60-month survival was 33.3%. In the normal CF group, 1-month survival was 96.3%, 12-month survival was 96.3%, and 60-month survival was 88.9%. The estimated survival in the impaired CF group was 35.91±13.00 months, and the estimated survival in the normal CF group was 109.77±6.92 months (0<0.001) (Figure 3).

In the tumor group, 1-month survival was 96.2±0.03%, 12-month survival was 92.3±0.52%, 60-month survival was 74.6±0.12%, and the estimated survival was 85.73±10.02 months. In the thrombus group, 1-month survival was 71.4±0.17%, 12-month survival was

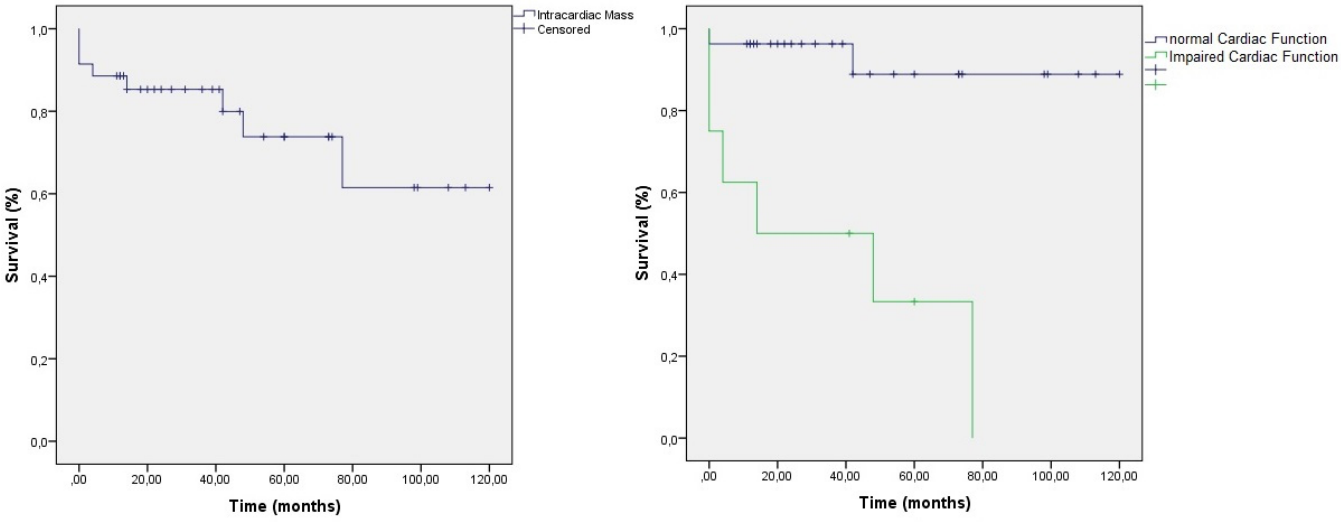

Figure 3. Kaplan-Meier survival analysis of all patients and the comparison of normal and impaired cardiac function

57.1±0.18%, 60-month survival was 57.1±0.18%, and the estimated survival was 70.51±21.63 months. The Kaplan-Meier estimates of overall survival after surgery did not differ significantly between the tumor and thrombus groups (p>0.05).

Discussion

Our study determined the prognostic importance of preoperative NLR, PLR, MPV, preoperative characteristics, and tumor types. The most important prognostic factor was preoperative CF. NLR was related to preoperative cardiac functional status but not to prognosis. MPV was related to postoperative atrial fibrillation and the localization of the mass.

Simple or complex excision, total artificial heart implantation, and cardiac transplantation are surgical treatment options[2]. In our cases, simple excision or patch reconstruction were the most commonly used methods.

The intravascular spread of pelvic or uterine leiomyomas has been described in this context[15,16]. In our series, one patient was operated on for leiomyoma spreading from the inferior vena cava to the heart.

Rarely, infective masses such as hydatid cysts settle in the heart and create a mass effect in the myocardium. The prevalence of Rosai-Dorfman disease (sinus histiocytosis) is also rare[17]. Since we examined cardiac masses, we included cases treated for hydatid cysts and Rosai-Dorfman disease in our study. Both the patients with hydatid cysts survived the follow-up period.

Half of the left heart's myxomas present with thromboembolism due to thrombus formation on them, and echocardiography is often sufficient to differentiate between tumor thrombus and vegetation[18,19]. If needed, MRI can be used for thrombus and tumor differentiation[20]. In our series, left atrial myxoma was presented with CVA in three cases due to thromboembolism of its surface.

Right heart thrombi are usually caused by peripheral embolization[21]. 10% of cases with PE have a thrombus in the right heart[22]. It is known that the presence of a thrombus in the right heart and shock in acute PE are indicators of decreased survival and a poor prognosis[23,24]. In our study, six patients had PE. All of them had tumors or thrombus in the right heart. Four patients with impaired CF and PE and a right heart thrombus had 50% early mortality. A higher rate of PE was found in the thrombus group (p=0.11). Additionally, NLR and the presence of PE were associated (p=0.031). As 4 of 6 patients with PE had acutely developed CF, the patient's clinical picture may

be the reason for the increased NLR rate in the thrombus group.

It has been reported that high MPV is a marker related to a tendency to thrombosis and is associated with higher platelet-related inflammation and thrombotic events[25]. However, there are conflicting findings regarding the association of MPV with the development of left atrial thrombosis and venous thromboembolism[7,8].

In our study, when the masses were divided into right- and left heart involvement, a higher MPV was found with the left heart involvement (p=0.006). Although only three patients had systemic emboli in masses in the left heart, given the increase in MPV, occult systemic emboli in the left systemic mass are possible. Interestingly, despite not reaching statistical significance, when thrombus and tumors were compared, MPV was found to be higher in the tumor group (p>0.05). This can be explained by the difference in the duration of the formation of tumors and thrombi. The longer contact and activation of platelets on an irregular surface in the left-sided masses may have affected the MPV. Meanwhile, considering that 4 of the 7 cases in the thrombus group were presented with acute PE, the acute formation of thrombi and its embolism may not have changed MPV at the time of diagnosis. However, our findings still preclude establishing a relationship between MPV and increased thrombotic processes.

It was found that the increased MPV value in the preoperative period was associated with postoperative AF (p=0.022). As stated above, the MPV was also increased in the masses located in the left heart (p=0.006). It can be argued that the surgical technique needed to reach the masses for excision in the left system may also affect the occurrence of AF. However, no relationship between AF and localization (right or left) in the heart is found (Table 4).

When only complications and mortality were analyzed, the only factor associated with one-year mortality and overall mortality was impaired CF before surgery. Interestingly, the association of impaired CF with 30-day mortality has not been demonstrated. This result shows that although the preoperative cardiac reserve is low, the patient can survive the early postoperative period, but the long-term unfavorable course cannot be prevented.

Study Limitations

The main limitation of our study is the inherited nature of a retrospective study. The small study population can be counted among the limitations. The small number of cases made it difficult to group them according to their clinical status, complications, and preoperative characteristics and compare them during statistical analysis. In addition, the general clinical status and diseases of the patients included in the study were heterogeneous. This prevents us from drawing firm conclusions about the significance of these factors under consideration. However, considering that these diseases are seen rarely, it can be considered that the results obtained from the analysis of the available data are still important. Studies with larger patient numbers may provide additional information on this topic.

Conclusion

In our study, the only factor that predicted mortality at one year and at the end of follow-up was the adequacy of preoperative cardiac function. No relationship between preoperative NLR value and survival could be demonstrated. On the other hand, there was a correlation between poor ventricular function and NLR. The relationship between the localization of the mass in the left heart and the formation of postoperative atrial fibrillation and MPV in the preoperative period is remarkable. No prognostic significance of PLR in intracardiac masses has been demonstrated.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Kocaeli University with the number of 2021/03.17; 2021/20; 4/02/2021.

Informed Consent: The study was designed as a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Design: Data Collection and/or Processing: Analysis and/or Interpretation: Literature Search: Writing: All authors contributed equally.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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The Predictive Role of Systemic Immune Inflammation Index to the Aortic Valve Calcification in the Elderly Population with Chronic Renal Failure

Ferhat Siyamend Yurdam[1], Mehmet Kış[2]

[1]Bakırçay University, Çiğli Training and Research Hospital, Clinic of Cardiology, İzmir, Turkey
[2]Dokuz Eylül University Faculty of Medicine, Department of Cardiology, İzmir, Turkey

Abstract

Objectives: Aortic valve calcification (AVC) is a chronic, degenerative and progressive condition that results of endothelial injury, cholesterol deposition, myofibroblast differentiation and subsequent valve calcification, involving complex pathophysiological mechanisms such as the activation of inflammatory and immune system cells. The frequency of AVC increased in the presence of chronic renal failure (CRF) and with age. The study aimed to reveal the relationship between AVC and systemic immune inflammation index (SII) that includes peripheral neutrophil, lymphocyte and platelet counts in the elderly population with chronic renal failure.

Materials and Methods: Patients over 65 years of age who applied to the cardiology outpatient clinic with chronic renal failure between March 2018 and October 2022 were included in the study. The patients were divided into two groups as group 1 (control group- undetected AVC on echocardiography) (70 patients) and group 2 (AVC detected on echocardiography) (70 patients). SII of all patients was defined as: SII=neutrophil count × platelet count/lymphocyte count. Our study was a retrospective, observational study.

Results: The mean SII value was statistically significantly higher in group 2 (754.2±268.7) than group 1 (622.79±297.2, p=0.007). In the univariable regression analysis of the factors affecting AVC in elderly patients with CRF, neutrophil [odds

Address for Correspondence: Ferhat Siyamend Yurdam, Bakırçay University Çiğli Training and Research Hospital, Clinic of Cardiology, İzmir, Turkey
e-mail: fyurdam83@hotmail.com **ORCID:** orcid.org/0000-0002-8494-2980
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ratio (OR): 0.752; 95% confidence interval (CI): 0.605-0.934, p=0.01], lymphocytes (OR: 2,197; 95% CI: 1,346-3,585, p=0.002), and SII (OR: 0.998; 95% CI: 0.997-1.000, p=0.009) were predictors. In the multivariable regression analysis: SII (OR: 1.002; 95% CI: 1.000-1.005, p=0.034), lymphocytes (OR: 5,660; 95% CI: 2,349-13,637, p<0.001) and neutrophil (OR: 497; 95% CI: 0.344-0.717, p<0.001) were found to be independent predictors. SII> 633.4, 64% sensitivity, and 65% specificity (receiver operating characteristic area under curve: 0.672, 95% CI: 0.582-0.762, p<0.001) are associated with aortic valve sclerosis.

Conclusion: High SII in the elderly with chronic renal failure is associated with the presence of AVCs.

Keywords: Aort calcification, systemic immune inflammation index, and predictivity

Introduction

Aortic valve calcification (AVC) is a chronic, degenerative and progressive condition that results of endothelial injury, cholesterol deposition, myofibroblast differentiation and subsequent valve calcification, involving complex pathophysiological mechanisms such as the activation of inflammatory and immune system cells. It is characterized by hyperechoic appearance on the valves and increased thickness of the valves on cardiac imaging (with echocardiography)[1]. Clinical factors associated with aortic sclerosis include risk factors similar to atherosclerotic heart disease. Persons prone to calcific aortic stenosis (AS) are patients with radiation exposure to the mediastinum, renal failure, familial hypercholesterolemia, or disorders of calcium metabolism[2,3]. The frequency of AVC increases in the presence of chronic renal failure and with age[4]. Progression in renal failure is a critical trigger for the initiation and progression of vascular/valve calcification[5]. The prevalence of calcific AVC in patients over 65 years of age is approximately 2-4%, and its frequency tends to increase with the aging population[6].

Recent studies have begun to show that inflammatory and immune system cells have an important role in the pathogenesis of atherosclerosis as well as play a role in the pathogenesis of heart valve calcification[7]. AVC pathophysiologically affected by the inflammatory process; studies predict the severity of aortic AS by looking at the ratio of blood cells such as neutrophils, lymphocytes, and platelets to each other[8].

Therefore, the systemic immune inflammation index (SII), which includes peripheral neutrophil, lymphocyte, and platelet counts, was developed[6]. In recent studies, high SII has been associated with negative outcomes in patients with oncology follow-up. This index has also been used as a predictive value for mortality in people with atherosclerotic cardiovascular disease[9,10].

The aim of the study aimed to reveal the relationship between AVC and SII in the elderly population with chronic renal failure.

Materials and Methods

Patients over 65 years of age who applied to the cardiology outpatient clinic with chronic renal failure between March 2018 and October 2022 were included in the study.

Exclusion criteria were defined as malignancy, active infection, chronic inflammatory disease, steroid use, severe kidney or liver failure, presence of a prosthetic heart valve, and in which cases could not be performed optimal echocardiographic examination. Demographic data, biochemical parameters, and imaging findings of the patients were recorded.

The patients were divided into two groups as group 1 (control group-undetected AVC on echocardiography) (70 patients) and group 2 (AVC detected on echocardiography) (70 patients). The hemogram and biochemical parameters of the patients at the time of admission were taken as a basis. SII of all patients was defined as: SII=neutrophil

count × platelet count/lymphocyte count. AVC was defined as a dense echocardiographic structure with highly echogenicity features localized to the valves in the parasternal long/short axis, apical five-three-chamber views.

The study was designed as a retrospective and observational. The İzmir Bakırçay University Non-Interventional Ethics Committee approved the study with decision number 2022/753.

Statistical Analysis

The IBM SPSS Statistics 24.0 Program was used for statistical analysis. Numerical variables are presented as mean and standard deviations. Categorical variables are reported as number (n) and frequency (%). In the comparison between the two groups, the independent sample t-test was used if the normal distribution was achieved, and the Mann-Whitney U test was used if the normal distribution could not be obtained. Then, regression analysis was performed to evaluate whether the SII was an independent predictor of AVC in elderly patients with CRF, and finally, receiver operating characteristic (ROC) curve analysis was performed for sensitivity and specificity, and the statistics were completed. The significance level for all hypotheses was accepted as <0.05.

Results

There was no statistically significant difference between the groups in terms of mean age, gender, and body mass index among the patients included in the study. Comorbidities of hypertension, diabetes, hyperlipidemia, and coronary artery disease were similar between the groups. In the echocardiography, the median and interquartile range (Q1-Q3) left ventricular ejection fraction (LVEF) value of the patients was 60% (55-60%), and there was no significant difference between the groups in terms of LVEF. Neutrophil values from biochemical parameters were lower in group 1 than in group 2 (5.24±1.46 vs 5.99±1.8, p=0.008, respectively). Lymphocyte values were higher in group 1 than in group 2 (2.62±0.87 vs 2.19±0.61, p=0.001, respectively). Cholesterol parameters were similar in the groups. The mean SII value was 688.5 (±289.9). It was statistically significantly higher in group 2 (754.2±268.7) than group 1 (622.79±297.2, p=0.007). All demographic data, laboratory results, and echocardiographic findings are shown in Table 1.

In the univariable regression analysis of the factors affecting AVC in elderly patients with CR, neutrophil [odds ratio (OR): 0.752; 95% confidence interval (CI): 0.605-0.934, p=0.01], lymphocytes (OR: 2,197; 95% CI: 1,346-3,585, p=0.002), and SII (OR: 0.998; 95% CI: 0.997-1,000, p=0.009) were predictors. In the multivariable regression analysis: SII (OR: 1,002; 95% CI: 1,000-1,005, p=0.034), lymphocytes (OR: 5,660; 95% CI: 2,349-13,637, p<0.001) and neutrophil (OR: 497; 95% CI: 0.344-0.717, p<0.001) parameters were found to be independent predictors of AVC (Table 2). SII> 633.4, 64% sensitivity and 65% specificity (ROC area under curve: 0.672, 95% CI: 0.582-0.762, p<0.001) are associated with AVC (Figure 1).

Discussion

According to the results of the study, higher SII is significantly associated with the presence of AVC in elderly patients with chronic renal failure.

In a study investigating the predictive value of SII in calcific severe AS, SII levels were found to be higher in the high flow-high gradient AS and low flow-low gradient AS group compared to the control group (525±188, 835±402 and 784±348, respectively) (p<0.001)[6]. In our study, the SII value was found to be higher in elderly patients with CRF with AVC compared to the other group. In a study on coronary artery disease in which inflammation is central to the etiopathogenesis such as heart valve calcification, the cut-off point value of SII ($694.3x10^9$) was revealed to predict major cardiovascular events better than traditional risk factors in patients with CAD after coronary intervention[9]. Similarly, in our study, the SII cut-off value was ($628.7x10^9$).

