E-ISSN 2148-9211

CVSI

CARDIOVASCULAR SURGERY *and* INTERVENTIONS

Official Electronic Journal of the Turkish Society of Cardiovascular Surgery

Turkish Society of Cardiovascular Surgery 1988

Volume: 8 / Number: 1 / March 2021

E-ISSN 2148-9211

Cardiovascular Surgery and Interventions

Volume 8 - Number 1 - March 2021

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It is published three times a year.

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The Cardiovascular Surgery and Interventions is indexed in the following database:
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Publisher
Bayçınar Tıbbi Yayıncılık ve Reklam Hiz. Tic. Ltd. Şti.
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Type of publication: Periodical
Publication date: March 29, 2021

The control of conformity with the journal standards and the typesetting of the articles in this journal, the control of the English abstracts and references and the preparation of the journal for publishing were performed by Bayçınar Medical Publishing.

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http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1008
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Cardiovascular Surgery and Interventions

Original Article Open Access

Status of preventive services against coronary risk factors in primary healthcare for patients undergoing coronary artery bypass grafting

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Received: October 23, 2020 ***Accepted:*** November 10, 2020 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: In this study, we aimed to investigate patients who underwent coronary artery bypass grafting (CABG) in our clinic and received preventive medical services in terms of coronary artery disease (CAD) risks in the primary care setting.

Patients and methods: The cross-sectional, descriptive study included a total of 147 patients (25 males, 122 females; mean age: 62.6±8.3 years; range, 45 to 75 years) scheduled for CABG surgery between March 2018 and December 2018. Demographic and clinical characteristics of the patients were recorded. The form prepared by the researchers was applied using the face-to-face interview technique to collect data.

Results: The patients admitted to primary healthcare facilities received more information about the increased risk of CAD for smoking, and they received more exercise and healthy diet recommendations ($p<0.001$). The patients admitted to primary care to receive healthcare services were more often screened for hypertension (HT), hyperlipidemia (HL), and diabetes mellitus (DM). Among patients with a diagnosis of HT, HL, and/or DM, those admitted to primary care services had statistically significantly more frequent controls ($p<0.001$).

Conclusion: In primary care, it is possible for patients to gain healthy lifestyle changes to protect them from CAD risks and to provide care and rehabilitation for individuals with chronic diseases. The strategies for primary healthcare services on this issue can be improved.

Keywords: Coronary artery bypass grafting, coronary risk, preventive health, primary care.

Similar to many countries, healthcare services in Turkey are organized as primary, secondary, and tertiary levels.[1] Primary healthcare is placed centrally in health services and essentially includes preventive services.[1] Preventive services include the protection of individuals who are not at the risk of disease, reduction of risk factors of individuals at risk, early diagnosis and treatment of existing diseases, and prevention of chronic diseases from causing permanent damage.[2] These main goals are achieved through periodic health examinations (PHEs) with established standards by various national and international organizations.[2] The PHE consists of surveillances that are recommended to be performed according to our national programs, which include the evaluation of healthy people according to age, sex, and risk groups on a regular basis using a series of standard procedures such as interviews, physical examination, laboratory tests, and immunization programs.[2,3]

Coronary artery disease (CAD) is a chronic disease which develops over years with well-known risk factors and is the most common cause of death in Turkey.[3,4] To reduce both the frequency and mortality rates of coronary heart disease and other cardiovascular diseases, cardiovascular risk factors must be controlled first.[3] Hypertension (HT), hyperlipidemia (HL), and diabetes mellitus (DM), obesity, physical activity, and smoking are modifiable cardiovascular risk factors. The Republic of Turkey, Ministry of Health recommends cardiovascular risk assessment at least once in all individuals over the age of 40 and in individuals under the age of 40, if there is a risk factor.[2] Again, to be performed in the primary care, there are PHEs such as measuring blood pressure of

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Citation:
Çakır M, Çakır H, Dönmez K, Karaagaç E, Yürekli İ, Öngel K, et al. Status of preventive services against coronary risk factors in primary healthcare for patients undergoing coronary artery bypass grafting. Cardiovasc Surg Int 2021;8(1):1-7.

individuals over 18 years old once a year, measuring cholesterol values over 35 years at least once and every five years afterwards, measuring fasting blood glucose once every three years for everyone over the age of 45 years, body mass index (BMI) once a year, and the results of these examinations affect the coronary risk.[2]

Coronary artery bypass graft surgery (CABG) is an effective treatment method widely used in the treatment of CAD.[5,6] It is well known that CABG prolongs the lifespan in the selected patient group.[5] Considering that the most common cause of deaths in the society is CAD, preventive services to reduce CAD and related deaths are essential. In this study, we aimed to investigate the patients who underwent CABG operations in our clinic and received preventive healthcare services in terms of CAD risks in the primary care setting.

PATIENTS AND METHODS

This single-center, cross-sectional, descriptive study was conducted at Izmir Katip Celebi University, Atatürk Training and Research Hospital, Cardiovascular Surgery Clinic between March 2018 and December 2018. A total of 147 patients (25 males, 122 females; mean age: 62.6±8.3 years; range, 45 to 75 years) scheduled for CABG surgery were included. Patients with renal failure, chronic obstructive pulmonary disease, thyroid dysfunction, psychiatric disease, and malignancy were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Izmir Katip Çelebi University Non-invasive Investigation Ethics Committee (No: 77/Date: 21.02.2018). The study was conducted in accordance with the principles of the Declaration of Helsinki.

1. What is your age? (Please write) …….. AND What is your gender? a. Female b. Male
2. How tall are you? (Please write) …… How many kg is your weight? (Please write) ……
3. What is your education level? a. Below 8 years b. 8 years and more
4. What is your marital status? a. Single b. Married
5. What is your income level? a. 1500 Turkish Liras and below b. 1501 - 3500 Turkish Lira c. 3501 Turkish Lira and above
6. How would you evaluate your overall quality of life? a. Low b. Middle c. High
7. Do you smoke? a. No I do not use b. Yes I'm using
8. Do you drink alcohol? a. No I do not use b. Yes I'm using
9. Do you exercise regularly? a. No b. Yes
10. Which health institution do you prefer most frequently when you get sick or for health checks? a. Primary health care b. Other institutions
11. Has your family doctor provided you with detailed information about smoking causing cardiovascular diseases and increasing the risk of disease? a) No b) Yes
12. Has your family doctor provided you with detailed information about excessive alcohol use causing cardiovascular diseases and increasing the risk of disease? a) No b) Yes
13. Has your family doctor advised you to exercise by giving detailed information about regular exercise protecting from cardiovascular diseases and reducing the risk of disease? a) No b) Yes
14. Has your family doctor advised you to eat a healthy diet by giving you detailed information about preventing cardiovascular diseases and reducing the risk of disease? a) No b) Yes
15. Did your family doctor give you detailed information and suggest weight control about being overweight causing cardiovascular diseases and increasing the risk of disease? a) No b) Yes
16. Has your family doctor ever measured your blood pressure before being diagnosed with heart disease? a) No b) Yes
17. Has your family doctor ever measured your blood cholesterol before being diagnosed with heart disease? a) No b) Yes
18. Has your family doctor ever measured your blood sugar before being diagnosed with heart disease? a) No b) Yes
19. Do you have a diagnosis of hypertension and do you use blood pressure medication? a) No b) Yes
20. Do you have a diagnosis of hyperlipidemia and do you use its medication? a) No b) Yes
21. Do you have a diagnosis of diabetes mellitus disease and do you use its medication? a) No b) Yes
22. How many times did you go to the Family Doctor for check-ups in the last 1 year for your hypertension? (Please write) ……..
23. How many times did you go to the Family Doctor for check-ups in the last 1 year for your hyperlipidemia? (Please write) ……..
24. How many times did you go to the Family Doctor for check-ups in the last 1 year for your diabetes mellitus? (Please write) ……..

Figure 1. 24-question sociodemographic data form.

Table 1
Sociodemographic data of patients and their healthcare center preferences

Sociodemographic features	Those who prefer primary care		Those who admitted to other institutions		*p*
	n	%	n	%	
Age (year)					0.022*
45-59	36	70.6	15	29.4	
60-75	48	50	48	50	
Sex					0.659
Female	13	52	12	48	
Male	71	58.2	51	41.8	
Body mass index (kg/m^2)					0.729
Normal (18.5-24.5)	20	62.5	12	37.5	
Overweight (25-29.9)	43	54.4	36	45.6	
Obese (30-40)	21	58.3	15	41.7	
Education					0.003*
Below 8 years	48	48.5	51	51.5	
8 years and more	36	75	12	25	
Marital status					0.405
Single	70	58.8	49	41.2	
Married	14	50	14	50	
Income rate					0.013*
1,500 Turkish Liras and below (low)	5	29.4	12	70.6	
1,501-3,500 Turkis Liras (medium)	55	56.7	42	43.3	
3,501 Turkish Liras and over (high)	24	72.7	9	27.3	
Perception of quality of life					<0.001*
Low	10	28.6	23	71.4	
Medium	53	61.6	33	38.4	
High	21	80.6	5	19.2	
Smoking					0.860
Not using	55	56.1	43	43.9	
Using	29	59.2	20	40.8	
Alcohol					0.078
Not using	50	51.5	47	48.5	
Using	34	68	16	32	
Exercise					0.018*
Yes	67	53.2	59	46.8	
No	17	81	4	19	

* Statistical significance (p<0.05).

In the study, a 24-question sociodemographic data form prepared by the researchers and a questionnaire for the status of receiving healthcare services for protection from CAD were used to collect data (Figure 1). The data were obtained using the face-to-face interview technique with patients. According to sociodemographic characteristics, age was divided into two subgroups (45-59 years and 60-75 years), education status into two subgroups (<8-year and ≥8-year compulsory education), marital status into two subgroups (single and married), BMI into three groups (normal, overweight, and obese), income in three subgroups (≤1,500 Turkish Lira [TL], 1,501-3,500 TL, and ≥3,501 TL), perception of quality of life in three subgroups (poor, medium and high), and smoking and alcohol use in two subgroups (non-users and users).

Since an average of 30 isolated CABG operations is performed each month in our clinic, the study

population was created with 300 individuals for the 10-month period for which data were collected. A total of 143 CABG planned patients were calculated for the study due to sample size to be achieved for the study with a 90% confidence interval, a 5% margin of error, and HT screening frequency of 48.6% by the statistics specified by The Republic of Turkey, Ministry of Health.[4]

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 16.0 software (SPSS Inc., Chicago, IL, USA). In this study the distribution of the data was tested with Kolmogorov-Smirnov. It was found that the data were not distributed normally. So the statistical comparison of mean values of two independent groups was performed using the Mann- Whitney U test. The between group comparisons of categorical variables were performed using the Chi-square test.

RESULTS

Of the patients, patients aged ≤59 years preferred primary healthcare services more than patients aged ≥60 years (p=0.022). The primary healthcare services were more preferred by those with an education status of ≥8 years, those with an income level of ≥3,500 TL, those with a good level of quality of life, and those who exercised regularly (p=0.003, p=0.013, p<0.001, and p=0.018, respectively) (Table 1).

When we examined whether the patients received lifestyle recommendations for protection from CAD, the patients who preferred primary healthcare facilities received more information that smoking increased the risk of CAD (p<0.001). Again, the patients who preferred primary healthcare facilities received more recommendations for coronary protection including exercise, healthy diet recommendations, and weight control recommendations (p<0.001) (Table 2).

Table 2
Patients' receiving lifestyle recommendations and chronic disease screening and their healthcare center preferences

	Those who prefer primary care		Those who admitted to other institutions		
Sociodemographic features	n	%	n	%	*p*
Getting information about smoking					<0.001*
Did not receive	30	38	49	62	
Received	54	79.4	14	20.6	
Getting information about alcohol					<0.001*
Did not receive	42	42.4	57	57.6	
Received	42	87.5	6	12.5	
Getting advice to exercise					<0.001*
Did not receive	34	40	51	60	
Received	50	80.6	12	19.4	
Getting healthy dietary advice					<0.001*
Did not receive	33	39.8	50	60.2	
Received	51	79.7	13	20.3	
Getting weight control advice					<0.001*
Did not receive	35	41.2	50	58.8	
Received	49	79	13	21	
Blood pressure measurement					<0.001*
Did not perform	29	36.3	51	63.7	
Performed	55	82.1	12	17.9	
Blood test recommendation for hyperlipidemia					<0.001*
Did not receive	19	33.3	38	66.7	
Received	65	72.2	25	27.8	
Blood test recommendation for diabetes mellitus					<0.001*
Did not receive	13	23.2	43	76.8	
Received	71	78	20	22	

* Statistical significance (p<0.05).

Table 3
Patients' chronic disease control visits and their health center preferences

	Those who prefer primary care				Those who admitted to other institutions				
	n	%	Median	25th-75th percentile	n	%	Median	25th-75th percentile	*p*
Presence of hypertension diagnosis									<0.001*
No	30	38			49	62			
Yes	54	79.4			14	20.6			
Presence of hyperlipidemia diagnosis									<0.001*
No	42	42.4			57	57.6			
Yes	42	87.5			6	12.5			
Presence of diabetes mellitus diagnosis									<0.001*
No	34				51	60			
Yes	50				12	19.4			
Continuous variables									
Hypertension control frequency			3	2-4			1	0-2	<0.001*
Hyperlipidemia control frequency			3	2-4			1	0-2	<0.001*
Diabetes mellitus control frequency			2.5	2-4			1	0-2	<0.001*

* Statistical significance (p<0.05).

More HT, HL, and DM screening were performed in the patients who essentially preferred primary care to receive healthcare services (p<0.001). Of the patients, the rate of blood pressure measurement was 45.6% (n=67), the rate of those who had cholesterol tests was 61.2% (n=90), and the rate of those who had blood glucose control was 61.9% (n=91) for screening purposes in the primary healthcare facilities. There was no significant difference in terms of patients' healthcare center preferences and the presence of HT, HL, and DM diagnoses (p>0.005). On the other hand, the patients with HT, HL, and DM who preferred primary healthcare facilities had statistically significantly more frequent controls for disease (p<0.001) (Table 3).

DISCUSSION

In the present study, we investigated whether the patients who were scheduled for CABG operation received primary healthcare services for CAD risks. Our study results showed that patients admitted to primary healthcare facilities were screened more for HT, DM, and HL and received more recommendations about the coronary injuries of smoking and coronary benefits of regular exercise and weight control. Among the patients with chronic diseases, those who preferred primary healthcare had also more frequent controls for the disease.