Notably the valves are usually calcified in aortic valve stenosis that occurs in elderly patients. Unlike rheumatic valve pathology, commissural fusion is not observed. Calcification usually starts from the base of the valve cusps and progresses toward the leaflets and restricts their movement. The calcification of the aortic valve cusps is quite common in the elderly. It is possible to detect AVC, a significant portion of the anatomical and functional changes, with a meticulous echocardiographic examination. Therefore, in our study, we used the echocardiography method in the diagnosis of AVC[11].

Chronic kidney disease is a disease with high renal and cardiovascular morbidity and mortality, negatively affecting the quality of life, and its incidence has increased significantly recently. In patients with CKD, calcification may occur in the myocardium, heart valves, and arteries due to calcium and phosphorus storage[12].

Table 1. Demographic, clinical, biochemical and imaging finding of study population

	Group 1 (n=70)	Group 2 (n=70)	Total (n=140)	p-value
Age (years) mean ± SD	73 (70-78)	71 (68-75)	72 (69-77)	0.15
Male sex, n (%)	30 (42.8)	39 (55.7)	69 (49.3)	0.12
Smoking, n (%)	8 (11.4)	9 (12.8)	17 (12.1)	0.79
BMI, kg/m^2, mean ± SD	24 (22-28)	24 (22-29)	24.2 (22.2-29)	0.7
Heart rate, /min	73.98±6.8	72.0±9.0	73.0±8.03	0.14
Hypertension, n (%)	39 (55.7)	34 (48.5)	73 (52.1)	0.39
DM, n (%)	13 (18.5)	12 (17.1)	25 (17.9)	0.82
CAD, n (%)	34 (48.5)	27 (38.5)	61 (43.5)	0.23
Hyperlipidemia, n (%)	26 (37.1)	24 (34.2)	50 (35.7)	0.72
Urea, mg/dL	37.15±14.69	36.5±15.31	36.82±14.95	0.79
Creatinine, mg/dL	1.96±0.56	1.88±0.57	1.92±0.56	0.42
WBC, × 10^9/L	8.61±2.17	9.12±3.58	8.85±2.91	0.33
Neutrophil, x10^9/L	5.24±1.46	5.99±1.8	5.62±1.68	**0.008**
Hemoglobin, g/dL	13.10±1.52	13.27±1.37	13.19±1.44	0.497
Platelet, x10^9/L	284.5±63.92	266±51.64	275.25±58.64	0.062
Lymphocyte, x10^9/L	2.62±0.87	2.19±0.61	2.41±0.78	**0.001**
Fasting blood sugar, mg/dL	104.61±21.05	108.42±22.8	106.52±21.95	0.3
SII	622.79±297.2	754.2±268.7	688.5±289.9	**0.007**
Total cholesterol, mg/dL	178.51±33.55	172.17±36.23	175.34±34.93	0.28
Triglyceride, mg/dL	181.37±100.6	194.27±99.32	187.82±99.82	0.44
HDL, mg/dL	44.34±15.99	40.18±9.17	42.26±13.15	0.06
LDL, mg/dL	102.41±27.66	97.57±29.17	99.99±28.43	0.31
Sodium, mEq/L	140.4±2.85	139.55±2.36	139.97±2.64	0.059
Potassium, mmol/L	4.38±0.41	4.33±0.42	4.35±0.41	0.42
Calcium, mg/dL	8.76±0.52	8.69±0.59	8.73±0.56	0.45
Phosphate, mg/dL	4.17±0.94	4.06±1.03	4.12±0.98	0.47
LVEF, % Median IQR (Q1-Q3)	60 (54-61)	59 (55-60)	60 (55-60)	0.20
LVEDD, mm	48 (45-51)	47 (44-50)	47.5 (45-50)	0.48
LVESD, mm	30 (26-34)	29 (26-33)	30 (26-34)	0.68
LA diameter, mm	38 (34-43)	38 (34-42)	38 (34-42)	0.92

BMI: Body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease, WBC: White blood cell, SII: Systemic immune inflammation index, HDL: High density lipoprotein, LDL: Low density lipoprotein, LVEF: Left ventricle ejection fraction, LVEDD: Left ventricle end diastolic diameter, LVESD: Left ventricle end systolic diameter, LA: Left atrium, Group 1: Non-calcific aortic valve, Group 2: Calcific aortic valve

It has been shown that the inflammatory process is effective in the pathogenesis of AVC, and a fibrotic and calcific structure is formed on the valve with the contribution of proinflammatory cytokines and immune system cells[13]. Based on this information, different biomarkers have been used to predict the severity of valve calcification[14]. In recent studies, the prognostic values were investigated by calculating the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio[15].

Neutrophil-lymphocyte ratio was found to be negative in mortality and 30-day results in patients who underwent aortic valve replacement[16]. In our current study, it was concluded that neutrophil values were high and lymphocyte values were low in the group with AVC, similar to other previous studies, i.e. is, the N/L ratio was high.

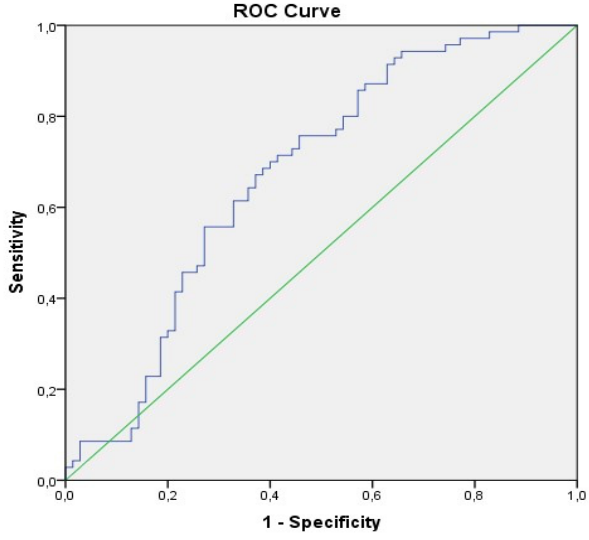

Figure 1. The cut-off value of the systemic immune inflammation index as a predictor of aortic valve calcification in the ROC curve
ROC: Receiver operating characteristic

As a component of the immune response, lymphocytes play an important role in the immune mechanisms. In patients with acute myocardial infarction, low lymphocyte concentration has been shown to be associated with adverse clinical outcomes in the progression of atherosclerosis (similar to the aortic calcification process)[17-19]. Increased lymphocyte apoptosis triggered by aggravated inflammation may decrease lymphocyte counts[20,21]. In conclusion, due to high neutrophil and platelet levels and decreased lymphocyte concentration, an elevated SII may be associated with increased inflammatory activity and therefore lead to poor clinical outcomes.

In a retrospective study conducted to reveal the relationship between mitral annular calcification (MAC) and the lymphocyte count was found to be borderline low in the MAC (+) group compared to the control group (1.86±0.63; 2.02 ±0.66, p=0.05)[22]. In our study, lymphocyte values were found to be lower in AVC group compared to other group.

Study Limitations

Apart from a retrospective feature, our study had limitations such as including a small patient population. Another limitation was that the SII value of the patients was calculated when the patients were admitted to the hospital, and there were no follow-up values.

Conclusion

High SII in the elderly with chronic renal failure is associated with the presence of AVCs. This study may lead to future large-scale randomized studies on the relationship of SII with AVC.

Table 2. Univariate and multivariate logistic regression analyzes in predicting aortic valve calcification in patients with CRF and elderly

	Univariate logistic regression			Multivariate logistic regression		
Variables	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Lymphocyte	2,197	1,346-3,585	**0.002**	5,660	2,349-13,637	**<0.001**
Neutrophil	0.752	0.605-0.934	**0.01**	0.497	0.344-0.717	**<0.001**
SII	0.998	0.997-1.000	**0.009**	1.002	1.000-1.005	**0.034**

SII: Systemic immune inflammation index, OR: Odds ratio, CI: Confidence interval

Ethics

Ethics Committee Approval: The İzmir Bakırçay University Non-Interventional Ethics Committee approved the study with decision number 2022/753.

Informed Consent: The study was designed as a retrospective and observational.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yurdam FS, Kış M, Concept: Yurdam FS, Design: Yurdam FS, Data Collection and/or Processing: Yurdam FS, Analysis and/or Interpretation: Kış M, Literature Search: Kış M, Writing: Yurdam FS.

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Aberrant Subclavian Artery: A Neglected Cardiovascular Pathology

Mehmet Akif Önalan[1], Didem Melis Öztaş[2], Burcu Bıçakhan[3], İbrahim Erdinç[4], Mert Meriç[5], Ufuk Alpagut[5], Murat Uğurlucan[6]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Cardiovascular Surgery, İstanbul, Turkey
[2]Biruni University Faculty of Medicine, Department of Cardiovascular Surgery, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Gaziosmanpaşa Training and Research Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey
[4]University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Clinic of Cardiovascular Surgery, İzmir, Turkey
[5]İstanbul University, İstanbul Faculty of Medicine, Department of Cardiovascular Surgery, İstanbul, Turkey
[6]İstanbul Medipol University Faculty of Medicine, Department of Cardiovascular Surgery, İstanbul, Turkey

Abstract

Objectives: The aberrant subclavian artery is among the congenital vascular anomalies of the aortic arch. Aberrant subclavian arteries can be seen in different types and on the right or left side. Aneurysmal dilatation, named Kommerell's diverticulum, may be seen in the descending thoracic aorta at the origin of the right aberrant subclavian artery. The aim of this study aimed to present our experience with aberrant subclavian artery pathology.

Materials and Methods: This was a retrospective review of our experience from two instutitions with 14 patients who had an aberrant subclavian artery between 2015-2021. Seven patients (62.5%) were male, and the median age at the time of surgery was 38.4 months (range: 6 months to 75 years). Patients were either asymptomatic, incidentally diagnosed, or presented with dyspnea and/or dysphagia lusoria.

Results: Asymptomatic patients were not interfered. There was no early or late mortality in 6 patients who underwent surgery. Three (50%) patients underwent aberrant right subclavian artery repair through right thoracotomy, two received a hybrid approach due to Kommerell's diverticulum, and one patient underwent aberrant left subclavian artery repair from left thoracotomy. The median postoperative duration of the intensive care unit and hospital stays were 1 and 6 days,

Address for Correspondence: Mehmet Akif Önalan, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Cardiovascular Surgery, İstanbul, Turkey
e-mail: mehmetakifonalan@gmail.com **ORCID:** orcid.org/0000-0002-0664-2878
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respectively. Patients were followed for a median of 3.6 years (range, 1.2-6.8 years) after intervention. No endoleak was observed in the follow-up of patients who underwent endovascular repair.

Conclusion: The data suggest that symptomatic aberrant subclavian artery pathology can be treated safely in selected patients with good early and mid-term results. The right or left side of the aberrant subclavian artery may change the surgical approach. Patients with Kommerell's diverticulum with a right aberrant subclavian artery can be treated with a hybrid approach using endovascular techniques.

Keywords: Aberrant subclavian artery, Kommerell's diverticulum, surgical approach, hybrid techniques

Introduction

The aberrant subclavian artery (ASCA) is a congenital aortic anomaly that was first described by Hunauld[1] in 1735[2]. The incidence of the left ASCA is approximately 0.05%, and the right ASCA is 0.5-1%[2]. Kommerell's diverticulum, a descending aortic aneurysm at the origin of an ASCA, occurs in approximately 60% of right ASCA patients[3].

ASCAs uncommonly cause symptoms such as chest pain, dysphagia, and dyspnea[4]. However, dysphagia due to ASCA is also referred to as "dysphagia lusoria", hassle in swallowing solid food is a pathognomonic sign fort he disease[5].

The right ASCA and left ASCA develop embryologically in different ways. The right ASCA occurs when the right fourth arch involute cranially to the seventh intersegmental artery. Left ASCA occurs by the anomalous regression of the left fourth arch and left dorsal aorta[6]. The right ASCA is more constant than the left ASCA, and it is usually related to other congenital cardiac anomalies[7].

It has been presented that ASCA and Kommerell's diverticulum may be predisposed to engage in aneurysmal degeneration, so compose important risk factors for distal embolization, compression of adjacent structures, aortic dissection, and rupture[8]. Several surgical and endovascular techniques have been suggested for the treatment of these aneurysms[9,10]. The aim of this study was to present our experiences with ASCA with different surgical techniques.

Materials and Methods

Medical records of 14 consecutive patients who were diagnosed with ASCA between January 2015 and December 2021 were retrospectively. Patients with different aortic arches or vascular ring pathologies were excluded from the study. The data were collected retrospectively from patients' previous hospital records. Our study was approved by the Institutional Ethics Committee of İstanbul Medipol University (approval no: 24/11/2022, date: 1011) and was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 14 patients met these criteria, including 7 males and 7 females. The median age of the patients was 38.4 years (range, 6 months to 75 years), and the median weight of the patients was 48.6 kg (range: 5 to 82 kg).

Preoperative thoracic computed tomography (CT) angiography (Figure 1) was performed in all patients to define aortic arch anatomy and to detect Kommerell's diverticulum or aneurysm if present. Thirteen patients had a right ASCA and one patient had left ASCA. Two of the 14 patients had Kommerell's diverticulum concomitant to the right ASCA.

Six of the were symptomatic and had dysphagia lusoria or respiratory problems due to tracheal compression. The remaining 8 patients were asymptomatic and diagnosed incidentally.

Surgical Technique

The operations were performed through right thoracotomy in the 3 patients with right ASCA. Systemic heparinization (100 U/kg) was performed after the

preparation of ASCA and the descending aorta. The right ASCA was carefully resected from the descending aorta, and the stump on the descending aorta was repaired primarily. The ASCA was anastomosed directly or with the use of a graft to the ascending aorta or the right common carotid artery. We used near-infrared spectroscopy for neurological monitorisation in all patients.

The left thoracotomy approach was used in a patient who had left ASCA with a right aortic arch and ligamentum arteriosum. This complete vascular ring pathology was repaired by the division of the ligamentum arteriosum.

The hybrid approach was preferred in 2 patients who had Kommerell's diverticulum. In these patients bilateral infraclavicular incision were performed and bilateral axillary arteries were dissected. An 8 mm ringed PTFE greft was placed subfascially and anastomosed end to side to the bilateral axillary arteries. Then the patients were then transferred to the angiography unit and the right femoral artery was dissected surgically for the endovascular procedure. The proximal of the right ASCA occluded endovascularly to prevent endoleak. The stent greft was placed distal to the left subclavian artery orifice until the midportion the descending thoracic aorta to exluded the aneurysm. The femoral artery was reconstructed primarily after the delivery system removal.

Except for the patient who was operated for the left ASCA, the other 5 patients received 100 mg aspirin and 75 mg clopidogrel for 3 months. After 3 months, these patients received only one antiplatelet therapy for lifelong. Control CT angiography was performed on all patients who underwent surgery at the 3rd postoperative month. In patients who underwent the thoracic endovascular aortic repair (TEVAR) procedure, additional control CTA was performed in the postoperative 1st year.

Statistical Analysis

IBM SPSS Statistics Software 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were reported as median ± range. Categorical variables were reported as n (%).

Results

Symptomatic patients were treated surgically, and asymptomatic patiens without Kommerell' diverticulum were followed up in this study. Three symptomatic patients who had right ASCA underwent ASCA surgical treatment through right thoracotomy and ASCAs were implanted into the ascending aorta (Figure 2) directly in one patient, with the use of a graft in another patient and directly to the right carotid artery in one patient. The two patients with Kommerell's diverticulum were treated with a hybrid approach and TEVAR procedures (Figure 3). The last symptomatic infant who had a complete vascular ring with left ASCA, right aortic arch, and left ligamentum arteriosum underwent vascular ring

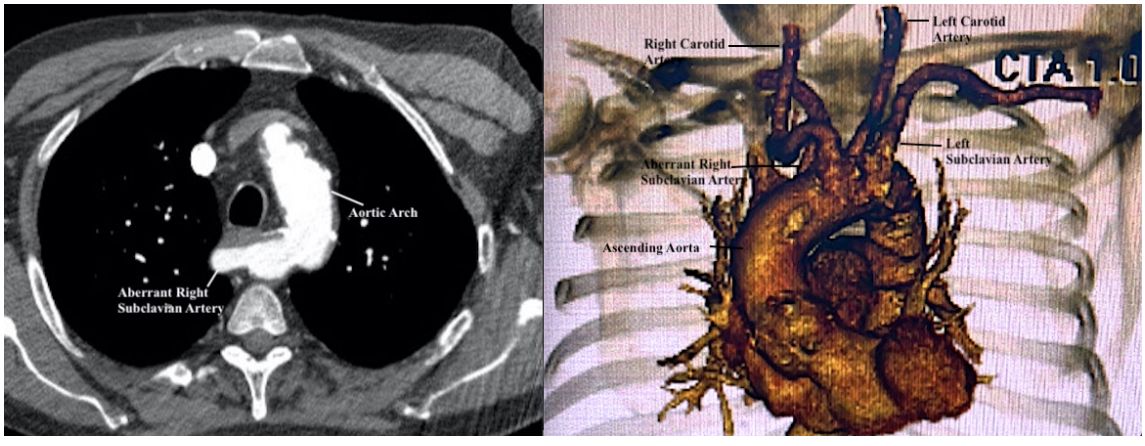

Figure 1. CT angiography view of the right ASCA
CT: Computed tomography, ASCA: Aberrant subclavian artery

division by the division of the ligamentum arteriosum through left thoracotomy.

Patients who underwent an operation had an uneventful postoperative course. No vascular or respiratory complications were observed. The median duration of intensive care unit stay after the operation was 1 day (range: 1-2 days) and the median duration of hospital stay after the operation was 6 days (range: 4-8 days). Postoperative early mortality, upper extremity ischemia, and wound problems were not observed, and all patients were discharged from the hospital uneventfully.

The median of follow-up for all patients was 3.6 years (range: 1.2-6.8 years). No endoleak, native, or bypass graft occlusion were observed in patients who received treatment. Significant regression in symptoms was observed in all patients immediately as wel as during the follow-up.

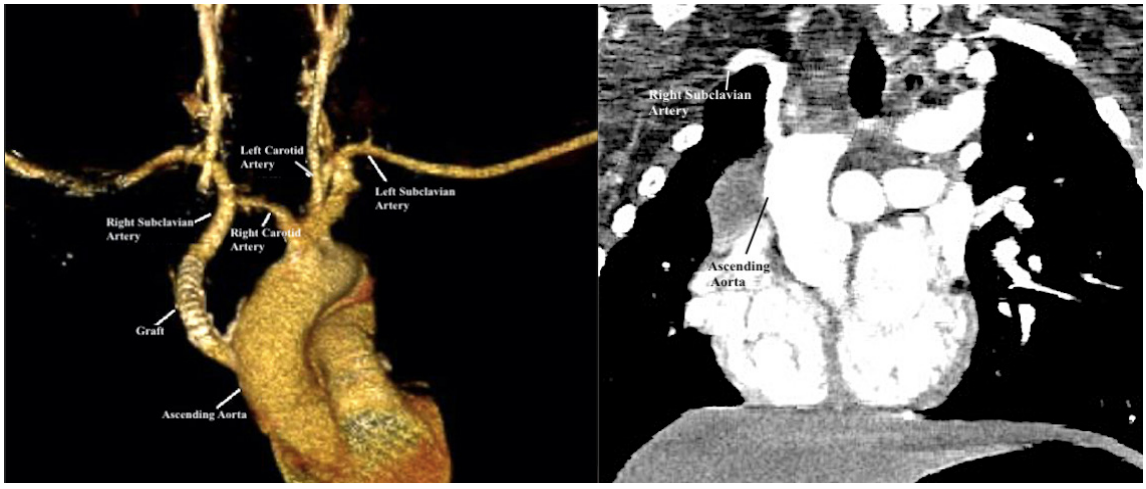

Figure 2. Conventional surgical treatment of right ASCA. Division from the descending aorta and re-implantation to the ascending aorta with an estension graft

ASCA: Aberrant subclavian artery

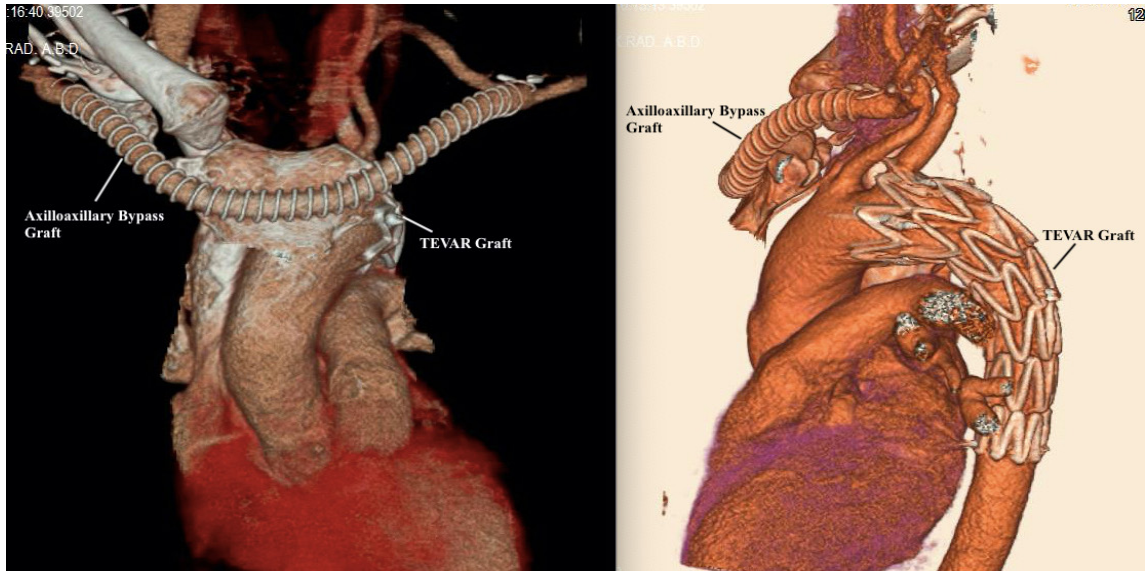

Figure 3. Hybrid treatment for Kommerell's diverticulum. Axilloaxillary bypass followed by TEVAR

TEVAR: Thoracic endovascular aortic repair

Discussion

This report presents our surgical experience and medical follow-up of the 14 patients who had ASCA. The primary goal of our surgical management in patients with ASCA is to relieve symptoms and prevent aortic dissection or rupture in patients with Kommerell's diverticulum.

The left ASCA originating from the right aortic arch is less common than the right ASCA. Kommerell's diverticulum may be found in up to 60% of patients with this variant[10,11]. Consistent with the literature in our study, only 1 (8.3%) patient had left ASCA, whereas 13 patients had right ASCA. However, in our study, unlike the literature, 14.2% of patients (2 patients) had Kommerell's diverticulum, which may be attributed to the small cohort size.

The course of aneurysms associated with Kommerell's diverticulum is not known precisely because of the rarity of the anomaly[12]. Nonetheless, rupture, or dissection of these aneurysms have been reported in the series[10,12]. Cinà et al.[10] reported that the rate of dissection or rupture was 53% among 32 patients, and Kouchoukos and Masetti[12] reported that the rate of dissection was 20% in 10 patients. In our series, only 2 patients had aneurysm related to Kommerell's diverticulum and none had rupture or dissection; however, patient patients were treated to prevent such complications.

A number of surgical approaches such as ASCA repair via right or left thoracotomy, and open surgical repair of Kommerell's diverticulum or hybrid approach with endovascular repair have been defined in the literature[9,10,13]. The thoracotomy has to be on the same side with the ASCA, ie through right thoracotomy for the right ASCA and through left throacotomy in the left ASCA with right aortic arch; otherwise, re-implantation attempts would end up with additional abberancy or when it is ligated and divised, the corresponding arm will receive pulseless nategrade flow. We preferred right thoracotomy approach in the right ASCA without Kommerell's diverticulum. We resected the right ASCA from the descending aorta and anastomosed the right subclavian artery to the right common carotid artery or the ascending aorta. We preferred left thoractomy approach in the left ASCA with a right aortic arch and performed division of the ligamentum arteriosum. The hybrid approach was preferred in the right ASCA with Kommerell's diverticulum. Kommerell's diverticulum was excluded with a stent graft following axilloaxillary bypass to establish the right upper extremity circulation. We did not prefer open surgical repair due to comorbidities in patients who had Kommerell's diverticulum concominat to the right ASCA as well as the considerable risks of the conventional open surgery.

The indication for surgical intervention in asymptomatic or symptomatic patients has not yet been clearly determined. According to a recently published consensus guideline, surgical treatment was recommended (Class 1) in symptomatic patients with ASCA and/or Kommerell's diverticulum[13]. The same consensus guideline recommends treatment when aneurysmal ASCA is greater than 3 cm in diameter and Kommerell's diverticulum is greater than 5.5 cm because of the risks of rupture and dissection[13]. Backer et al.[14] suggested that the size of the Kommerell's diverticulum being 1.5 times larger than the subclavian artery might be a point to consider surgical or endovascular intervention. We preferred the hybrid approach with TEVAR and axilloaxillary bypass in two patients with aneurysmal dilatation.

While dysphagia as a symptom is more common in grown -up patients with ASC, respiratory problems are more common in infants[15]. In our study, only one infant patient was operated against respiratory and alimentation symptoms, and the remaining patients were treated for dysphagia lusoria and/or Kommerell's diverticulum.

Study Limitations

There are 2 major limitations of the study regarding with the retrospective nature of the design and limited cohort size despite the inclusion of two centers.

Conclusion

In conclusion, according to the results of the current research, symptomic patients with ASCA or patients with Kommerell's diverticulum may be treated with conventional surgical techniques or hybrid methods safely with good mid term results. Asymptomatic patients may be followed uneventfully. Studies with multiple centers, including an increased number of patients and long-term outcomes, are warranted to establish a consensus regarding the pathology.

Ethics

Ethics Committee Approval: Our study was approved by the Institutional Ethics Committee of İstanbul Medipol University (approval no: 24/11/2022, date: 1011).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Önalan MA, Öztaş DM, Alpagut U, Uğurlucan M, Concept: Öztaş DM, Erdinç İ, Design: Öztaş DM, Alpagut U, Uğurlucan M, Data Collection and/or Processing: Önalan MA, Öztaş DM, Meriç M, Analysis and/or Interpretation: Bıçakhan B, Erdinç İ, Uğurlucan M, Literature Search: Önalan MA, Bıçakhan B, Writing: Önalan MA, Meriç M, Uğurlucan M.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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After Arterial Switch Surgery Myocardial Performance Index Left Ventricular Function does it Provide as much Information as a Cardiac MRI?

Kaan Yıldız[1], Yasin Ertuğ Çekdemir[2], Muhammet Salman[2], Mustafa Kır[1], Handan Güleryüz[2], Öztekin Oto[3], Nurettin Ünal[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey
[2]Dokuz Eylül University Faculty of Medicine, Department of Radiology, İzmir, Turkey
[3]Dokuz Eylül University Faculty of Medicine, Department of Cardiovascular Surgery, İzmir, Turkey

Abstract

Objectives: In this study, a comparison of cardiac magnetic resonance imaging (MRI) and simultaneous transthoracic echocardiography data were obtained from patients with great artery transposition (TGA), who underwent arterial switch operation (ASO) surgery. In to discover the most effective and optimal viewing method during long-term follow-ups.

Materials and Methods: This retrospective cohort included 20 TGA patients (16 male, 4 female), which had ASO surgery. Along with cardiac MRI and transthoracic echocardiography data were obtained from the images. The mean age was 93.00±29.82 months (60-144). Seventeen patients had TGA only. However, 3 patients with TGA included an existing ventricular septal defect.

Results: We showed a meaningful correlation between echocardiographic variables (left ventricle dilatation of the left ventricle function of the aorta failure, myocardial performance index) and MRI parameters (ejection fraction of left ventricle dilatation of the left ventricle function of the aorta insufficiency).

Address for Correspondence: Kaan Yıldız, Dokuz Eylül University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey
Phone: +90 532 215 37 35 **e-mail:** drkaanyildiz@gmail.com **ORCID:** orcid.org/0000-0001-9722-6994
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Conclusion: TGA patients require careful pre and post operative evaluation, anatomical and a functional use of cardiac indicators. For this purpose, both echocardiography and MRI are useful, safe, and trustworthy methods of diagnosis. Choosing the optimal imaging technique and lifetime reoccurring assessments of the left ventricle function is of vital importance in foreseeing complications, preventing morbidities, and creating a protocol. In clinical practice, the myocardium performance index provides values similar to that of the MRI about the left ventricle dilatation and left ventricle dysfunction. These results provide awareness about the use of specific parameters and the use of information based on quantitative data.

Keywords: Great artery transposition, arterial switch, myocardial performance index, echocardiography, magnetic resonance imaging, pediatric

Introduction

In the long-term follow-up of patients undergoing arterial switch operation (ASO), the left ventricle (LV) functions, which is the systemic ventricle, are of primary importance. Various non-invasive diagnostic methods are available for the diagnosis of pediatric congenital heart diseases and for the determination of ventricular functions[1]. Two dimensional echocardiography is the most widely used method in clinical practice. Although echocardiography is a common, inexpensive and non-invasive method, it depends on the operator and in some cases, the desired quality images may not be obtained due to the limited acoustic windows[2].

Cardiac magnetic resonance imaging (MRI) is another non-invasive technique used to determine LV function. Cardiac MRI, with its high spatial resolution and three-dimensional representation of structures, is an excellent technique for evaluating both left and right ventricular function. Highly accurate and reproducible quantitative measurements can be obtained with multiplane imaging in compliant patients without sedation[3,4]. Cardiac MRI cannot be performed in all centers because it requires a special technique and interpretation by experienced specialists. Data obtained with the correct imaging technique in cardiac MRI minimize operator-related errors that may occur in echocardiography[5]. Serial imaging should be performed in patients undergoing ASO to demonstrate structural changes in tissues associated with surgery. Cardiac MRI has been used frequently recently to evaluate ventricular functions, to measure the peak rates of regurgitation in the aorta and pulmonary arteries, and to show stenosis[6]. On the other hand, different parameters obtained from echocardiographic variables can be used to evaluate LV functions similar to that of an MRI and provide beneficial and sufficient data. A method is a tissue Doppler echocardiography myocardium, which can give information about diastolic performance directly, independent of the cardiac preload. The interpretation of speed values obtained by measurement of diastolic time intervals and different examination positions can be used to evaluate diastolic functions at a local and global level. The early detection of the loss of diastolic function before that of the systolic function is possible with a tissue Doppler and myocardium performance index (MPI)[7,8].

Our aim was to compare transthoracic echocardiography (TTE) and tissue Doppler findings and discover the most optimal and effective imaging method in TGA patients undergoing ASO for long-term follow-up.

Materials and Methods

This retrospective cohort was conducted between 01.09.2018 and 31.08.2019 in the radiology and pediatric cardiology departments of the tertiary health center. It has been ensured that the principles of confidentiality of the identity and medical information of the patients are strictly adhered to.

Cardiac MRI and TTE images obtained from the hospital records of 20 TGA patients (16 boys, 4 girls) were analyzed retrospectively. The mean age was 93.00±29.82 months (range: 60-144). Seventeen patients had TGA only, and 3 patients had TGA together with VSD.

It was planned to reach all patients with available cardiac MRI and concurrent echocardiography recording; therefore, so the exact number of patients was unpredictable. It is planned to compare and evaluate the parametric findings detected in cardiac MRI and echocardiography. The compatibility of techniques and their advantages over each other in determining LV functions and valve regurgitation in patients undergoing ASO for TGA was investigated using numerical measurements. Inclusion criteria were TGA patients aged 5 years and older who had undergone ASO and had no history of sedation or anesthesia. The study was approved by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval no: 2018/20-38, date: 02.08.2018).

TTE

The TTE examination using the Philips Affinite 50c system (Philips, Netherlands) was carried out. Consecutive cardiac loops with enough technical quality were repeated thrice to provide a measurement for analysis. LV functions four apical chamber and parasternal long axis in their windows were evaluated. Aorta lid insufficiency was viewed using an apical five-chamber window. The tissue Doppler method with MPI was measured. Echocardiographic measurements for MPI were obtained from the apical four-chamber view. A cursor was placed on the myocardial segment of the left ventricular posterior wall and interventricular septum. Myocardial tissue velocities were recorded by placing pulsed wave tissue Doppler at the level of the basal segments of each.