Previous studies have shown that health systems organized based on effective primary care, in which well-trained family physicians work, provide more effective healthcare, both economically and clinically, than passive ones.[1,7] Coronary artery disease patients are one of the most common patient groups seen by family physicians in the primary care setting.[3] The World Health Organization emphasized that 3.8 million men and 3.4 million women died annually due to CAD in 2008 and that 11.1 million individuals were estimated to die for CAD in 2020.[8] According to the Turkish Adult Risk Factor Study (TEKHARF) data, which is a 26-year cohort study conducted in our country, deaths due to coronary heart disease are the first among all-cause of mortality with a prevalence of 42%.[9]

According to data from the 2016 Health Survey of Turkey by the Turkish Statistical Institute (TSI), the rate of individuals who had their blood pressure measured using the primary healthcare services were found to be 48.6%.[4] In our study, 45.6% of the patients had their blood pressure measured in primary healthcare. Also, based on TSI data, the rates of patients who benefitted from preventive care in Turkey for cholesterol and blood glucose level measurement were 36.7% and 39.7%, respectively.[4] In our study, these rates were 61.2% and 61.9%, respectively. The reason why the cholesterol and blood glucose measurements

of the patients included in our study were performed more frequently may be that the patients preferred the primary healthcare more in the Aegean region and the number of family medicine specialists in the Aegean region was higher.[4,10]

In our study, the patients with a diagnosis of chronic disease preferred primary healthcare more frequently. In the study of İlhan et al.,[11] those with chronic diseases also preferred primary healthcare services more frequently. Again, in the systematic review prepared by Reynolds et al.,[12] the patients with chronic diseases visited primary healthcare services more commonly. Primary healthcare services can be expected to be preferred by individuals with chronic diseases due to their easy accessibility and providing comprehensive, continuous, and coordinating care.[7,12] Protection from chronic diseases and treating and rehabilitating individuals with chronic diseases have an important place in the practice of family medicine.[7] It can be predicted that the coronary risks of patients with HT, HL, and DM, which are the risk factors for CAD, can be also reduced by effective care in the primary healthcare facilities.

Furthermore, in our study, we found that the individuals who chose primary healthcare received more physical exercise and healthy diet recommendations, and obtained more information about the coronary risks of smoking. It is well known that even simple suggestions of physicians for patients to quit smoking affect patients to quit smoking.[13] It is also stated that giving "quit smoking" advice, particularly by primary care physicians provides more effective results.[14] Studies have shown that patients adapt more to physical activity and healthy dietary recommendations in primary care, providing the chance to protect patients from many diseases.[15,16] Currently, smoking, physical inactivity, and unhealthy diet pose serious risks for CAD, and healthy lifestyle recommendations of primary care physicians are of utmost importance in reducing patients' CAD risks. By protecting patients from coronary risks, the rate of CABG operations and, consequently, health expenses and loss of job can be reduced, as well.

Due to the data collected from a single city, the results of the study cannot be generalized to the overall population in Turkey. In addition, data were collected only from a tertiary health institution. Further studies in larger populations would provide more information on this issue.

In conclusion, performing necessary examinations in accordance with the PHE recommendations of the Republic of Turkey, Ministry of Health for patients admitting to primary healthcare is of a paramount importance in terms of protection from CAD. In primary healthcare, it is possible for patients to gain a healthy lifestyle, to be protected from chronic diseases, and to provide care and rehabilitation for individuals diagnosed with chronic diseases. Therefore, the main goals should be to increase the strategies for primary healthcare services, to increase the knowledge and awareness of primary care physicians on this issue with in-service training, and to provide a more multidisciplinary service to patients.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):8-12
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1010
www.e-cvsi.org
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Cardiovascular Surgery and Interventions

Original Article Open Access

Aortofemoral bypass in occlusive TASC-C and TASC-D lesions: Midterm results of 28 cases

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Received: October 25, 2020 ***Accepted:*** December 25, 2020 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: This study aims to evaluate the three-year patency rates of aortofemoral bypass surgery in the clinical and radiological diagnosis of Trans-Atlantic Inter-Society Consensus (TASC)-C and TASC-D aortoiliac lesions.

Patients and methods: Medical records of a total of 28 patients (21 males, 7 females; mean age: 64.8±8.6 years; range, 58 to 72 years) with TASC-C and TASC-D aortoiliac lesions who underwent aortofemoral bypass surgery between September 2014 and December 2018 were retrospectively analyzed. Demographic and clinical characteristics of the patients were recorded. All operations were performed by a single surgical team by placing a Y graft in the anatomical location and using open median laparotomy technique. The Y graft bypass results with peri- and postoperative data were evaluated.

Results: Dacron Y grafts were used in 18 of TASC-C (25%) and TASC-D (75%) lesions, and polytetrafluoroethylene Y grafts were used in 10 of them. No reoperation or amputation was performed in any patient during follow-up. The mean patency of vascular Y grafts was 92% after three years. There was no significant difference between the graft types and postoperative patient values ($p>0.05$). Mortality was observed in one patient due to systemic inflammatory response syndrome.

Conclusion: The patency of vascular grafts for aortoiliac occlusive disease is satisfactory in TASC-C and D lesions.

Keywords: Aortoiliac occlusive disease, bypass grafting, cardiovascular diseases, vascular prosthesis.

Aortobifemoral bypass (ABFB) surgery is usually the most common procedure used in occlusive aortic and iliac artery diseases such as Leriche syndrome. In recent years, minimally invasive, endovascular and laparoscopic interventions and successful surgeries from certain centers have been reported.[1] Advantages of non-open surgical other alternative treatments are low hospital stay, low cost, and faster recovery However, it is important to acknowledge the possible disadvantages of these methods. Certainly, they have less patency rate and do not usually provide complete revascularization. They are less effective in patients with common disease patterns.

Patients usually present with claudication complaints. Some patients present with the complaints of impotence, pain in the hips, and wounds in the feet. Chronic development of atherosclerosis and collateral flow over time may overshadow lower extremity ischemia for a long time and, therefore, these patients remain asymptomatic for a long time.

In the contemporary era, endovascular interventions are more likely to be more than performed ABFB. Despite these changes, perioperative mortality and morbidity remain low with excellent long-term outcomes. In the present study, we aimed to evaluate the operation success rates, three-year primary patency, and complication for Trans-Atlantic Inter-Society Consensus (TASC-C and D aortoiliac lesions treated by surgical anatomic bypass grafting procedure.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ankara Training and Research Hospital between September 2014 and December 2018.

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Citation:
İlkeli E, Düzgün AC. Aortofemoral bypass in occlusive TASC-C and TASC-D lesions: Midterm results of 28 cases. Cardiovasc Surg Int 2021;8(1):8-12.

Medical records of a total of 28 patients (21 males, 7 females; mean age: 64.8±8.6 years; range, 58 to 72 years) with TASC-C and TASC-D aortoiliac lesions who underwent aortofemoral bypass surgery were retrospectively analyzed. The aortoiliac lesions of the patients were categorized in Table 1 according to the TASC classification.[2] A written informed consent was obtained from each patient. The study protocol was approved by the Ankara Training and Research Hospital Ethics Committee (27.08.2020-357/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Age, sex, comorbidities, type of laparotomy, type of anesthesia, duration of aortic cross-clamp, duration of operation, length of intensive care unit (ICU) and hospital stay, early postoperative complications, blood products used in the operation, antibiotherapy, heparin use, and surgical anastomosis characteristics were recorded. The Y graft types were examined. The Y graft interposition was performed in all patients. Intra- and postoperative complications were recorded.

The patients were evaluated by computed tomographic angiography (CTA) every six months during the first year after the first bypass grafting. In the following years, graft patency was evaluated once with CTA. Ultrasonography was used to control bypass grafts in selected patients.

The graft patency rates, redo operations, complications, and mortality calculations were made from the three-year follow-up data of the patients.

Surgical technique

All patients were operated in the supine position under general anesthesia. A midline abdominal incision was made and the transperitoneal aorta was approached. Suprailiac aorta and bilateral iliac vessels were exposed, and systemic heparin was administered to all patients before cross clamp. A cross-clamp was placed on the non-calcified part of the aorta in the suprailliac section after heparinization. The proximal anastomosis was made above the iliac bifurcation level with end to side position according to calcification of aortoiliac occlusive disease. Distal anastomosis was performed with an end-to-side fashion to the common femoral arteries just proximal to the bifurcation. Routine activated coagulation time (ACT) control and protamine sodium were not measured after the operation.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Fisher's chi-square test was used to compare Dacron and polytetrafluoroethylene (PTFE) grafts. A p value of <0.05 was considered statistically significant.

RESULTS

Hypertension was seen in 18, DM in 15, coronary artery disease in 16, peripheral artery disease in six, and chronic obstructive pulmonary disease in eight patients. Of the patients, 14 were smokers. Four of the patients previously underwent coronary artery bypass surgery (Table 2).

Twenty patients were evaluated preoperatively by CTA scanning. Digital subtraction angiography (DSA)

Table 1
TASC II classification of aortoiliac occlusive disease[2]

TASC-A	Unilateral or bilateral CIA lesion, unilateral or bilateral stenosis in ≤3 cm EIA.
TASC-B	≤3 cm stenosis in the infrarenal aorta, unilateral CIA occlusion, single/multiple stenoses between 3 and 10 cm in total in the EIA (not spread to CFA) unilateral EIA occlusion (CFA/IIA origins are not included.
TASC-C	Bilateral CIA occlusion, bilateral EIA stenosis (3-10 cm, not involving CFA), unilateral EIA stenosis (extending to CFA) unilateral EIA occlusion (involves IIA/CFA origins), unilateral calcified EIA occlusion (IIA/CFA involves origins or not
TASC-D	Diffuse disease involving infrarenal aortic occlusion, aorta and both iliac arteries requiring treatment diffuse multiple lesion involving unilateral CIA, EIA and CFA. Iliac stenosis in patients with unilateral occlusion, bilateral EIA occlusion, AAA requiring treatment (other lesions not suitable for endograft and requiring open aortoiliac surgery

TASC: Trans-Atlantic Inter-Society Consensus; CIA: Common iliac artery; EIA: External iliac artery; IIA: Internal iliac artery; CFA: Common femoral artery; AAA: Abdominal aortic aneurysm.

Table 2
Demographic and clinical characteristics of patients

	n	%
Sex		
Male	21	75
Female	7	25
Hypertension	18	64
Diabetes mellitus	15	54
Coronary artery disease	16	57
Peripheral artery disease	6	21
COPD	8	29
Smoking	14	50
Operation history	4	14
Imaging		
Computed angiography	20	71
Digital subtraction angiography	8	29
TASC Classification		
TASC-D	21	75
TASC-C	7	25

COPD: Chronic obstructive pulmonary disease; TASC: Trans-Atlantic Inter-Society Consensus.

was performed in eight patients. For aortoiliac lesions according to the TASC, 75% were type D and 25% were type C lesions. A Dacron Y graft was used in 18 patients and a PTFE Y graft was used in 10 patients.

All patients were successfully revascularized with graft on anatomical position. The mean operation time was 97±42 min and the mean aortic-cross clamp time was 14±09 min. All patients were followed in the ICU after the operation. The mean length of ICU stay was 16±05 h, while the mean length of hospital stay was 4±08 days (Table 3).

During early follow-up, one patient was reoperated for postoperative bleeding, and three patients underwent reoperation for distal embolism. Surgical embolectomy was performed for all these three patients. Embolectomy was successful in two patients; however, femoropopliteal bypass was required in one patient. One patient died in the early postoperative period due to postoperative systemic inflammatory response syndrome (SIRS).

There was no significant difference between the graft type and operation time, length of ICU and hospital stay, early postoperative complications, blood products used in the operation, and mortality. ($p>0.05$) A total of 60 units of erythrocyte suspension and 24 units of fresh frozen plasma were used in a total of 28 patients. After the operation, clopidogrel 75 mg once a day and acetylsalicylic acid 100 mg once a day were prescribed as dual therapy for all patients.

The primary patency rates at three years after ABFB were 94% for the Dacron grafts, and 90% for the PTFE grafts, respectively ($p>0.05$). A Y graft thrombosis was observed in two cases. Reoperation and amputation were not performed in any patient during follow-up (Table 4).

DISCUSSION

Currently, thromboendarterectomy, ABFB, and endovascular intervention options are available in the treatment of aortoiliac occlusive disease.[3]

Table 3
Intraoperative data

	Mean	Min-Max
Mean operation time (min)	97.42	86-108
Mean duration of aortic cross clamp (min)	14.69	11-17
Mean intensive care duration (h)	16.05	10-21
Mean duration of total hospital stay (day)	4.08	3-6
Erythrocyte suspension (unit)	60	
Fresh frozen plasma (unit)	24	
Reoperation		
Bleeding	1	
Distal embolism	3	
Death	1	

Min: Minimum; Max: Maximum.

Table 4
Patency rates according to graft types after three years

	n	Primary patency	%
Dacron graft	18	17	94
PTFE graft	10	9	90

PTFE: Polytetrafluoroethylene; Postoperative graft patency rates after three years (p>0.05).

Control of DM, antiplatelet and statin therapy, antihypertensive therapy, quitting smoking and exercise play an important role in medical treatment. It has been reported that cilostazol, a phosphodiesterase III inhibitor, reduces claudication complaints and may be beneficial in providing graft patency and preventing restenosis.[4]

The five-year patency rates of aortoiliac bypass grafting vary between 80 and 95.10% and between 75 and 80% annually. The Dacron and PTFE bypass surgeries performed in aortic and iliac vessels with large calibration and high flow patterns have excellent long-term results.[5] Randomized multi-center studies have shown no significant difference between the five-year patency rates between both grafts.[6]

Arterial autologous grafts are the best choice for revascularization. However, this option for coronary arteries is not available for aorta, iliac, and distal arterial structures. Endovascular interventions have been increasingly used, particularly in peripheral infrainguinal lesions.[7] Currently, endovascular interventions are often preferred to surgery in low-calibrated vascular structures. Endovascular approach has become more preferred, particularly when comorbid diseases and advanced age pose a risk. The results of bypass with artificial grafts in distal peripheral vascular diseases are not satisfactory. Therefore, many vascular surgeons today have adopted endovascular atherectomy, balloon, or stent procedure for more peripheral lesions.

Aortoiliac occlusive disease is often considered as Leriche syndrome. The lesions are classified as Type A, Type B, Type C, and Type D by the TASC.[8] In recent years, widespread stent-balloon applications have been applied to TASC-C and TASC-D lesions. However, the long-term results are still unclear. Although recent studies indicate a patency rate of 60 to 86%, based on all studies, five-year patency rates do not exceed 80%.[9-11] These results indicate that aortoiliac bypass grafting is still the best revascularization option for TASC-C and TASC-D lesions. In our study, the bypass procedure was successfully applied to all patients. In another study comparing the results of endovascular stenting and bypass grafting in aortoiliac lesions, the authors recommended iliac artery stenting, particularly in elderly and those having severe comorbidities, since the patency rates were lower than surgical treatment.[12] Since the study includes Type B lesions, it can be also considered that the surgical option remains up-to-date in all aortic and iliac lesions. In addition, since unilateral and bilateral lesions were not distributed homogeneously in the study, we consider that stent-balloon results were exaggerated. In laparoscopic vascular surgery, the disadvantages of this technique are the long operation time and insufficient aortic exposure, the inability to place a safe cross-clamp, the use of expensive disposable instruments, excessive aortic calcification, previous abdominal operations and obesity.

Since bypass surgery is mostly performed with artificial grafts, there is a risk of infection, thrombosis, and aneurysm. Many laboratory and clinical studies have been conducted showing that PTFE graft is more resistant to infection.[13] In our study, we did not observe such complications in any of the patients. One of our patients died from SIRS within a few hours after the operation; however, it was not related to a complication of infection.