MRI

MRI 1.5 Tesla Philips Ingenia system (Philips, Netherlands) performed. All patients had a regular cardiac rhythm, and ventricular visualization was achieved using cine images starting from the entry point of the ventricles,

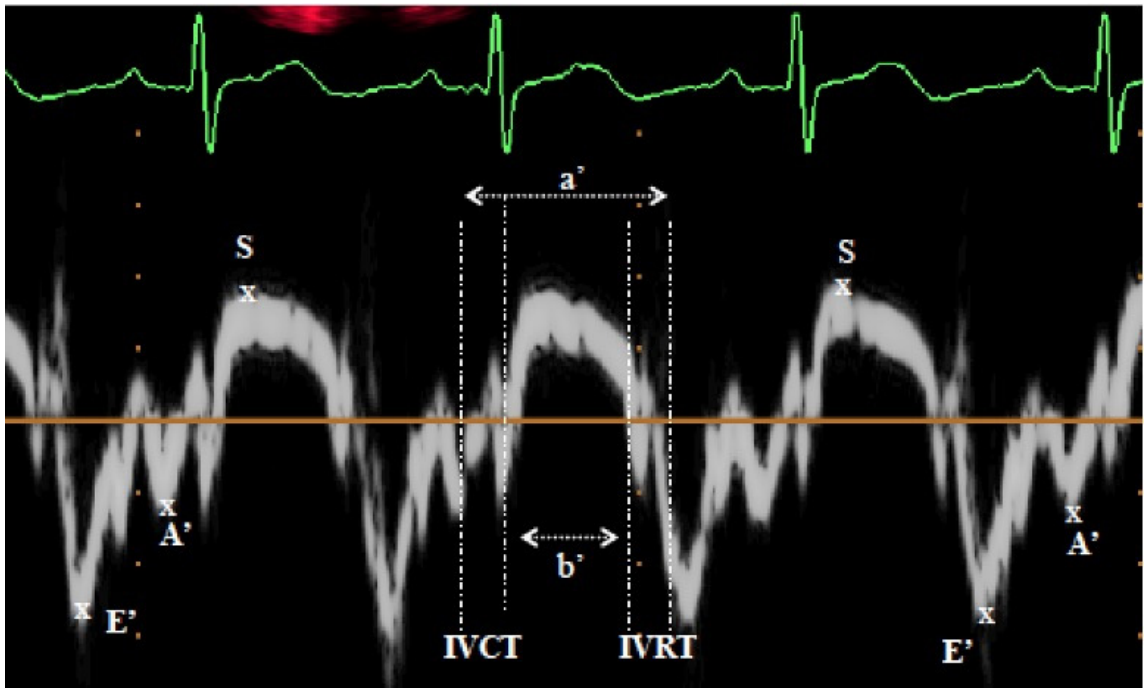

Figure 1. Identification of signals obtained by tissue Doppler echocardiography

leading to the apex at a orthogonal long axis of the LV with more than 10 mm adjacent breath holding.

Ventricular mass was calculated using end-diastole epicardial and endocardial surfaces. Myocardial volume applied the Simpson's rule for calculation, and myocardial mass density was accepted as 1.05 g/m^3. Septum was accepted as part of the LV, and end-systole endocardial-volume measurements were used for the calculation of the ejection fraction.

Outcome Measures

LV and aorta lid functions were digitally calculated as parameters. Echocardiograms with tissue Doppler get MPI, neoaorta and neopulmonary artery diameters and deficiencies, visibility of right and left pulmonary artery branches, LV dilatation, ejection fraction, systolic, and diastolic functions were considered. Cardiac LV function in MRI values, aorta, and pulmonary artery functions with dynamic MR views were calculated by digital aspects. LV ejection with cardiac MRI fraction, LV end diastolic and systolic volumes of neoaortic with neopulmonary artery diameters and deficiencies, and right and left pulmonary artery visibility are evaluated. In this study, LV function values, aorta, and pulmonary lid function using MR and echocardiography were the parameters determined as dependent variables.

Echocardiography Variables

1. With or without LV dilatation specified. If the LV volume was larger than the right ventricle (RV) volume, it was accepted as a pathological result.

2. LV dysfunction were defined as, without: 1, with: 2

3. Measurements for aorta lid insufficiency were calculated according to the apical five -chamber window and its length of jet. 1: normal, 2: mild, 3: moderate, 4: significant

4. The calculation was performed in accordance with the study of MPI, MPI = (isovolemic contraction duration + isovolemic relaxation duration)/ejection duration[9].

Statistical Analysis

Descriptive statistics for digital variables average, standard deviation, minimum, and maximum values with categorical variables for number and percent values are given. The correlation values between indicators and other data types with different correlation (pearson, tetracolic, polychoric and eta correlation coefficients) coefficients are examined. Analysis was carried out using the IBM SPSS program version 21.0.

Results

In our study, basic patient information is presented in Table 1. Our patient population (n=20) consisted of 16 men with a mean age of 93.00±29.82 months (range: 60-144) and 4 women. In 17 patients, only TGA was seen; with TGA in 3 patients together, there was VSD. The mean body mass index is 16.37±2.34 kg/m^2 and mean age for ASO was 7.30±10.53 days.

The data obtained from this series of echocardiography and MRI are shown in Table 2. During the echocardiography

Table 1. Baseline descriptives for demographic data

		Number	Percentage
Gender	**Female** **Male**	4 16	20.0 80.0
Diagnosis	**TGA** **TGA + VSD**	17 3	85.0 15.0
		Mean - Standard deviation	**Min.-Max.**
Age (months)		93-29.82	60-144
Age at the time of ASO (days)		7.30-10.53	1-48
BMI (kg/m^2)		16.37-2.34	12.9-23.2

TGA: Transposition of the great arteries, VSD: Ventricular septal defect, ASO: Arterial switch operation, BMI: body-mass index, Min.: minimum, Max.: maximum

of one patient, LV dilatation and dysfunction detection was observed. The MPI average was 0.38±0.04.

In one patient, LV dilation and dysfunction was detected from MRI images. The average values of LV end diastolic volume and ejection fraction for values were 78.98±47.21 and 62.43±7.52, respectively. The average degree of aorta failure (%) was 8.138.

Table 3, summarizes the echocardiographic and MRI variables between the relationship correlation matrix. Analysis of our data of LV dilatation on echocardiography, LV end systolic volume on MRI (r=0.75), LV dysfunction (r=0.99), and aorta failure degree (r=0.90) revealed a strong and positive relationship.

In echocardiography aortic failure LV dilatation (r=0.92) and LV dysfunction (r=0.94) on MRI showed a strong and positive correlation. In echocardiography, aortic failure with the LV ejection fraction displayed an opposite relationship (r=-0.85).

MPI, LV dilatation (r=0.81), and LV dysfunction (r=0.94) on MRI had a strong and positive correlation.

Table 2. Descriptive data for echocardiography and magnetic resonance imaging parameters for our series

		Mean (Number)	Standard deviation (%)	Minimum	Maximum
Echocardiography					
LV dilatation	**No** **Yes**	19 1	95.0 5.0		
LV function	**No** **Yes**	1 19	5.0 95.0		
AI grade	**1** **2** **3** **4**	13 5 1 1	65.0 25.0 5.0 5.0		
MPI		0.38	0.04	0.30	0.43
MRI					
LVEDV		78.98	47.21	44	270
LVEF		62.43	7.52	50	75
LV dilatation	**No** **Yes**	19 1	95.0 5.0		
LV function	**No** **Yes**	3 17	5.0 95.0		
AI %		8.13	13.48	0.80	43.5

LV: Left ventricular, AI: Aortic insufficiency, MPI: Myocardial performance index, EF: Ejection fraction, LVEDV: Left ventricular end diastolic volume, MR: Magnetic resonance

Table 3. Correlation matrix for the relationship between parameters derived from echocardiography and magnetic resonance imaging

				Magnetic resonance imaging			
		LVEDV	**LV (EF)**	**LV dilatation**	**LV function**	**Root of aorta**	**AI %**
Echocardiography	**LV dilatation**	0.75	**0.40**	**1.00**	**0.99**	0.36	**0.90**
	LV function	0.93	**-0.88**	**0.98**	**1.00**	0.38	**0.94**
	AI	0.05	**-0.85**	**0.92**	**0.94**	0.82	**0.95**
	LV (MPI)	0.31	0.12	**0.81**	**0.93**	**-0.19**	0.91
	Root of Aorta	0.23	0.28	**0.23**	**0.93**	0.65	**0.89**

Bold figures indicate high degree of relationship, while negative figures indicate an inverse relationship between variables
LV: Left ventricular, AI: Aortic insufficiency, MPI: Myocardial performance index, EF: Ejection fraction, LVEDV: Right ventricular end diastolic volume

Echocardiography of LV with MPI in MRI between aortic roots had an opposite relationship (r=-0.19).

Discussion

LV dysfunction can be seen in patients who underwent an ASO. Careful monitoring and follow-up are essential for the prediction and prevention of complications that may lead to morbidity and mortality[10]. In this patient group, evaluation of the hemodynamic profile for multiple viewing methods was confirmed. There have been significant advances in the clinical diagnosis and treatment of patients with TGA due to the utility of recent advancements in viewing methods. TGA patients require lengthy surveyance due to their recurring anatomic and hemodynamic abnormalities. Therefore, TGA patients undergoing ASO require an optimal viewing protocol and an integrated algorithm. The widespread availability and utility of an echocardiography is the factor for its essential role in the diagnosis of TGA in patients. Two -dimensional TTE and Doppler echocardiography provide sufficient information about the anatomical and hemodynamic evaluation before operations. TTE can be used during the postoperative period for recognition of residual, recurrent, or new pathologies[11,12].

On the other hand, in TGA patients, especially after an operation, an MRI of both cardiac anatomy and function can provide valuable information. Cardiovascular MRI is the gold standard in analyzing the size of LV and function quantitatively. MRI provides high -quality images without any ionizer radiation. An MRI can be performed to evaluate myocardial performance and vitality along with a reliable assessment of lid functions and extracardiac structures. For MRI, the most important disadvantage is that it requires the patient to be still for about 30 to 45 min. In these cases, sedation or anesthesia may be required[4,13].

There can be difficulties in observing the pulmonary branches during echocardiographic imaging in cases where the LeCompte maneuver is performed in TGA patients undergoing secondary ASO, due to the disruption of the acoustic window[14]. In our study in TTE, low detection levels of right and left pulmonary artery branches have been observed. Pulmonary arteries were clearly visible during the cardiac MRI and the necessary measurements could be performed. In our study, the branches of the pulmonary artery could not be visualized adequately in TTE, and the stenosis in the pulmonary artery could not be evaluated. In cardiac MRI, stenosis in the pulmonary artery bifurcation area is clearly shown.

Aortic root measurements and aortic insufficiency degree revealed similar results to that of previous literature publications[15,16]. Our results are three-dimensional to your character attributed atrial dimension and your function to the evaluation and myocardial your border perfect one way to the definition permission given for ASO applied patients for advanced one-choice method aspect cardiac of MRI the benefit other in studies is support[17]. Our results highlight the benefit of an MRI as an improved method of imaging for patients who underwent TGA, as was seen in other studies. Allowing for perfect evaluation of the myocardial border and a three-dimensional character attributed to the atrial dimension and function[16].

MPI, is a non-geometric index for ventricular function. It is easily applicable to evaluate the function of the Right and LV. Also, MPI's are not affected by blood pressure, heart speed, and ventricle geometry. Therefore, MPI has a great prognostic value in different clinical situations. In the study, a correlation was shown between ventricle function and MPI measurements of an MRI performed in the following 90 days to evaluate RV functions compared with an MPI[17]. A report regarding pediatric patients with a heart transplant provided 85% specificity and 82.5% sensitivity for acute cardiac rejection[18,19]. With dilated cardiomyopathy in patients made one in the study, a study concerning dilated cardiomyopathy patients highlighted the advantage of using the MPI ejection fraction and the LV independently on predicting patients with a risk of cardiovascular mortality from heart failure[20]. In our study with tissue Doppler data, a strong and positive correlation was shown for MPI, LV dilatation on MRI, and LV dysfunction. This compatibility provides an alternative

important contribution for evaluating LV function in young patients who require sedation for an MRI or are clinically unsuitable for MRI. Patients with good systolic function but high MPI may develop ventricular dysfunction before clinical indication; therefore, it is vital and practical in prognosis and follow-up.

Study Limitations

The weakest aspect of this study is that it is a retrospective study with data from a single center with a small sample size. Additionally, parameters derived from MRI and echocardiography require further verification compared with other invasive and non-invasive methods. Also, long-term confirmation of our results can provide more correct data.

Conclusion

TGA patients require careful pre and post operative evaluation, anatomical and a functional use of cardiac indicators. For this purpose, both echocardiography and MRI are useful, safe, and trustworthy methods of diagnosis. Choosing the optimal imaging technique and lifetime reoccurring assessments of the LV function is of vital importance in foreseeing complications, preventing morbidities, and creating a protocol. In clinical practice, MPI, can provide values close to an MRI about LV dilatation and LV dysfunction. These results raise awareness about the importance of specific parameters in using information based on quantitative data. These results raise awareness about the importance of specific parameters in using information based on quantitative data.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval no: 2018/20-38, date: 02.08.2018).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Güleryüz H, Oto Ö, Ünal N, Concept: Yıldız K, Ünal N, Design: Yıldız K, Çekdemir YE, Data Collection and/or Processing: Çekdemir YE, Salman M, Analysis and/or Interpretation: Salman M, Literature Search: Yıldız K, Writing: Yıldız K.

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31
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Analysis of Associated Genes and Biological Pathways Between Inflammatory Dilated Cardiomyopathy and Ischemic Cardiomyopathy by Bioinformatics

Weichen Si

Shanghai University of Traditional Chinese Medicine, Shanghai City, China

Abstract

Objectives: To screen the associated genes and biological pathways of inflammatory dilated cardiomyopathy (DCMi) and ischemic cardiomyopathy (ICM) a transcriptome data method.

Materials and Methods: The differential genes (DEGs) were analyzed by the transcriptome data of DCMi and ICM in the comprehensive gene expression database, then the cluster analysis and Hub gene candidate genes were identified by Cytoscape, and the biological pathway of candidate genes was studied by GO and KEGG enrichment analysis.

Results: The common DEGs of DCMi and ICM were RPS4Y1 and MYH6. The biological processes in the GO analysis of DCMi are mainly related to the development and regulation of muscle and cardiomyocytes, while ICM is mainly related to biological processes such as extracellular matrix and collagen. Through KEGG analysis, we found that the DEGs in DCMi were mainly enriched in the PPAR signaling pathway (inhibition). In ICM, mainly enriched in ECM-receptor interaction (activation).

Conclusion: Our results reveal the related genes and biological pathways of DCMi and ICM, and we believe that the activation of the PPAR signaling pathway is expected to alleviate and improve myocardial inflammation. In ICM, it is possible to regulate the signal pathway of ECM- receptor interaction by increasing the transcriptional levels of COL3A1, COL1A1, and COL1A2, thus further promoting the progression of the disease.

Keywords: Bioinformatics, inflammatory dilated cardiomyopathy, ischemic cardiomyopathy, genes

Address for Correspondence: Weichen Si, Shanghai University of Traditional Chinese Medicine, Shanghai City, China
e-mail: weichens14@163.com **ORCID:** orcid.org/0000-0002-8036-9427
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Introduction

Myocarditis is a long-term chronic myocardial inflammation with heterogeneous clinical manifestations, and its pathogenesis involves immune activation, including pro-inflammatory cytokines and autoantibodies triggered by the innate immune system[1]. Myocarditis can be caused by a variety of infectious pathogens, such as viruses, bacteria, chlamydia, rickettsia, fungi, and protozoa, as well as toxicity and hypersensitivity, among which the viral infection is deemed the most common cause of myocarditis[2], in the United States and Europe, coxsackievirus and parvovirus B19 are the main causes of myocarditis[3]. Patients with myocarditis often have systemic symptoms such as fever, myalgia, respiratory symptoms, gastroenteritis, chest pain, and palpitation. These non-specific symptoms are almost indistinguishable from those of acute coronary syndrome (ACS), non-ischemic cardiomyopathy, valvular disease, and pericarditis, so they bring greater challenges to the diagnosis and treatment of myocarditis[2]. Myocarditis will not only develop into inflammatory cardiomyopathy, and related studies have shown that about 1/3 of patients with myocarditis will develop inflammatory dilated cardiomyopathy. However, it is a serious disease associated with heart failure (HF)[4,5].