It is very rare to encounter major complications while open ABFB surgery. Immediate complications in this surgery are vascular damage, bleeding, intestinal damage, ileus, myocardial infarction, and renal failure. Late complications are aorto-enteric fistula, sexual dysfunction, infection, graft thrombosis and anastomotic pseudoaneurysms.[14]

Postoperatively, we reoperated one of our patients for bleeding. However, we could not find the bleeding focus, and 0.25 mg protamine sulfate was administered systemically. The heterogeneous nature of unfractionated heparin, polydispersity of molecular weight or different chemical properties may cause different responses in patients. Therefore, ACT monitoring is required in routine operations. Heparin has advantages due to its short half-life, its ability to be monitored with activated partial thromboplastin time, and to be completely neutralized with protamine sulphate. Since heparin has a short half-life and we follow bleeding drainage, we did not perform postoperative ACT control routinely.

Cross-clamp time is important in surgical vascular interventions. Insufficient blood supply to the distal arterial vessels can always cause serious ischemic events. It can cause limb loss or amputation. Acute spinal cord ischemia after ABFB has been reported in the literature.[15,16] In vascular surgery, keeping the ischemia time as short as heparinization time can prevent unpredictable ischemic complications. In our study, the mean operation and cross-clamp time are consistent with the literature. The bypass option is always more advantageous in terms of cost, compared to endovascular treatment. Routine use of the retroperitoneal approach cannot be recommended for standard aortoiliac occlusive disease, although it is advantageous in certain situations. It makes it difficult to tunnel the graft, particularly in patients with obesity.

The main limitations of the present study are the lack of a large sample size and inability to compare the results with endovascular treatment. Further, multi-center, large-scale studies are needed to compare open surgical results with endovascular treatment. In particular, the small sample size of the study limits the generalizability of findings or the ability to provide detailed clinical results.

In conclusion, endovascular interventions are currently performed more commonly than bypass surgery in the treatment of aortoiliac occlusive disease. However, the surgical success and patency rates with Y graft are still higher in TASC-C and D lesions. As a result, there is no second treatment option that has achieved surgical treatment success in aortoiliac occlusive, bilateral vascular diseases. Open surgical treatment should be the preferred treatment due to long-term patency rate for all patients, except for elderly and those having severe comorbidities.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):13-19
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1065
www.e-cvsi.org
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Cardiovascular Surgery and Interventions

Original Article Open Access

The association of blood transfusion and acute kidney injury in diabetic coronary artery bypass grafting patients

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Received: January 29, 2021 ***Accepted:*** February 25, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: This study aims to investigate the association between blood transfusion and acute kidney injury (AKI) in diabetic coronary artery bypass grafting (CABG) patients.

Patients and methods: Between October 2016 and September 2019, a total of 270 elective CABG patients with diabetes (62 males, 208 females; mean age: 63.2±9.3 years; range, 40 to 86 years) were retrospectively analyzed. The patients were divided into two groups according to presence of cardiac surgery-related AKI. Risk factors were compared between the groups.

Results: No significant difference was found between the groups in terms of baseline characteristics, except for body mass index, EuroSCORE II, and platelet count. The significant factors in the univariate analysis were included in the logistic regression. Only blood transfusion was found to be associated with AKI with red blood cell, fresh frozen plasma, platelet, and complete transfusions ($p<0.001$, $p<0.001$, $p=0.002$, and $p<0.001$, respectively).

Conclusion: Our study results suggest that perioperative red blood cell, fresh frozen plasma, platelet, and complete transfusions are associated with postoperative AKI in diabetic CABG patients.

Keywords: Acute kidney injury, blood transfusion, coronary artery bypass grafting, diabetes mellitus.

Coronary artery bypass grafting (CABG) is safely performed with low mortality and morbidity rates thanks to the increased surgical experience in recent years. Despite the increase in surgical experience, CABG may demand additional medical requirements that bring along inevitable complications. Blood transfusions are one of the most common requirements accompanying CABG and may result in undesirable side effects, such as acute kidney injury (AKI).[1]

Blood transfusion is frequently required after cardiac operations and the causes for transfusion requirement are several. Surgical bleeding during both the intra- and postoperative periods is very common in CABG patients.[2] Antiaggregant and/or anticoagulant medications are frequently used during the perioperative period. The use of a cardiopulmonary bypass may lead to coagulopathy as a result of platelet dysfunction and a deteriorated coagulation cascade. Fluid replacement, particularly with crystalloids to provide hemodynamic stability, may cause dilutional anemia. All these factors play a role in the need for blood transfusion after CABG surgery.[3,4]

Blood transfusions are associated with AKI in CABG patients.[5,6] Meanwhile, anemia itself has been shown as another cause of AKI.[7] Maintaining a balance is important not to cause anemia, while also avoiding an unnecessary blood transfusion.

Patients undergoing CABG surgery have a high rate of diabetes mellitus. Diabetes mellitus increases the complication rates associated with AKI, impaired wound healing, and mortality.[8,9] As diabetic patients are more susceptible to postoperative complications, special implementations with these patients may provide better outcomes after CABG. This is why we

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Citation:
Özhan A, Akgül E, Parlar Aİ, Çekirdekçi A. The association of blood transfusion and acute kidney injury in diabetic coronary artery bypass grafting patients. Cardiovasc Surg Int 2021;8(1):13-19.

have given a special interest in investigating the group of diabetic patients.

In this study, we aimed to investigate the risk factors, particularly blood transfusions in diabetic CABG patients, associated with AKI.

PATIENTS AND METHODS

The single-center, retrospective study was conducted at Kütahya Health Sciences University, Evliya Çelebi Training and Research Hospital, Department of Cardiovascular Surgery between October 2016 and September 2019. A total of 270 elective CABG patients with diabetes (62 males, 208 females; mean age: 63.2±9.3 years; range, 40 to 86 years) who were followed up to two weeks until discharge were included in the study. All patients included in the study were elective CABG patients, all of whom had normal regulation of blood glucose at least one week before surgery to eliminate the negative effects of uncontrolled blood glucose. Patients with emergency CABG surgery, off-pump surgery, simultaneous operations with CABG, cardiac reoperations, preoperative renal impairments, and in-hospital mortality were excluded from the study to standardize the results and avoid potential pre-existing negative impacts on renal function. All patients were operated at the same center using the same anesthesia, cardiopulmonary bypass, and operation protocols. Data including baseline demographic characteristics and follow-up were retrieved from hospital database. A written informed consent was obtained from each patient. The study protocol was approved by the Kütahya Provincial Health Directorate Ethics Committee (No: 2021/16). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Acute kidney injury was classified in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[10] The patients' final measurement values before surgery were defined as the baseline measurements. The serum creatinine level at 48 h after surgery was recorded. An increase in baseline creatinine of over 50% (i.e., 0.3 mg/dL increase) was defined as Stage 1 AKI, an increase of ≥100% as Stage 2 AKI, and an increase of ≥200% as Stage 3 AKI. None of the patients had Stage 2-3 AKI. The patients having no AKI constituted the AKI-negative group, while the patients diagnosed with Stage 1 AKI constituted the AKI-positive group. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) and the Cockcroft-Gault formula for estimating creatinine clearance (CrCl).[11]

Administering red blood cell (RBC) transfusion was decided, when a hematocrit level below 25% or hemoglobin level below 8 g/dL was detected in the perioperative period. Administering a fresh frozen plasma (FFP) transfusion was decided, when the international normalized ratio was above 1.4 or activated clotting time or activated partial thromboplastin time was two-times higher than the baseline value. Administering a platelet transfusion was decided, when a platelet count was below 100 (10^3/μL) and ongoing hemorrhage or drainage was detected.

The primary outcome measure of the study was AKI as defined in accordance with the KDIGO criteria.

Statistical analysis

Statistical analysis was performed using the Jamovi version 1.2.27 software (https://www.jamovi.org). The Shapiro-Wilk test, skewness and kurtosis values, histograms, and Q/Q plots have been used to identify distribution patterns. Descriptive data were expressed in mean±standard deviation (SD) or median (interquartile range [IQR]) for continuous variables and in number and frequency for categorical variables, where applicable. For the nominal variables, the chi-square test was used to compare the groups. As the number of patients with postoperative AKI was less than 30 (n=19), the Mann-Whitney U test was used to compare the non-parametric data. Multivariate analysis was performed on the variables which were found to be statistically significant in the univariate analysis or that are established risk factors as defined in the literature. A p value of <0.05 was considered statistically significant.

RESULTS

Of all 270 elective diabetic CABG patients included in the study, 19 patients were in the AKI-positive group with Stage 1 AKI, while 251 were in the AKI-negative group. Among the patients, 118 (43.7%) had hypertension. There was no significant difference in the baseline demographic characteristics of the groups including age, sex, presence/lack of hypertension, chronic pulmonary disease, and

Table 1
Baseline demographic and clinical characteristics of patients

	AKI-negative (n=251)					AKI-positive (n=19)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			62.9±9.3					66.8±8.45			0.073
Female	190	75.7				18	94.7				0.057
Hypertension	112	44.6				6	31.6				0.269
Chronic pulmonary disease	41	16.3				0	0				0.056
Peripheral vascular disease	60	23.9				5	26.3				0.813
Body mass index (kg/m^2)			27.9±4.0					25.4±4.6			0.010
EF			48.6±9.9					47.9±10.2			0.794
EuroSCORE II				1.86	1.29-3.10				2.45	1.81-3.78	0.024
Baseline laboratory values											
Hematocrit (%)			39.3±5.6					40.2±4.1			0.526
Hemoglobin (g/dL)			13.5±1.9					13.9±1.4			0.434
Platelet (10^3/μL)				239	201-286				209	185-235	0.045
Creatinine (mg/dL)				1.00	0.86-1.17				1.03	0.84-1.21	0.582
Creatinine clearance (mL/min)			81.8±26.7					70.0±21.4			0.062
Glomerular filtration rate (mL/min/1.73 m^2)			64.9±20.7					56.9±19.8			0.106

AKI: Acute kidney injury; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 2
Comparison of patient groups according to postoperative renal measurements and perioperative blood transfusion

	AKI-negative (n=251)			AKI-positive (n=19)			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
Creatinine (postoperative)		1.06	0.92-1.23		1.32	1.22-1.54	<0.001
CrCl (postoperative)	70.3±23.4			45.6±15.0			<0.001
eGFR (postoperative)	60.1±19.2			39.7±11.3			<0.001
Perioperative blood transfusion							
RBC (unit)	1.6±1.3			4.0±1.3			<0.001
FFP (unit)	2.8±1.3			4.4±1.6			<0.001
Platelet (unit)		0	0-0		0	0-1	0.002
nonRBC (unit)	3.1±1.6			5.3±2.3			<0.001
Complete transfusion (unit)	4.7±2.5			9.2±3.2			<0.001

AKI: Acute kidney injury; CrCl: Creatinine clearance; eGFR: Estimated glomerular filtration rate; FFP: Fresh frozen plasma; RBC: Red blood cell.

peripheral vascular disease; and baseline hematocrit, hemoglobin, and creatinine levels, except for the body mass index, EuroSCORE II, and baseline platelet count (Table 1).

Postoperative renal measurements such as creatinine levels, CrCl, and eGFR revealed statistically significant differences between the groups (Table 2). Of the patients, 41 had no RBC transfusion during the perioperative period; all patients had at least one unit of transfusion (RBC or non-RBC transfusion). The AKI-positive group was found to have higher transfusion rates, including RBC (p<0.001), FFP (p<0.001), platelet (p=0.002), and complete (p<0.001) transfusions. None of the patients had any permanent postoperative renal impairment.

The factors found to be significant in the univariate analysis and the established risk factors described in the literature for AKI were examined (Table 3). For renal impairment, the eGFR was taken into account to represent renal function. No statistically significant relationship was found for age, hypertension, EuroSCORE II, or baseline eGFR with AKI in the logistic regression analysis. Perioperative RBC transfusions, non-RBC transfusions (summation of the FFP and platelet transfusions), and complete transfusions were found to be associated with AKI. The $R^2_{Nagelkerke}$ was greater than 20% and accuracy exceeded 90% for all three univariate logistic regression analyses, all of which had values of p<.001.

Table 3
Univariate logistic regression analysis results for acute kidney injury

	Odds ratio	95% CI	*p*	$R^2_{Nagerkerke}$	Accuracy
Age	1.050	0.995-1.108	0.075	-	-
Hypertension	0.573	0.211-1.555	0.274	-	-
EuroSCORE II	1.093	0.912-1.310	0.336	-	-
Baseline eGFR	0.981	0.958-1.000	0.107	-	-
RBC (unit)	2.572	1.838-3.597	<.001	0.335	91.9%
nonRBC (unit)	1.829	1.423-2.352	<.001	0.216	93.7%
Complete transfusion (unit)	1.543	1.321-1.802	<.001	0.310	93.7%

CI: Confidence interval; eGFR: Estimated glomerular filtration rate; RBC: Red blood cell.

The receiver operating characteristic (ROC) curve analysis was performed for the statistically significant variables (i.e., RBC, non-RBC, and complete transfusions) to define a cut-off value for each; however, reliable cut-off values could not be obtained due to the limited number of patients in the AKI-positive group. The statistically insignificant results of the ROC analysis are not presented.

DISCUSSION

Diabetic patients are prone to complications after CABG surgery, and a special interest and implementations are required during the perioperative period. Diabetic CABG patients are at an increased risk for cerebrovascular disease, AKI, sternal infections, and mortality and require transfusions more often.[12] Diabetes mellitus is an independent risk factor for AKI, even when blood transfusions are not considered. Endothelial dysfunction and impaired microcirculation are considered to be responsible for its pathogenesis.[12,13]

Several factors have been found to be associated with increased blood transfusion. According to Klein et al.,[14] age, sex, body surface area, logistic EuroSCORE, preoperative hemoglobin and creatinine were associated with increased blood transfusion.

Blood transfusions are a specific topic that may complicate and lead to AKI in CABG patients and requires a rigorous approach.[15] Cardiovascular surgeons tend to avoid redundant blood transfusions, and studies defining the safe limits for blood transfusion have been previously published.[16] Restrictive or liberal thresholds for RBC transfusions were investigated by Mazer et al.[17] The transfusion criteria were defined as a hemoglobin level of <7.5 mg/dL for the restrictive threshold approach and a hemoglobin level of <9.5 mg/dL for the liberal threshold approach. The study showed the restrictive threshold approach to not be inferior to the liberal threshold approach with respect to mortality, infection, neurological complications, pulmonary impairment, and AKI. The six-month follow-up results of the study also supported the initial results.[18]

Lower body mass index, higher logistic EuroSCORE II, and lower preoperative platelet counts in our cohort were found to be associated with Stage 1 AKI. Receiving blood transfusion during the perioperative period was also found to be associated with a higher incidence of Stage 1 AKI in terms of RBC, FFP, platelet, and complete transfusions.

In their propensity score-matched retrospective study, Kocyigit et al.[19] found receiving blood transfusion not to be associated with new-onset dialysis or discharge creatinine level in diabetic CABG patients. The Koster et al.'s[20,21] studies also found no significant association between blood transfusion and renal impairment in terms of RBC and apheresis platelet concentrates. However, according to Amini et al.,[22] AKI was associated with RBC transfusions and diabetes, in addition to advanced age, on-pump cardiac surgery, and prolonged mechanical ventilation.