Ischemic heart disease (IHD) is one of the myocardial diseases with high morbidity and mortality[6]. Myocardial ischemia is called IHD, which can be divided into ACS and chronic coronary syndrome according to the cause of the disease[7]. ACS mainly results in a sudden limitation of coronary blood flow caused by acute lumen reduction or occlusions, such as thrombosis superimposed on atherosclerotic plaques and myocardial damage caused by sudden ischemia[8,9]. Chronic coronary syndrome, also known as chronic stable angina pectoris, refers to the chronic reduction of the coronary artery lumen due to atherosclerotic lesions, which limits coronary blood flow and causes ischemia when myocardial metabolic demand increases temporarily[6]. Long-term ischemia of the heart can lead to permanent myocardial dysfunction, HF, and even death[6].

Although inflammatory dilated cardiomyopathy and ischemic cardiomyopathy have different pathogenesis, both of them may eventually develop into HF. This may suggest that there may be a deeper link between DCMi and ICM. We hope to obtain the DEGs of DCMi and ICM through bioinformatics analysis, and through the further study of these candidate genes and biological pathways, to explore the pathogenesis and relationship between the two diseases, provide theoretical guidance for follow-up clinical research.

Materials and Methods

Search and Acquisition of Data

Use the "GEOquery" package of R software (version 4.0.2 r-project.org/) to download the microarray (microarray dataset) expression data sets GSE4172 and GSE5406 from GEO[10] (https://www.ncbi.nlm.nih.gov/geo/) database). The annotation platform of the gene expression profile GSE4172 is GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus2.0 Array. There were 12 samples, 4 healthy (control) and 8 DCMi. The annotation platform of the gene expression profile GSE5406 was GPL96 [HG-U133A] Affymetrix Human Genome U133A Array, 15 healthy samples, and 107 ICM samples.

Data Preprocessing and Differentially Genes Screening (DEGs)

We use "hgu133a" and "hgu133plus2" R packages in Bioconductor to obtain soft files on GPL96 and GPL570 platforms respectively and extract gene annotation information. In gene annotation, unannotated probes and probes mapped to multiple genes are screened. If multiple probes are mapped to the same gene, one of them is randomly retained in the data and represents the gene expression value. DEGs were screened by the limma package (version 4.0.3)[11]. The screening criteria for differential genes in GSE4172 were $p<0.05$ and $|\log2FC| \geq 1.5$. The DEGs in GSE5406 were screened by $p<0.05$ and $|\log2FC| \geq 1$. Pheatmap (version 4.0.3) and ggplot2 R

package (version 4.0.3) were used to process the screened differentially expressed genes and draw heat map and volcano map[12].

PPI Network Construction and Hub Gene Acquisition

All DEGs were uploaded to STRING (v.11.0) [STRING: functional protein association networks (string-db.rg)] to obtain a protein-protein interaction analysis of DEGs to predict the correlation of protein function. Then, we use Cytoscape (version 3.7.2) to analyze and visualize the biological networks and nodes of DEGs. MCC is the plug-in of cytoHubba and was calculated the top 10 Hub genes in DEGs. Finally, we used the MCODE plug-in (version 1.6.1) to cluster the DEGs. Degree cutoff, node score cutoff, and K-Core were set 2 and K-Core was set 100.

Correlation Analysis Between Gene Ontology and Function

To further explore the biological function of DEGs enrichment, we used "clusterProfiler" R package (3.18.1) to analyze the enrichment of gene ontology (GO) terms, including biological processes, molecular functions and cellular components. Then, to explore the signal pathways affected by differential genes, we used the "ggplot2" R package to analyze the KEGG pathways of up-and down-regulated genes. The standard for significant enrichment of differential genes in DCMi and ICM was adj ($p<0.05$)[13].

Results

Identification of Differential Genes

A total of 495 differential genes related to DCMi were identified in GSE4172, of which 258 were up-regulated and 237 down-regulated (Figure 1). A total of 37 differential genes related to ICM were identified in GSE5406, including 12 up-regulated and 25 down-regulated (Figure 1). Among them, there are two common genes. These common differential genes mainly include RPS4Y1 and MYH6.

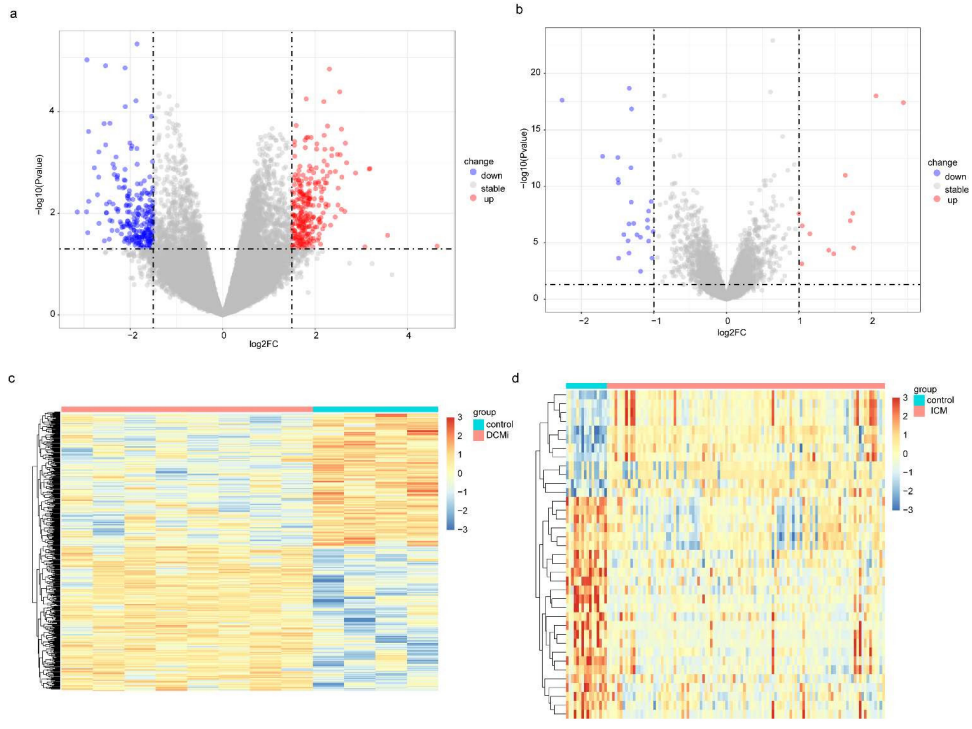

Figure 1. Volcano map and heat map of differential genes
(a) and (b) are the volcano maps of DCMi and ICM, respectively. (c) and (d) are heat maps of DCMi and ICM, respectively (DCMi: |log2FC|≥1.5, p<0.05. ICM: |log2FC|≥1.0, p<0.05)

Obtaining Hub Gene and Clustering Analysis

The top 10 genes ranked by DCMi and ICM were obtained according to the MCC algorithm (Table 1). The Hub genes of DCMi were mainly members of the fibroblast growth factor receptor family, including FGFR2 and FGFR4 (Figure 2). However, the Hub genes of ICM mainly include fibrosis-related genes such as COL3A1, COL1A1, and COL1A2 (Figure 2). Through cluster analysis, 9 clusters were obtained by DCMi (Figure 2 and Table 2), in which MYH6 is the common DEGs of DCMi and ICM. Two clusters were obtained by ICM (Figure 2 and Table 3).

Table 1. Calculates the Hub gene of the top ten of DCMi and ICM according to the MCC algorithm

Rank	DCMi		ICM	
	Name	Score	Name	Score
1	SHC1	111	COL1A1	181
2	SOS1	86	COL3A1	180
3	FGFR2	69	COL1A2	174
4	CTNNB1	64	LUM	144
4	JAK2	64	COL15A1	120
6	PDGFA	54	MXRA5	120
7	ADIPOQ	44	OGN	48
8	NTRK1	41	ASPN	24
9	FLT4	34	MYH6	20
10	FGFR4	33	MYOT	12

GO Analysis

To further study the effects of DEGs on disease-related signaling pathways, we enriched the DEGs of the two diseases by GO analysis (Figure 3). The results showed that DEGs of DCMi were mainly enriched in biological processes such as muscle organ development, regulation of muscle tissue development and regulation of striated muscle tissue development, and the common genes in the above biological processes included FGFR2, MYF5, SOX15, G6PD, RBP4 and BCL2, LUC7L, CTNNB1, RGS4, ARNTL, and CYP26B1 (Figure 3). The DEGs of ICM were mainly enriched in the extracellular matrix (ECM) organization, extracellular structure organization, and response to transforming growth factor-beta, in which the common genes in the above biological processes include COL3A1, COL1A1, and COL1A2 (Figure 3). In molecular function, ICM was enriched to contain the collagen ECM. Additionally, ICM is also enriched in a collagen trimer in cellular components. To sum up, the enrichment of DCMi is mainly related to muscle development and regulation, however, the accumulation of ICM in GO is mainly related to the ECM, collagen, and so on.

KEGG Enrichment Analysis

The DEGs of DCMi were enriched in 12 signal pathways by KEGG enrichment analysis (Figure 4a, $p \leq 0.05$). Among them, there were 2 up-regulated signal pathways and 10 down-regulated signal pathways. Up-regulated genes were mainly enriched in ABC transporters, while down- regulated genes were mainly enriched in

Table 2. Clustering results of differential genes in DCMi

Cluster	Gene	Nodes	Edges	Scores
1	*IKBKAP*, *NVL*, *TWISTNB*, *WDR3*, *NOM1*, *DDX52*	6	12	4.800
2	*WASL*, *DAAM1*, *MYH6*, *FMN1*, *TPM1*	5	9	4.500
3	*MAP3K1*, *FLT4*, *PDGFA*, *JAK2*, *SHC1*, *FGFR4*, and *NTRK1*	7	11	3.667
4	*RIMS1*, *UNC13C*, *PPFIA4*, *ERC2*	4	5	3.333
5	*CTNNB1*, *TCF7L2*, *ADIPOQ*, and *HIST1H2BN*	4	5	3.333
6	*CFD*, *RBP4*, *RARRES2*	3	3	3.000
7	*SREBF1*, *LPIN1*, *GPAT2*	3	3	3.000
8	*PMS1*, *XRCC6BP1*, *ZSWIM7*	3	3	3.000
9	*KIF17*, *TRAF3IP1*, *NPHP1*	3	3	3.000

the Peroxisome proliferator-activated receptor (PPAR) signaling pathway. The DEGs of ICM were predicted to have 18 signal pathways by KEGG enrichment analysis (Figure 4b). Among them, the up-regulated genes were enriched to 11 signal pathways, and the down-regulated genes were enriched to 7 signal pathways. Up-regulated genes were mainly enriched in the AGE-RAGE signaling pathway, diabetic complications, ECM-receptor interaction, and Diabetic cardiomyopathy. The down-regulated genes of ICM were mainly enriched in Mineral absorption and other pathways.

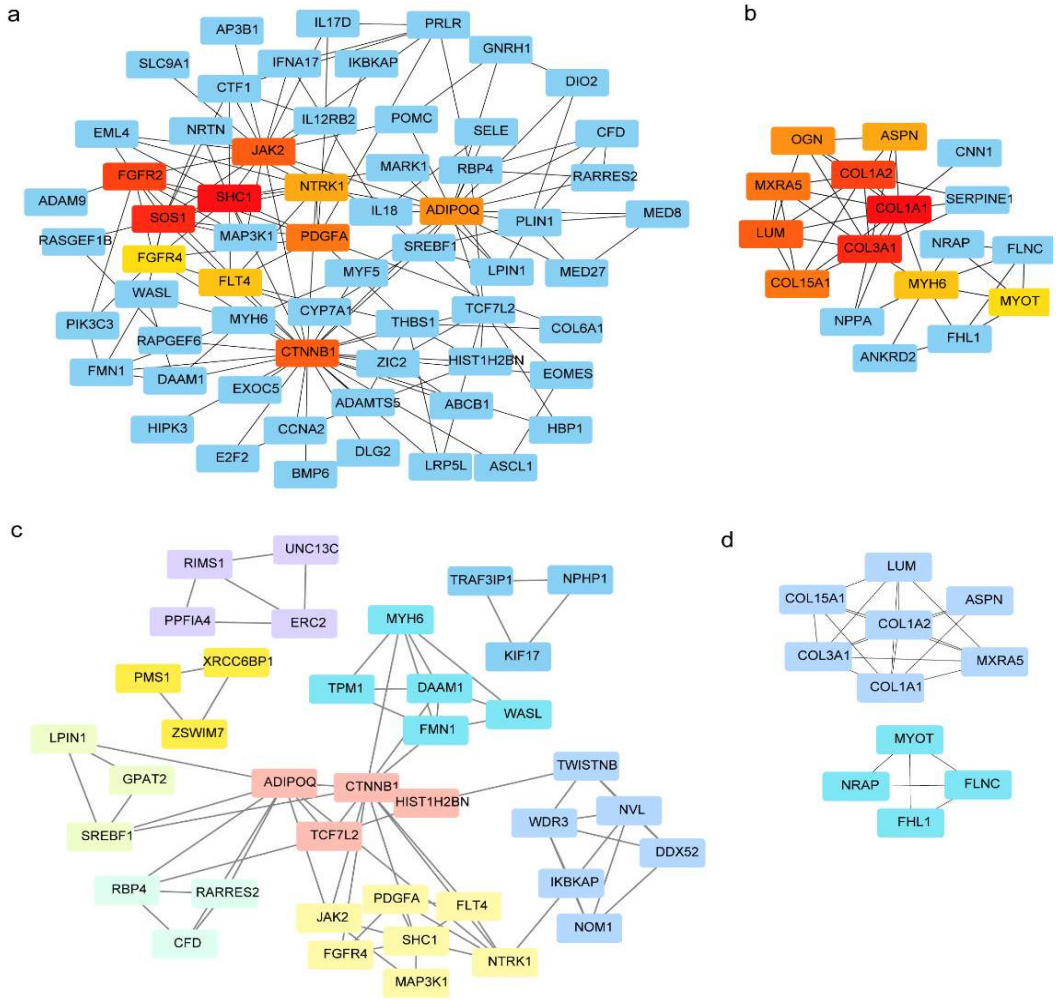

Figure 2. Hub genes and cluster analysis
(a) is the differential genes of DCMi calculated by the MCC algorithm and the top ten Hub genes, and (b) is the differential genes of ICM calculated by the MCC algorithm and the top ten Hub genes. (c) is the result of DCMi cluster analysis, and (d) is the result of ICM cluster analysis (different colors represent different clusters)

Table 3. Clustering results of differential genes in ICM

Cluster	Gene	Nodes	Edges	Scores
1	*COL3A1, LUM, COL1A2, COL15A1, COL1A1, MXRA5, ASPN*	7	18	6.000
2	*NRAP, FLNC, MYOT, FHL1*	4	5	3.333

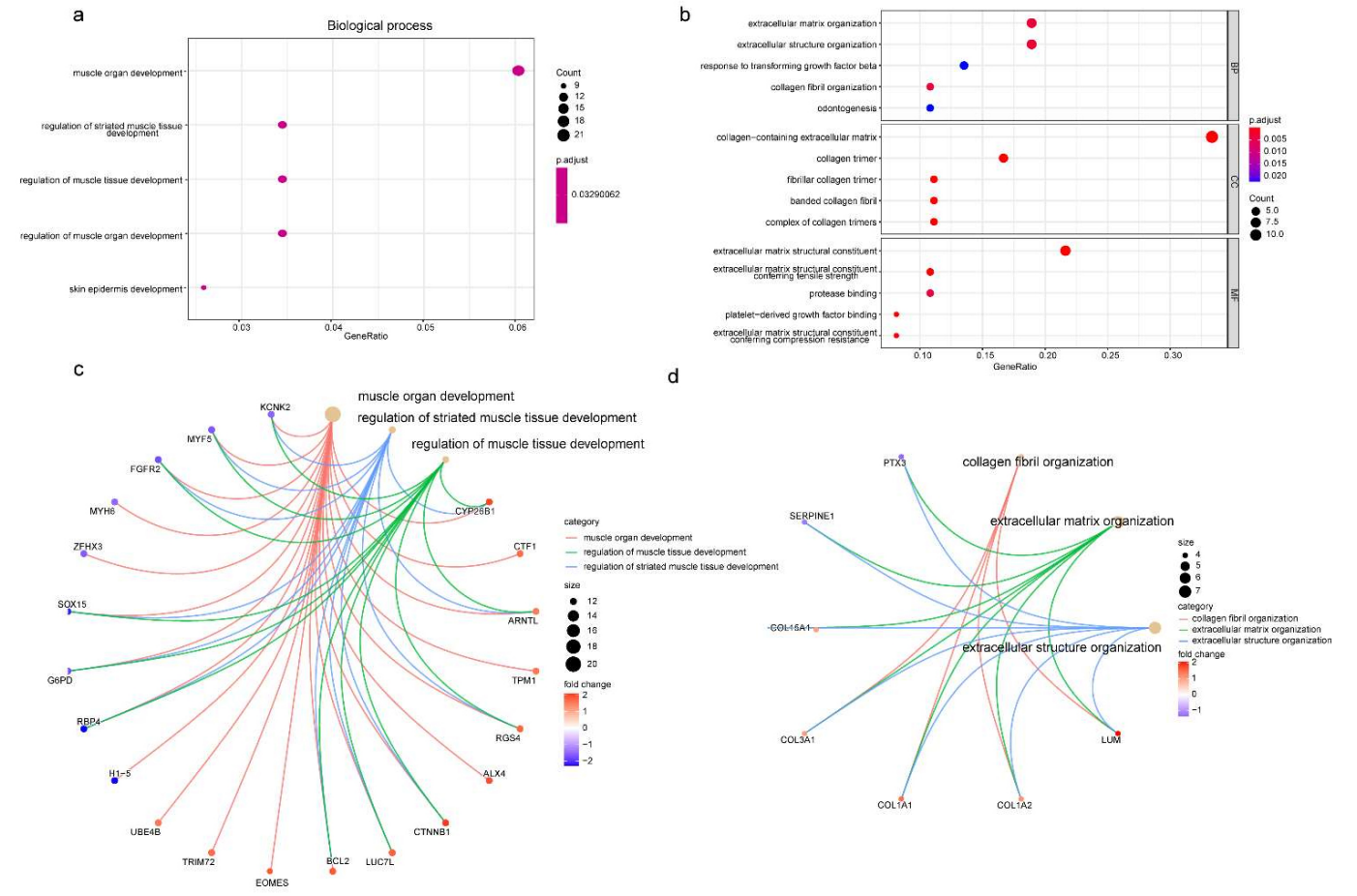

Figure 3. GO analysis results of DEGs
(a) is the result of GO analysis of differential genes of DCMi, and (b) is the result of GO enrichment of differential genes of ICM. (c) is the display of common genes in the first three biological processes of DCMi enrichment, and (d) is the display of common genes in the first three biological processes of ICM enrichment

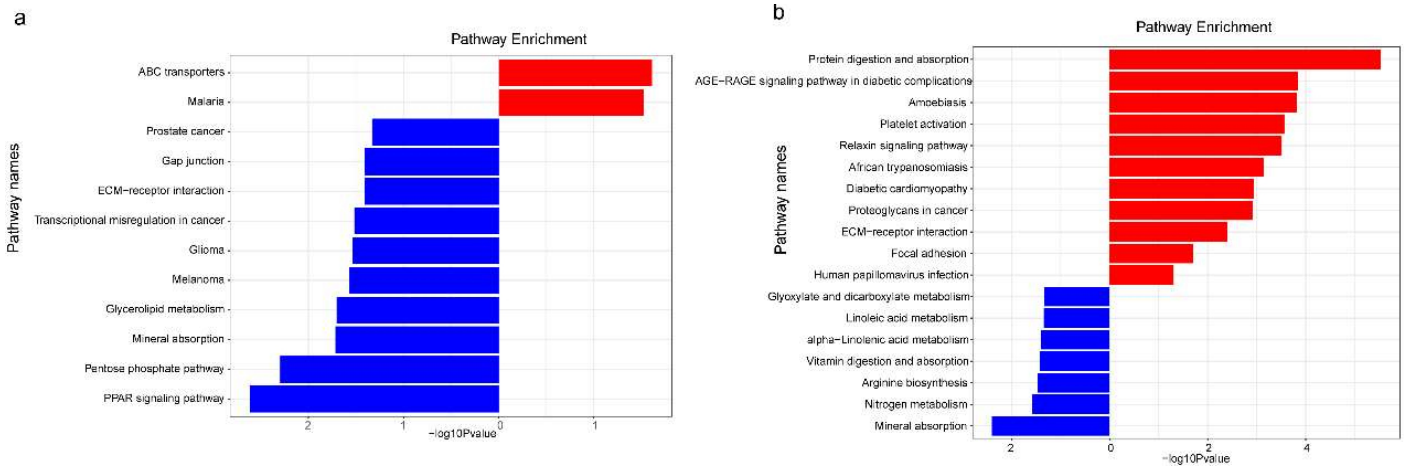

Figure 4. Enrichment of the KEGG signal pathway of DEGs. (a) and (b) are the result of KEGG enrichment in DCMi and ICM

Discussion

Through the analysis of the microarray expression data sets of DCMi and ICM, we found that the common genes of the two diseases include RPS4Y1 and MYH6. A comprehensive analysis of Hub genes and GO enrichment, we found that the DEGs of DCMi enriched in the biological process mainly include FGFR2 and MYF5. In ICM, the DEGs involved in the biological process are mainly fibrosis-related genes such as COL3A1, COL1A1, and COL1A2.

RPS4Y1 encodes the ribosomal protein S4, which is central to the correct development of individuals. RPS4Y1 can accelerate the loss of HUVEC activity induced by high glucose, so RPS4Y1 may inhibit cell viability by inducing mitochondrial- dependent apoptosis[14]. On the other hand, RPS4Y1 may lead to cell death by mediating pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and IL-8. Previous studies have shown that the expression of inflammatory factors such as IL-1β, IL-6, and TNF-α are significantly up- regulated in DCMi and ICM, so the up-regulated expression of RPS4Y1 in DCMi and ICM is likely to promote the development of the disease through inflammatory factors.

The *MYH6* gene encodes the α heavy -chain subunit of cardiac myosin and is central to myocardial development. The down-regulation of *MYH6* gene expression may cause the atrial septal defect, and the mutation of the *MYH6* allele can inhibit hypertrophic cardiomyopathy[15]. In our study, the mRNA levels of MYH6 in both DCMi and ICM were significantly down-regulated, so we think it may be related to the development of the disease[16].

Through KEGG analysis, we found that the down-regulated genes in DCMi were mainly enriched in the PPAR signaling pathway. PPARs, a transcription factor belonging to the nuclear receptor superfamily, contains the following three subtypes: PPARα, PPARγ, and PPARβ/δ. It heterodimerizes with the retinoid X receptor and binds to a specific response element called the PPAR response element in the target gene promoter[17]. PPARα and PPARγ have been demonstrated to be expressed in many cell types[18,19]. PPARγ is expressed in cardiomyocytes and is central to cardiovascular diseases such as atherosclerosis, cardiac hypertrophy, and myocardial infarction, and the lack of PPARγ signal transduction may be a reason for developing diabetic cardiomyopathy[20,21]. IL-17 is secreted by T-helper 17 (Th17) cells, a subgroup of CD4+T cells. IL-17 is involved in the pathogenesis of autoimmune myocarditis. IL-17 neutralization can reduce the severity of myocarditis[22]. PPARα may provide a new idea for treating autoimmune myocarditis. Our results also found that the PPAR signal pathway was inhibited in DCMi, so we think it may promote the progression of the disease.

In ICM, the up-regulated genes were mainly enriched in ECM-receptor interaction. Myocardial ECM is central to maintaining normal cardiac structure and function. Under normal circumstances, the synthesis and degradation of myocardial collagen fibers are in dynamic balance. In many cardiovascular diseases, the quantity, proportion, structure, and morphology of myocardial interstitial collagen change, accompanied by the imbalance of collagen production and degradation (collagen production increase and degradation decrease). Finally, myocardial interstitial fibrosis leads to an increase in myocardial stiffness, and even HF[23].

Our study found that the Hub gene of ICM mainly includes COL3A1, COL1A1, and COL1A2, in which COL3A1 and COL1A2 encode type I and III collagen (ColI and ColIII), respectively. ColI and ColIII are the main fibrous collagen produced by fibroblasts, including cardiac fibroblasts[24]. ColI and ColIII are the main components of ECM proteins, accounting for 80% and 12%, respectively[25]. Related studies have shown that COL3A1 and COL1A2 are mainly highly expressed in ICM and dilated cardiomyopathy in cardiovascular diseases[26,27]. Our results show that the differential genes in ICM are significantly enriched in the ECM-receptor interaction signal pathway. Therefore, we believe that ICM may regulate the ECM-receptor interaction signal pathway by increasing the transcriptional levels of COL3A1, COL1A1, and COL1A2, to further promote the progress of the disease.

Conclusion

We found that RPS4Y1 and MYH6 are common genes for DCMi and ICM. In DCMi, the PPAR signaling pathway is inhibited in DCMi, which may lead to uninhibited differentiation of Th17 cells and promote IL-17 secreted by Th17 to further mediate the pathogenesis of myocarditis. In ICM, it is possible to regulate the signal pathway of ECM- receptor interaction by increasing the transcriptional levels of COL3A1, COL1A1, and COL1A2, thus further promoting the progression of the disease.

Ethics

Ethics Committee Approval: This study does not require.

Informed Consent: This study does not require.

Peer-review: Externally peer-reviewed.

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Research Article

39

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Association Between Triglyceride-Glucose Index and Heart Rate Recovery Affecting Circadian Rhythm of Blood Pressure in Patients with Normoglycemic Primary Hypertension

Birsen Doğanay[1], Veysel Başar[2]

[1]Ankara City Hospital, Clinic of Cardiology, Ankara, Turkey
[2]Hisar Hospital Intercontinental, Clinic of Cardiovascular Surgery, İstanbul, Turkey

Abstract

Objectives: Although the cause of the disturbance of circadian blood pressure (BP) variation is not fully understood, insulin resistance (IR) and autonomic dysfunctions are thought to play a role. This study aimed to evaluate the relationships between the triglyceride-glucose (TyG) index, as a reliable surrogate for IR, and cardiac autonomic function as measured using heart rate (HR) recovery (HRR) levels according to circadian rhythm types of BP in patients with normoglycemic primary hypertension (NPHT).

Materials and Methods: This retrospective study included 254 patients with NPHT patients. The definition of non-dipper BP pattern included a <10% decline in night-time BP. The HRR levels were analyzed by subtracting HRs at 1-3 min from the maximal HR recorded during stress tests.

Results: Mean TyG index was higher in the non-dipper group than the dipper group (8.9±0.5 vs. 8.5±0.6, p<0.001), while mean HRR1 (26.8±8.7 vs. 31.7±9.6 bpm, p<0.001) value was lower. There was a negative correlation between HRR1 and TyG index (r=-0.316, p<0.001) and the blunted decline in night-time BP (r=-0.328, p<0.001). TyG index (β ±

Address for Correspondence: Birsen Doğanay, Ankara City Hospital, Clinic of Cardiology, Ankara, Turkey
e-mail: doganay.brsn@gmail.com **ORCID:** orcid.org/0000-0003-4659-3596
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SE=-0.55±0.20, p<0.001) and HRR1 (β ± SE=0.58±0.14, p<0.001) levels were determined as independent predictors of blunted decline in night-time BP.

Conclusion: The elevated TyG index was associated with belated recovery of HR and it was an important predictor of blunted declines in night-time BP. Patients with NPHT may be at a risk of autonomic dysfunction due to increased IR.

Keywords: Blood pressure, circadian rhyth, heart rate, insulin, hypertension

Introduction

Blood pressure (BP) levels vary throughout the day, depending on the circadian rhythm of metabolism[1]. A decrease of less than 10% in BP levels compared to daytime values during sleep is defined as a non-dipper pattern (NDP)[2]. It is known that NDP increases the risk of organ damage and cardiovascular (CV) events in patients with hypertension[3,4].

Although the cause of the disturbance in the circadian BP variation is not fully understood, insulin resistance (IR) and autonomic dysfunctions are thought to play a role[5,6]. Patients suffering from NDP are prone to impaired autonomic functions, including sympathetic or parasympathetic activities[7]. Heart rate (HR) recovery (HRR), an easy and non-invasive indicator of autonomic function, is defined as the HR reduction after exercise. Delayed HRR is an important indicator of major CV events[8,9]. Increasing evidence suggested a significant association between HRR and circadian BP patterns[10,11].

The triglyceride-glucose (TyG) index, a surrogate marker of IR, has been implicated as a newly identified CV risk factor. IR may be involved in the pathogenesis of hypertension and autonomic nervous system dysfunction by mediating low-grade systemic inflammation[12]. Increased insulin levels may be associated with increased activation of the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) activity, and variation in BP levels[13]. However, the relationships between the TyG and HRR and circadian BP patterns in normoglycemic primary hypertensive patients (NPHT) have not yet been investigated.

This study evaluated the relationships between the TyG index and cardiac autonomic function as assessed by HRR indices according to the circadian rhythm types of BP in NPHT.

Materials and Methods

A total of 1,264 patients with 24-h ambulatory BP monitoring (ABPM) in the Cardiology Clinic from 01.2019 to 01.2020 were assessed retrospectively. The study was designed considering the revised Declaration of Helsinki (2013, Brazil), following all relevant ethics protocols, and was accepted by the Ankara City Hospital Clinical Research Ethics Committee (date: 11.2022, decision no: E1-22-3054). Because of the retrospective design, the waiver of informed approval was deemed appropriate by the ethics committee that approved the study. Based on a previous study, we determined the effect size of the TyG index as 0.5 between the NDP and dipper pattern (DP)[14]. Accordingly, the sample dimension was calculated to be at least 172 with an effect size of 0.5, 90% power, and %5 alpha error probability.

Inclusion criteria were newly diagnosed NPHT patients with complete ABPM and treadmill exercise test data and no comorbidities. Exclusion criteria were previously documented hypertension, diabetes mellitus, rheumatic diseases, documented coronary artery disease, malignancy, active or chronic infection, acute or chronic kidney disease, peripheral artery disease, presence of nephrotic proteinuria, cerebrovascular disease, heart failure, liver diseases, use of antioxidants and lipid-lowering drugs, congenital or acquired valve disease, and

thyroid disease. After the exclusion process, 254 newly diagnosed primary hypertensive patients were included in the study.

All patients' clinical, ABPM, and treadmill exercise test data were obtained from the hospital's electronic information system or patient files.

Laboratory Measurements

Blood samples were drawn in the morning hours after all patients had fasted overnight. Complete blood counts were evaluated with a Sysmex XE 2100 hematology analyzer (Roche Diagnostic Corp., USA) using blood samples obtained. A photometric method was applied for assessing hemoglobin levels, an impedance method for thrombocytes and erythrocytes, and optic laser scattering for leukocytes. Lipid panels were evaluated using a Beckman Coulter LH 780 device (Beckman Coulter, Ireland). An enzymatic colorimetric method was applied for assessing lipid level measurements. The Friedewald formula was used in calculating the levels of low-density lipoprotein (LDL). Glucose was assessed with ultraviolet hexokinase using a Beckman Coulter AU 5800 autoanalyzer (Beckman Coulter, USA), and C-reactive protein (CRP) was assessed immunoturbidimetrically. The TyG index was calculated with the following formula: TyG = ln [Fasting triglyceride (mg/dL) x Fasting glucose (mg/dL)] / 2.

In-Office Blood Pressure Measurements

All participants rested for 5 min for BP measurements after admission to the hospital. Their BP levels were subsequently measured 3 times at 5-min intervals via an Omron M3 sphygmomanometer (Omron Healthcare, Japan). All measurements were averaged.

Ambulatory Blood Pressure Monitorization

A WatchBP device (Microlife WatchBP AG, Switzerland) was used to assess 24-h ABPM. Data from the first hour of monitoring were excluded from the analysis. The BP readings were automatically recorded at 15-min intervals for 24 h. Records were included in the analysis if greater than 85% of the raw records were valid. The pure reduction and percentage reduction in systolic BP for the night-time to day-time period were assessed. Bedtime was determined from the patients' diaries documenting the time of going to bed and getting up. The night-time BP levels following bed-time were evaluated from the ABPM records. Mean BP levels for the remainder of the h were evaluated as day-time BP. Diastolic BP plus 1/3 of the pulse pressure was assessed as mean BP. The percentage (%) decline in night-time BP was determined with the following formula over the averages: (daytime BP - night-time BP / daytime BP × 100). NDP was defined as the decline of night-time BP levels by <10% than day-time BP levels, while a >10% decline was defined as the DP.

The definition of hypertension is based on the European Society of Cardiology and the European Society of Hypertension.