Although blood transfusions have been shown to be associated with negative outcomes, postoperative anemia after CABG surgery is also related to the increased morbidity.[23] To maintain vital functions at the cellular level and avoid anemia induced hypoxia, keeping hemoglobin levels within the safe range, while avoiding unnecessary blood transfusions is essential.

The use of erythropoietin, oral or intravenous iron replacement, and a predeposit autologous donation may help prevent blood transfusions in the preoperative period. During the intraoperative and early postoperative periods, the use of tranexamic acid and cell salvage may be beneficial. Minimal invasive approaches including thoracoscopic, robotic-assisted, or transcatheter techniques are applicable. Endoscopic harvesting of the saphenous vein may also have relevance.[24-26]

Our study presents the results from a limited number of patients. This is the main limitation of the study. The Stage 1 AKI-positive group had a low number of patients; as such, propensity score-matching may not be applicable. Variables that may affect renal impairment such as how many years the patient has been diagnosed as diabetic, their insulin use and dosage amounts, glycated hemoglobin (HbA1c) levels, drainage amounts, use of inotropic agents, and presence of an intra-aortic balloon pump were not studied. This is another limitation of our study. The retrospective design of the study is the third limitation. However, a sample of patients from a single cardiac center provides similar surgical and anesthetic management for the entire study group, which relatively strengthens the results of our study.

In conclusion, our study results suggest that perioperative RBC, FFP, platelet, and complete

transfusions are associated with postoperative AKI among diabetic CABG patients. Further large-scale, prospective, randomized-controlled studies are needed to gain a better understanding of blood transfusion-associated AKI in this population.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):20-27
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1043
www.e-cvsi.org
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Cardiovascular Surgery and Interventions

Original Article Open Access

Evaluation of pregnant women admitted to Dokuz Eylül University Teratogenicity Information Service due to use of medications affecting the cardiovascular system

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Received: December 25, 2020 ***Accepted:*** January 13, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: This study aims to evaluate the demographic characteristics, maternal and neonatal outcomes of pregnant women receiving cardiovascular medications (CVMs) during pregnancy and admitted to the Teratogenicity Information Service (TIS).

Patients and methods: In this descriptive, cross-sectional, retrospective study, a total of 47 pregnant women (mean age: 34.0±5.5 years; range, 19 to 41 years) who were admitted to the TIS of Dokuz Eylul University were included between January 2014 and December 2016. Demographic characteristics, types of the CVMs, concomitant medication and/or substance use, medical and obstetric histories of cases, and maternal and neonatal outcomes were evaluated.

Results: The most commonly used drugs were beta-receptor antagonists. The mean gestational age at the time of delivery was 35.9±8.2 weeks and 42 infants (89.4%) were healthy. Five pregnancies (10.6%) ended in miscarriage or elective termination. No malformation was found in healthy live newborns.

Conclusion: The use of CVMs during pregnancy remains as a challenging issue, as their potential effects on the developing fetus are not fully known. Based on these study results, it is difficult to determine safety of CVMs during pregnancy and establish a causal relationship between maternal/neonatal outcomes and CVMs exposure.

Keywords: Cardiovascular system medicines, maternal and neonatal outcomes, pregnancy.

The use of medications during pregnancy is a common problem across the globe. In 80% of all pregnancies, prescription or non-prescription medications are used.[1] It has been estimated that malformation affects one to three in every hundred babies, and teratogenic drugs/substances can be only held responsible for less than 10% of these malformations.[2,3]

In developed countries, cardiac diseases are the most common causes of maternal mortality during pregnancy. According to the epidemiological studies, approximately every year 0.2% of all pregnant women die from cardiac reasons.[1-4] Additionally, in the United States, 11% of the maternal deaths during pregnancy are caused by cardiac diseases.[5] Physiological changes in pregnancy may adversely affect the prognosis of an existing cardiovascular disease and may alter the effects of medications which affect the cardiovascular system. Also, the effects of the cardiovascular medications (CVMs) on the fetus are not fully known. It is also an undeniable fact that ethical concerns limit the controlled studies on this subject. Thus, the data regarding the use of CVMs during pregnancy and their effect on pregnancy outcomes are limited in Turkey.

In the present study, we aimed to evaluate the demographic characteristics of pregnant women referred to the Teratogenicity Information Service (TIS) during pregnancy and to identify the characteristics of the CVMs exposures and the pregnancy outcomes.

PATIENTS AND METHODS

This descriptive, cross-sectional, retrospective study was conducted at Dokuz Eylul University, TIS

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Citation:
Gökalp G, Şahin O, Hocaoğlu N, Kalkan Ş. Evaluation of pregnant women admitted to Dokuz Eylul University Teratogenicity Information Service due to use of medications affecting the cardiovascular system. Cardiovasc Surg Int 2021;8(1):20-27.

between January 2014 and December 2016. Initially, a total of 491 pregnant women were admitted to the TIS for teratogenicity risk evaluation and 62 (12.6%) of these admissions were due to the use of CVMs during pregnancy. Fifteen cases with missing data were excluded from the study. Finally, a total of 47 pregnant women (mean age: 34.0±5.5 years; range, 19 to 41 years) were included in the study. Participants who exposed to CVMs alone and together with the other medicines and/or substances were also evaluated. A written informed consent was obtained from each participant. The study protocol was approved by the Dokuz Eylul University, Faculty of Medicine, Non-Interventional Research Ethics Committee (No: 3494-GOA/2017). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The data of the pregnant women included in the study were obtained from the registration forms filled out during the initial admission to TIS. The data collected from the registration forms were as follows: demographic data (age, educational status, presence of consanguineous marriage), medical, family and obstetric history (gestational week, last menstrual period, number of pregnancies, number of live/stillbirths in previous pregnancies, presence of anomalies in previous pregnancies), and CVMs and exposure characteristics (name, content, dose, total amount, and duration). The gestational week was calculated according to the ultrasound data or the last menstrual period. To obtain the verbal consent and investigate the pregnancy outcomes and confirm the data, a phone interview was conducted with each mother. In addition, data related to the

Table 1
Maternal demographic and obstetric characteristics

	n	%	Mean±SD
Gestational age at admission (week)			9.2±4.7
Age (year)			
≤35	21	44.7	
>35	26	55.3	
Consanguineous marriage			
2nd degree	2	4.3	
3rd degree	1	2.1	
None	44	93.6	
Maternal education status			
None	3	6.4	
Primary/secondary school	25	53.2	
High school/university	19	40.4	
Substance/illicit drug use			
Smoking	10	21.3	
Alcohol	4	8.5	
None	33	70.2	
Radiation exposure			
Direct graph	10	21.3	
CT	1	2.1	
None	35	76.6	
Gravidities/parities			
1	9/11	19.1/23.4	
2	18/32	38.3/68.1	
3 and more	20/4	42.6/8.5	
Previous miscarriages/elective terminations			
0	30	63.8	
1-2	15	31.9	
3 and more	2	4.3	

SD: Standard deviation; CT: Computed tomography.

pregnancy outcomes (term birth, preterm delivery, miscarriage, elective termination, stillbirth, baby healthy, presence/absence of anomaly) and possible complications during pregnancy were obtained by phone interviews. Pregnant women who did not give a verbal consent were excluded from the study. Pregnancy outcomes were classified using the International Classification of Diseases 10th revision (ICD 10) definitions of World Health Organization (WHO).[6] Elective termination was defined as the voluntary abortion, miscarriage as a pregnancy loss before 22 completed weeks of gestational age, stillbirth as the birth with no signs of life after 22 completed weeks of gestational age, and preterm birth was defined as the birth before 37 completed weeks of gestational age.[6]