Treadmill Exercise Testing

To investigate the BP response to exercise in all participants, a treadmill exercise test was applied. It was aimed to obtain the age-adjusted maximal HR through the modified Bruce protocol. All participants achieved 85% of their age-estimated maximum HR. Data from 12-lead ECG with the Mason-Likar modification were logged at 25 mm/s paper speed. All patients who reached the highest workload experienced at least 3 min recovery deprived cool-down. Metabolic equivalents during peak exercise were assessed as exercise capacity. Systolic and diastolic BP levels recorded at the point of maximum exercise were defined as SBPme and DBPme, respectively. HRR indices were assessed by subtracting the HRs in the first 3 min of recovery from the maximal HR during exercise. Accordingly, HRR1 for the 1st minute, HRR2 for the 2nd minute, and HRR3 for the 3rd minute were calculated.

Transthoracic Echocardiographic Examination

Echocardiographic measurements were assessed using a Vivid 7 Dimension CV Ultrasound System (General Electric Vingmed, Norway) by an experienced cardiologist. The left ventricular ejection fraction was evaluated via the modified Simpson method.

Statistical Analysis

IBM SPSS Statistics for Windows 20.0 (IBM Corp., USA) was used in the analysis of all data obtained in this study. Considering the results of the Kolmogorov-Smirnov test, numerical data with a normal distribution were identified and presented as mean ± standard deviation, while data found to have non-normal distribution were presented as median values with interquartile ranges. The Mann-Whitney U test and Student's t-test were used when comparing two groups of data with a normal distribution. Categorical variables were assessed with numbers with percentages (%), and Fisher's exact and chi-square tests were used in drawing comparisons between these groups of data. Relationships between numerical variables were assessed with Pearson correlation analysis. Multivariate linear regression analysis was assessed to identify any effects of the considered variables on decreases in the values of night-time BP (%). Values of $p<0.05$ were acceded as statistically significant.

Results

The mean age of the hypertension patients was 56.6±14.6 years and the majority of them were male (62.6%). Baseline characteristics are presented in Table 1. NDP was detected in 52.4% (n=133) of the patients. Demographic findings did not show significant differences between the NDP and DP groups. Mean neutrophil level (5.3±2.1 vs. 4.6±1.5 x10^3/µL, p=0.003), mean monocyte level (0.7±0.2 vs. 0.6±0.2 x10^3/μL, p=0.009) were higher in the NDP group than the DP group, while median lymphocyte level (2.4 vs. 2.5 x10^3/µL, p=0.046) was lower. The mean TyG index was higher in the NDP group than in the DP group (8.9±0.5 vs. 8.5±0.6, p<0.001). From echocardiographic findings, the mean left ventricular end-diastolic diameter (46.5±3.5 vs. 45.6±3.1 mm, p=0.032) and mean septum wall thickness (13.2±2.5 vs. 12.5±2.3 mm, p=0.021) were higher in the NDP group.

While the mean decline in night-time BP was 7.1%±2.5 in the NDP group, it was 15.4%±4.6 in the DP group (Table 2). Mean HRR1 (26.8±8.7 vs. 31.7±9.6 bpm, p<0.001) and mean HRR2 values were lower in the NDP group than the DP group. No correlation was found with NDP in terms of other parameters of the treadmill exercise test (Table 2).

A positive correlation was found between the TyG index and 24-hour systolic BP (r=0.418; p<0.001) and diastolic BP levels (r=0.412; p<0.001). A negative correlation was found between HRR1 values and the TyG index (r=-0.316; p<0.001) and the decline in night-time BP levels (r=-0.328; p<0.001) (Figure 1). Demographic and clinical

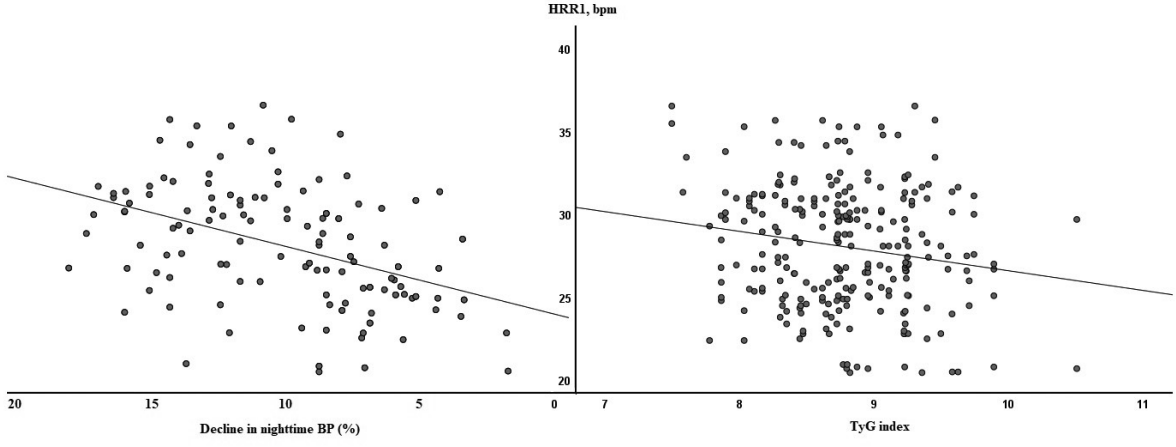

Figure 1. Relationship between HRR1 and TyG index and decline in night-time BP (%)
TyG: Triglyceride-glucose, BP: Blood pressur

parameters associated with decline in night-time BP (%) in Table 3 were included in the multivariable regression model. TyG index (β ± SE=-0.55±0.20, p<0.001), HRR1 (β ± SE=0.58±0.14, p<0.001) and DBPme (β ± SE=0.17±0.07, p=0.024) levels were determined as independent predictors of decline in night-time BP levels (%) (Table 4). Accordingly, it was determined that a 1-unit increase in the TyG index decreased the decline in night-time BP (%) levels by 0.55 folds, regardless of other risk factors. It was determined that 1 bpm increase in HRR1 level increased the decline in night-time BP (%) levels by 0.58 folds, regardless of other risk factors.

Table 1. Demographic characteristics and clinical parameters in normoglycemic primary hypertensive patients.

Variables	All population n=254	Non-dipper n=133	Dipper n=121	p-value
Demographic findings				
Age, years	56.6±14.6	55.5±15.8	57.7±13.1	0.218
Gender, n (%)				
Male	159 (62.6)	86 (64.7)	73 (60.3)	0.476
Female	95 (37.4)	47 (35.3)	48 (39.7)	
BMI, kg/m^2	24.4±3.6	24.6±3.5	24.2±3.8	0.328
Smoking, n (%)	109 (42.9)	60 (45.1)	49 (40.5)	0.458
Baseline HR, bpm	81.7±13.5	81.2±11.2	82.4±15.5	0.477
In-office SBP, mmHg	149.4±11.5	150.1±12.4	148.7±13.1	0.383
In-office DBP, mmHg	91.8±10.5	92.1±10.7	91.5±10.2	0.648
Laboratory findings				
Hemoglobin, g/dL	14.5±1.7	14.6±1.7	14.4±1.8	0.102
Glucose, mg/dL	87.3±7.4	87.4±5.5	87.1±9.1	0.688
WBC, x10^3/μL	8.4±2.3	8.6±2.4	8.2±2.1	0.135
Platelet, x10^3/μL	273.6±57.4	273.9±53.7	273.2±61.5	0.915
Neutrophil, x10^3/μL	5.0±1.8	5.3±2.1	4.6±1.5	0.003
Lymphocytes, x10^3/μL	2.5 (1.9-3.2)	2.4 (1.9-3.0)	2.6 (2.1-3.4)	0.046
Monocytes, x10^3/μL	0.7±0.2	0.7±0.2	0.6±0.2	0.009
Cholesterol, mg/dL	210.4±40.3	214.2±36.5	204.1±43.1	0.044
Triglyceride, mg/dL	140 (97-222)	158 (116-235)	127 (90-190)	0.036
HDL, mg/dL	49.3±12.2	47.4±11.5	51.2±12.7	0.016
LDL, mg/dL	123.8±39.1	118.9±33.8	129.2±43.6	0.036
Creatinine, mg/dL	0.8±0.2	0.8±0.2	0.8±0.1	0.245
CRP, mg/L	2.4 (1.3-5.2)	2.7 (1.7-5.8)	2.2 (1.2-4.3)	0.547
TyG index	8.7±0.5	8.9±0.5	8.5±0.6	<0.001
Echocardiographic findings				
Ejection fraction, %	64.2±5.3	63.8±5.2	64.5±5.4	0.294
Left atrium diameter, mm	34.7±3.6	34.6±3.9	34.9±3.3	0.581
LVEDD, mm	46.0±3.2	46.5±3.5	45.6±3.1	0.032
LVESD, mm	30.9±3.2	31.1±3.2	30.8±3.3	0.463
SWT, mm	12.8±2.3	13.2±2.5	12.5±2.3	0.021
PWT, mm	13.1±2.1	13.3±2.4	12.9±2.0	0.153

Data shown as mean±standard deviation or median (IQR) or number (percentage)
BMI: Body mass index, CRP: C-reactive protein, DBP: Diastolic blood pressure, HDL: High density lipoprotein, HR: Heart rate, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, SBP: Systolic blood pressure, SWT: Septum wall thickness, PWT: Posterior wall thickness, WBC: Leukocytes

Table 2. Ambulatory blood pressure monitorization and treadmill exercise test findings

Variables	All population n=254	Non-dipper n=133	Dipper n=121	p-value
ABPM findings				
24 hours				
SBP, mmHg	149.1±11.5	152.1±11.7	145.7±10.2	<0.001
DBP, mmHg	90.7±10.3	90.9±10.0	90.4±10.7	0.712
Day-time				
SBP, mmHg	152.0±11.6	153.1±11.7	150.8±11.3	0.109
DBP, mmHg	93.6±11.1	92.4±10.3	94.8±11.8	0.079
Night-time				
SBP, mmHg	138.6±16.5	148.9±13.7	127.3±11	<0.001
DBP, mmHg	81.2±11.8	86.4±11.0	75.5±9.8	<0.001
Decline in night-time BP, %	11.4±3.4	7.1±2.5	15.4±4.6	<0.001
Treadmill exercise test				
Duration of exercise test, min	9.1±2.3	9.3±2.4	9.0±2.1	0.292
Peak exercise capacity, METs	13.0±2.4	13.2±2.5	12.8±2.3	0.187
Maximal HR, bpm	164.5±11.2	163.9±10.4	165.1±11.8	0.390
SBPme, mm High	144.1±16.3	148.2±16.9	143.8±15.7	0.904
DBPme, mm High	96.7±12.8	98.6±12.5	94.2±13.4	0.873
HRR1, bpm	29.4±9.3	26.8±8.7	31.7±9.6	<0.001
HRR2, bpm	48.1±10.2	46.6±11.5	49.4±10.3	0.043
HRR3, bpm	63.1±14.5	62.4±15.1	63.8±13.8	0.379

Data shown as mean±standard deviation
BP: Blood pressure, DBP: Diastolic blood pressure, DBPme: Diastolic blood pressure at maximum exercise, HR: Heart rate, HRR: Heart rate recovery, METs: Metabolic equivalent levels, SBP: Systolic blood pressure, SBPme: Systolic blood pressure at maximum exercise

Discussion

To the best of our knowledge, this study is the first to report the relationship between HRR and the TyG index in terms of decline in night-time BP in NPHT patients. The results of this study showed that a high TyG index, reflecting IR, was negatively associated with HRR1 after the exercise stress test and declined in night-time BP. The TyG index was higher in the NDP group compared with the DP group, and it was an independent predictor of decline in night-time BP.

IR and impaired lipid metabolism make an important contribution to the development of hypertension[12]. There are a number of mechanisms suggested in the relationship between insulin or IR and increased BP levels. These include the activation of the SNS and RAAS with increased insulin levels, increased sodium reabsorption from the renal tubules due to hyperinsulinemia, and higher extracellular osmotic pressure than intracellular osmotic pressure due to hyperglycemia[15,16]. The TyG index showed superior diagnostic performance compared with the homeostasis model assessment of insulin resistance (HOMA-IR) in evaluating IR[17]. Increasing evidence suggests that the TyG index may be a valid population-based screening tool for hypertensive patients. A population-based study with 9 years of follow-up showed that increased TyG index was associated with cases of newly diagnosed hypertension[18]. In the current study, there was a positive correlation between the TyG index and BP levels. The above-mentioned mechanisms are also implicated in the NDP pattern of circadian BP[19,20]. Therefore, the TyG index may be an important screening tool for circadian BP variations in hypertensive patients.

Variations in circadian BP can be assessed by 24 h ABPM. It has been shown that BP changes occurring

Table 3. Parameters associated with the decline in night-time BP (%)

Variables	Decline in night-time BP (%)	
	r	p
Age	-0.088	0.160
Gender	0.024	0.708
BMI	-0.104	0.309
Smoking	0.090	0.153
Hemoglobin	0.122	0.648
Glucose	-0.288	0.018
WBC	-0.201	0.168
Platelet	-0.148	0.319
Neutrophil	-0.080	0.205
Lymphocyte	0.245	0.041
Monocyte	-0.064	0.310
Cholesterol	-0.231	0.047
Triglyceride	-0.282	0.026
HDL	0.297	0.014
LDL	-0.247	0.046
Creatinine	0.139	0.227
CRP	-0.198	0.105
TyG index	-0.328	<0.001
Basal HR	0.163	0.257
Ejection fraction	0.208	0.092
Left atrium diameter	0.119	0.259
LVEDD	-0.278	0.035
LVESD	-0.198	0.218
SWT	-0.289	0.029
PWT	-0.203	0.147
Duration of exercise test	0.118	0.358
Peak exercise capacity	0.168	0.269
Maximal HR	0.154	0.213
SBPme	0.302	<0.001
DBPme	0.311	<0.001
HRR1	0.468	<0.001
HRR2	0.279	0.035
HRR3	0.166	0.267

BMI: Body mass index, CRP: C-reactive protein, DBP: Diastolic blood pressure, DBPme: Diastolic blood pressure at maximum exercise, HDL: High density lipoprotein, HR: Heart rate, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, SBP: Systolic blood pressure, SBPme: Systolic blood pressure at maximum exercise, SWT: Septum wall thickness, PWT: Posterior wall thickness, WBC: Leukocytes

during the day can trigger CV events such as cardiac arrest, myocardial infarction, and cerebrovascular events such as hemorrhagic and ischemic stroke[21]. The NDP was found to carry higher risks of CV and cerebrovascular complications than the DP[22]. Previous studies have reported that patients with metabolic syndrome or diabetes are more prone to the NDP[23,24]. It has also been shown that IR, as assessed by HOMA-IR, is more prevalent in patients with NDP[25]. In a study of newly diagnosed hypertensive patients, TyG index and HOMA-IR levels were higher in the NDP group, and the TyG index showed a better diagnostic performance than HOMA-IR in predicting the NDP[14]. TyG index were independent predictors of declines in night-time BP and were higher in patients with NDP.

Increased insulin levels or IR plays a role in the activation of the SNS[16]. Changes in HRR levels within the first few minutes after cessation of physical exercise reflect the balance between parasympathetic and sympathetic activation[26,27]. A weakened HRR indicates a predominance of sympathetic activity and impaired parasympathetic activity. Thus, it reflects autonomic nervous system dysfunction. The finding of a negative correlation between HRR1 and the TyG index supports the role of IR in sympathetic and parasympathetic activation. Increased sympathetic activity, increased hemodynamic stress, and CV workload are associated with cardiac morbidity and mortality[28].

Therefore, a weakened HRR is associated with CV dysfunction and events[8,29]. A prospective study involving a 4-year follow-up of healthy subjects reported that reduced HRR2 was associated with the development of hypertension[11]. NPHT patients with NDP were found to exhibit lower HRR1 levels. A study of primary hypertension patients reported that HRR1 levels were lower in patients with NDP, and there was a positive correlation between HRR1 and decline in night-time BP percentage[10]. The study of hypertensive patients conducted by Kim et al.[30] reported similar results. In another study, it was shown that HRR values were lower

Table 4. Independent predictors of the decline in night-time BP (%)

Variables	Univariable model			Multivariable model		
	β±SE	95% CI Lower, Upper	p-value	β±SE	95% CI Lower, Upper	p-value
Glucose	-0.15±0.07	-0.30; -0.03	0.018	-	-	-
Lymphocyte	0.18±0.07	0.0, 0.32	0.041	-	-	-
Cholesterol	-0.24±0.11	-0.47; -0.02	0.047	-	-	-
Triglyceride	-0.18±0.06	-0.30; -0.06	0.026	-	-	-
HDL	-0.03±0.01	-0.0, 0.02	0.014	-	-	-
LDL	0.05±0.02	-0.10; -0.01	0.046	-	-	-
TyG index	-0.51±0.17	-0.85; -0.17	<0.001	-0.55 ± 0.20	-0.95; -0.15	<0.001
LVEDD	-0.37±0.16	-0.69; -0.05	0.035	-	-	-
SWT	-0.40±0.18	-0.76; -0.04	0.029	-	-	-
SBPme	0.15±0.04	0.0, 0.30	<0.001	-	-	-
DBPme	0.16±0.05	0.0, 0.32	<0.001	0.17 ± 0.07	0.0, 0.31	0.024
HRR1	0.57±0.09	0.4, 0.75	<0.001	0.58 ± 0.14	0.3, 0.86	<0.001
HRR2	0.24±0.11	0.0, 0.46	0.035	-	-	-
				Adjusted R^2=0.285; p<0.001		

β: Regression coefficient, CI: Confidence interval, DBPme: Diastolic blood pressure at maximum exercise, HDL: High density lipoprotein, HR: Heart rate, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, SBPme: Systolic blood pressure at maximum exercise, SE: Standard error, SWT: Septum wall thickness, PWT: Posterior wall thickness

in hypertensive patients with uncontrolled BP values than hypertensive patients with controlled BP value[31]. In this study, HRR1 and HRR2 were associated with a decline in night-time BP percentage, whereas HRR3 was not. The reactivation of the parasympathetic nervous system exerts a stronger effect in the first 60 seconds after the end of exercise and mediates the response to activity in arterial baroreceptors[32]. Catecholamines, which play an important role in the autonomic nervous system, reach peak levels during peak exercise and may not return to normal levels until about 90 seconds of recovery[33]. These findings observed within the first 2 min of the recovery phase may be associated with a better reflection of autonomic nervous system dysfunction in this phase. This may have caused a meaningless relationship between the 3rd minute of the recovery (HRR3) and the decline in night-time BP percentage. On the other hand, decreased HRR1 levels were the strongest predictors of decline in night-time BP percentage. These results demonstrate that the SNS plays a role in unsuccessful night-time BP reduction. Therefore, the TyG index may be an effective predictor of variations in the circadian BP and autonomic nervous system beyond CV events[34].

Study Limitations

This study has some important limitations. Initially, it had a retrospective design and the sample dimension was relatively small. Second, the relationship among the TyG index and NDP and HRR has been linked to the autonomic nervous system. To fully clarify that relationship, evaluation of sympathetic activation with gold-standard measurement methods such as cardiac metaiodobenzylguanidine scintigraphy with ^{123}iodine labeling would have added more power to the study. Finally, the relationship among the TyG index, HRR, and target organ damage resulting from hypertension could not be evaluated, because the retrospective design.

Conclusion

Elevated TyG index was associated with delayed HRR and NDP after exercise stress tests. Increased TyG index

and decreased HRR1 levels were important predictors of decline in night-time BP percentage. NPHT patients may be at risk of autonomic dysfunction due to increased IR.

Ethics

Ethics Committee Approval: Ethics Committee Approval was obtained from the Ankara City Hospital Clinical Research Ethics Committee (date: 11.2022, decision no: E1-22-3054).

Informed Consent: The study was designed as a retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Doğanay B, Design: Doğanay B, Data Collection and/or Processing: Doğanay B, Başar V, Analysis and/or Interpretation: Doğanay B, Başar V, Literature Search: Doğanay B, Başar V, Writing: Doğanay B, Başar V.

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E Journal of Cardiovascular Medicine
Case Report
49
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An Interesting Cutaneous Complication of Transvenous Transient Pacemaker Insertion at the Catheter Exit-Site

Kassem Riad Elizzi, Hüseyin Ede, Shahul Hameed Khan, Nidal Ahmad Asaad

Hamad Medical Corporation, Heart Hospital, Clinic of Cardiology, Doha, Qatar

Abstract

Post-intervention complications after transvenous cardiac procedures are mostly related to venous structures and heart chambers. Cutaneous and subcutaneous complications are usually ignored. However, these complications can lead to devastating conditions such as extreme bleeding, infection, and ecchymosis, etc. The development of a fibroepithelial polyps following transvenous pacemaker insertion is very rare. The vascularity of this lesion necessitates prompt diagnosis and treatment to avoid unwanted outcomes. Here, we report an interesting case of a traumatized fibroepithelial polyp with hemorrhage as a complication of central line insertion for transvenous transient pacemaker lead in a 60-year male patient.

Keywords: Fibroepithelial polyp, internal jugular vein, pacemaker, transvenous

Introduction

The internal jugular vein is a vital access port for vital procedures in cardiology practice such as transvenous pacemaker lead insertion, endomyocardial biopsy, central venous line, and right-sided hemodynamic monitoring via Swan-Ganz catheter[1,2]. Central line-related complications depend on the duration of catheter presence, the patient's clinical characteristics, the operator's experience, the use of ultrasound guidance, and wound care. Among these complications are exit-site or systemic infections, central line thrombosis, hematoma, pneumothorax, embolism, and other mechanical vascular complications[3]. Non-infectious skin lesions of catheter insertion are usually limited to the

Address for Correspondence: Hüseyin Ede, Hamad Medical Corporation, Heart Hospital, Clinic of Cardiology, Doha, Qatar
e-mail: huseyinede@gmail.com **ORCID:** orcid.org/0000-0003-1218-257X
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subcutaneous layer of the skin, mostly ecchymosis, and it resolves with local medical care. Here, we present an interesting case of a traumatized fibroepithelial polyp with hemorrhage as a complication of central line insertion developed after transvenous transient pacemaker lead insertion in a 60-year male patient.

Case Report

A 60-year-old male patient with a past medical history of diabetes mellitus (HA1c: 6.0% at admission under oral antidiabetics) and chronic kidney disease (creatinine, 419 micromol/L; glomerular filtration rate, 18 mL/min) was admitted to the medical ward due to dizziness, loss of consciousness of less than one minute in duration, and jerky movements. As a part of his neurologic investigations, brain computed tomography and brain magnetic resonance imaging were performed and the results were unremarkable. During electroencephalography testing, the patient was detected to have an eight-second advanced atrioventricular block (P-waves without escape rhythm) followed by a complete heart block (30 beats per minute with narrow-complex QRS escape rhythm) along with concomitant jerky movement and loss of consciousness. The patient was transferred to the intensive care unit promptly after the insertion of bedside temporary transvenous pacing under ultrasound guidance via the right internal jugular vein (Figure 1). His echocardiography revealed a normal left ventricular ejection fraction without the valvular or pericardial disease. Thus, it was understood that his neurological findings were due to hypoxic spells during the complete heart block episodes. On the next day, coronary angiography was performed via the right radial artery with 15-milliliter iohexol contrast, it showed non-obstructive mild coronary artery disease for medical treatment. The patient did not develop contrast nephropathy at the follow-up. Routine screening of the nose as per the hospital policy showed that the patient was a carrier for methicillin-sensitive *Staphylococcus aureus*. Following the decolonization of methicillin-sensitive *Staphylococcus aureus* by having a daily shower with 4% chlorohexidine and topical application of 2% mupirocin bilaterally twice a day over the inner nasal area for five days, a dual-chamber permanent pacemaker was implanted in the left deltopectoral area by using the left subclavian vein 7 days after the day of transient transvenous pacemaker insertion (Figure 2). At the same

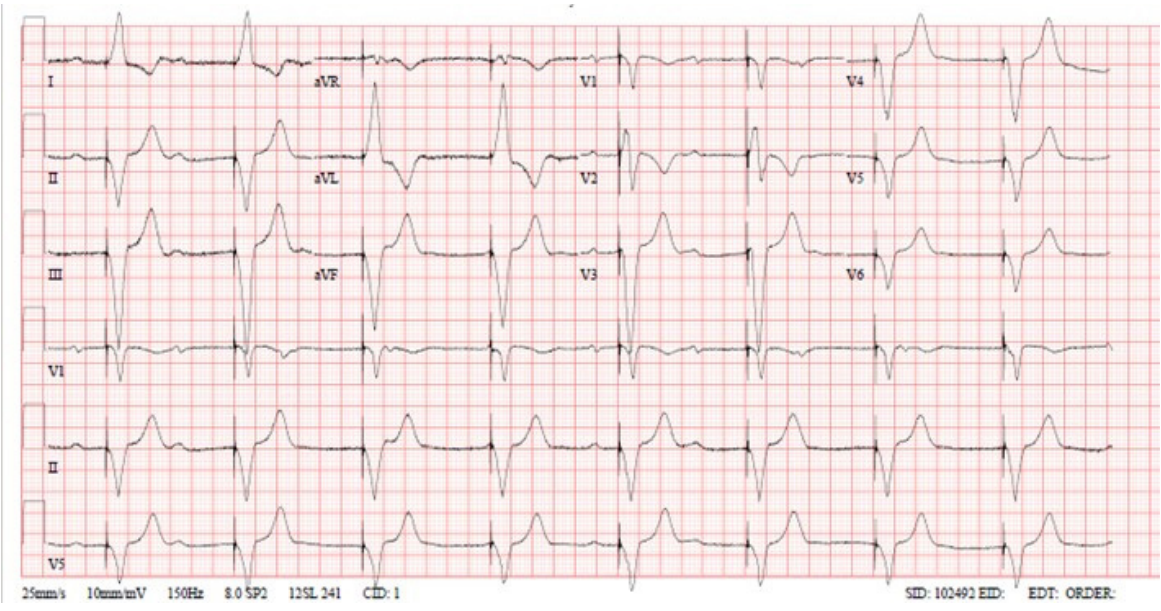

Figure 1. Electrocardiography of the patient with tranvenous temporary pacemaker

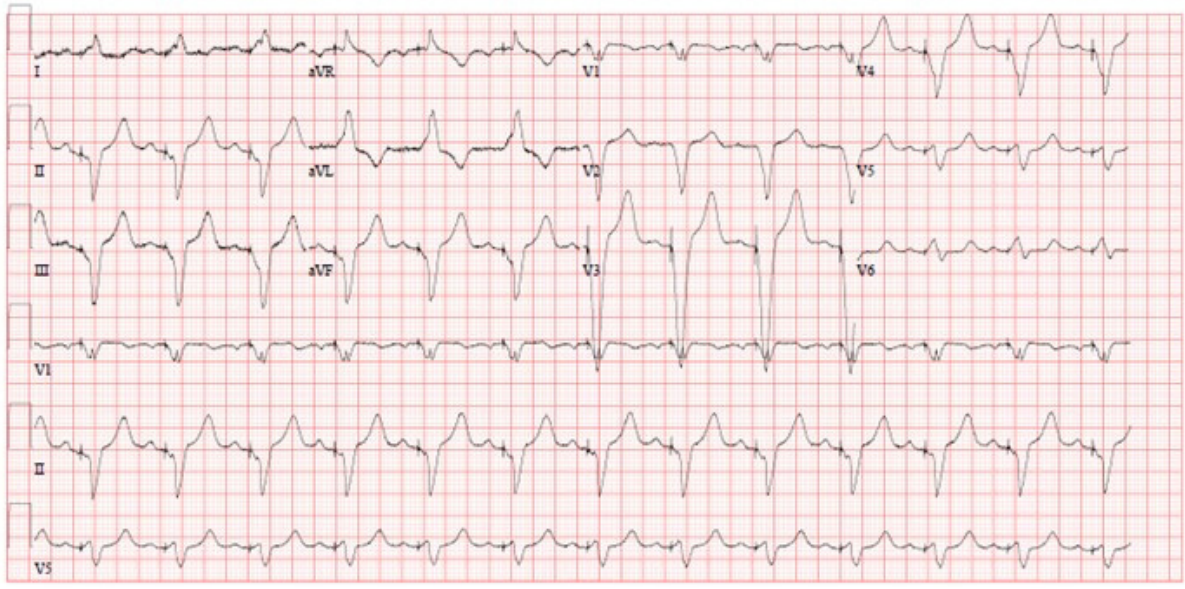

Figure 2. Electrocardiography of the patient with dual-chamber permanent pacemaker

session, the transient transvenous pacemaker lead in the right internal jugular vein was removed.

The patient received intravenous cefazolin 2000 mg twice a day for 72 h followed by oral cefuroxime axetil 500 mg daily for two weeks. One month after the removal of the catheter at the right internal jugular, the patient was re-admitted due to a right neck lesion over where the right jugular vein puncture site was perfomed before (Figure 3). The superficial lesion over the right neck was red-colored, actively bleeding, painless, protruding, and pulsatile. It had been gradually increasing in size before the admission. It was lateral to the right internal jugular vein, heterogeneous in echogenicity, and 1.9x1.7x1.9 cm in size on the ultrasound examination. Intraoperatively, it was shown that the lesion had involvement with the arterial muscular branch with significant active bleeding. It was removed by excisional biopsy under general anesthesia followed by bleeding control. The biopsy result confirmed a traumatized fibroepithelial polyp (FEP) with hemorrhage. The lesion was negative for granuloma or malignancy. The patient was discharged without complication. No recurrence was seen in the one-year follow-up of the patient.

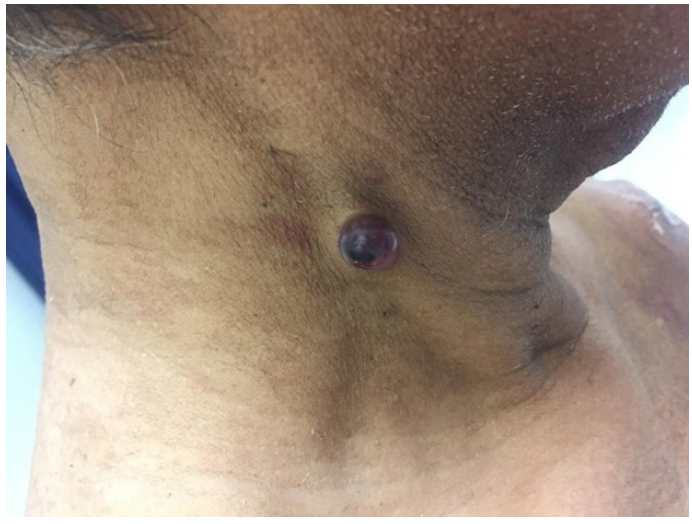

Figure 3. The photograph of the lesion over the right neck approximately 1 month after the removal of the catheter

Discussion

Central venous lines are inevitable routes to save lives. Internal jugular veins are one of the most frequently used access to obtaining central venous lines. However, complications will also be expected according to the operator's experience, the anatomic site of the access route, the use of ultrasound guidance[4,5]. Most of these

complications are mechanical, vascular, embolism, or infection-related[6,7]. In this case report, we present a case of traumatized FEP with hemorrhage as a complication of central line insertion developed after transvenous transient pacemaker lead insertion in a 60-year male patient.

Although post-insertion subcutaneous hematoma is a very common and well-known complication and can be easily mixed with FEP, cutaneous FEP formation together with vascular involvement has not been reported in the literature.

The etiology of fibroepithelial polyps is not clearly explained, but may involve trauma, the presence of diabetes, chronic irritation, allergic factors, and hormonal changes[8,9]. In our case, the patient had long-lasting trauma due to catheter *in situ* and the presence of diabetes mellitus. Ignoring such lesions can lead to excessive growth and bleeding complications[9]. In our case, the lesion had vascular involvement with active bleeding. Thus, the excisional removal of the lesion under general anesthesia cured the patient totally.

Although there may be a role of infection in the formation of dermal polyps among renal transplant patients or in veneral/urologic polyps, the role of local infection in the formation of polyps over transvenous line insertion exit-sites needs further investigation. Most likely, the underlying mechanisms of polyp formation depend on the location of the polyps and host factors[10,11]. The pathological examination of the lesion in our case did not show any significant culture growth.

In conclusion, skin lesions developed after the catheter insertion should be evaluated carefully, possible vascular connection and/or vascularity should always be kept in mind, and their excisional removal should be done under a surgical setting.

Ethics

Informed Consent: The patient's consent was obtained for the article.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Elizzi KR, Ede H, Khan SH, Asaad NA, Design: Elizzi KR, Ede H, Khan SH, Asaad NA, Data Collection and/or Processing: Elizzi KR, Ede H, Khan SH, Asaad NA, Analysis and/or Interpretation: Elizzi KR, Ede H, Literature Search: Elizzi KR, Ede H, Writing: Elizzi KR, Ede H, Khan SH, Asaad NA.

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