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and frequency for categorical variables. In the comparison of the two groups, the chi-square (χ^2) test was used for categorical data. The Fisher's exact test was used, when the χ^2 assumption was not met. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, the mean gestational age at the time of admission to the TIS was 9.2±4.7 (range, 5 to 25)

Table 2
The association between some properties of pregnants and pregnancy outcomes

	Pregnancy outcomes						
	Healthy birth		Abortus		Total		
	n	%	n	%	n	%	p
Having a baby with anomalies in previous pregnancies							
No	40	90.9	4	9.1	44	100	0.29
Yes	2	66.7	1	33.3	3	100	
Maternal age (year)							
≤35	20	95	1	5	21	100	0.3
>35	22	84.6	4	15.4	26	100	
Consanguineous marriage status							
No	40	90.9	4	9.1	44		0.70
2nd degree	2	100	-	-	2	100	
3rd degree	-	-	1	100		100	
Substance use							
No	28	84.8	5	15.2	33	100	
Cigarette	10	100	-	-	10	100	0.16
Alcohol	4	100	-	-	4	100	
Radiological examination							
No	30	85.7	5	14.3	35	100	
Direct graph	10	100	-	-	10	100	0.23
Computed tomography	1	100	-	-	1	100	
Magnetic resonance imaging	1	100	-	-	1	100	
Education status							
None	1	100	-	-	1	100	
Primary/secondary school	25	92.6	2	7.4	27	100	0.62
High school/above	16	84.2	3	15.8	19	100	

weeks. The rate of consanguineous marriage was 6.4% (n=3). The maternal and obstetric characteristics are summarized in Table 1.

There was no significant relationship between the presence of consanguineous marriage and pregnancy outcomes (χ^2=0.199, p=0.655) (Table 2).

When the presence of chronic disease was evaluated, it was found that 89.4% (n=42) of pregnant women had an existed chronic disease and the most commons were hypertension (HT, 28%), diabetes mellitus (DM) and hypothyroidism (11.9%, Figure 1). No statistically significant relationship between presence of a chronic disease and pregnancy outcomes was found (χ^2=0.032, p=0.858) (Table 2). The characteristics of illicit drug/alcohol use, radiation exposure or smoking are presented in Table 1.

Approximately one third of pregnant women (29.8%, n=14) used CVMs alone and 70.2% (n=33) reported concomitant medicine exposures (Table 3). The most frequently exposed concomitant medicines were central nervous system drugs (30.3%) and analgesics (18.2%). The proportion of the mothers who used only one group of CVMs and more than one group CVMs were 76.6% (n=36) and 23.4% (n=11), respectively (Table 3). There was no significant difference between using one or more than one group of CVMs and pregnancy outcomes (χ^2=2.787, p=0.095).

The most frequently exposed CVMs were beta adrenergic receptor antagonists (beta-blockers), diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCB), angiotensin receptor blockers (ARB), antiaggregants, antilipidemics and antiarrhythmics (Table 2). There was no statistically significant difference between groups of CVMs exposed during pregnancy and the termination of pregnancies (p>0.05).

When gestational outcomes were examined, the mean gestational week at delivery was 35.9±8.2 weeks. Of all 47 pregnancies with CVMs exposure, 42 (89.4%) pregnancies resulted in live births. Three (6.4%) pregnancies ended in elective termination and two (4.3%) pregnancies ended in miscarriage (Table 4). No malformation was detected in any of the live births. Neonatal jaundice developed in four (9.8%) infants and one (2.1%) infant needed incubator care.

There was no statistically significant difference between pregnancy outcome and educational status, substance use of radiation exposure during pregnancy (p>0.05). It is stated that while the 21 (44.7%) pregnant women's age was under 35 years, the 26 (55.3%) pregnant women's age was over 35 years. There was no significant difference between maternal age and the termination of pregnancies (χ^2=0.140, p=0.308) (Table 2).

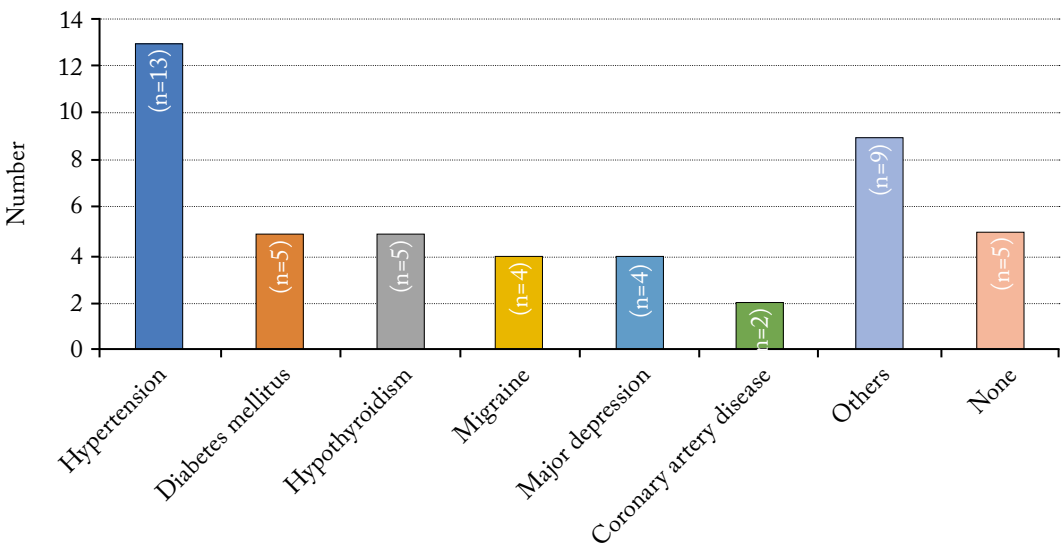

Figure 1. Chronic diseases of the pregnants.

Table 3
Distribution of the medication exposures

Groups of the medicines	n	%
Cardiovascular system medicines (CVSMs)*	55	100.0
Beta blockers	24	43.6
Diuretics	7	12.7
Angiotensin converting enzyme (ACE) inhibitors	6	10.9
Calcium channel blockers	5	9.0
Angiotensin receptor blockers (ARBs)	4	7.3
Antiarrhythmic	3	5.5
Antiaggregants	3	5.5
Hypolipidemics	3	5.5
Only one group CVSM exposure**	36	76.6
More than one group CVSM exposure**	11	23.4
Concomitant medicines***	33	100.0
Central nervous system medicines	10	30.3
Analgesics	6	18.2
Antidiabetics	5	15.2
Antibiotics	3	9.1
Others	9	27.2

CVMs: Cardiovascular medications; * Percentages are based on the total number (55) of CVMs; ** Percentages are based on the total number (47) of pregnants; *** Percentages are based on the total number (33) of concomitant medicines.

Table 4
Properties of the cases ended in miscarriage or elective termination

	Case 11	Case 17	Case 24	Case 36	Case 41
Age (year)	39	36	40	36	31
Gestational week	7	8	6	5	8
Chronic disease	Yes (Hypothyroidism)	Yes (DM)	None	Yes (Hyperthyroidism)	None
Presence of birth defect in recent pregnancies	None	None	None	None	Yes
Consanguineous marriage	None	Yes (3rd degree)	None	None	None
Substance/illicit drug use	None	None	None	None	None
Radiation exposure	None	None	None	None	None
Miscarriage or elective termination	Miscarriage	Elective termination	Elective termination	Elective termination	Miscarriage
Used CVSMs	Metoprolol, spironolakton, amiodarone	Fosinopril sodium	Metoprolol	Metoprolol, diltiazem	Nebivolol
Concomitant medications	None	Metformin hydrochloride, noretisterone	Hydroxyzine hydrochloride	Benzathine benzylpenicillin, acetylsalicylic acid	Duloxetine hydrochloride

DM: Diabetes mellitus; CVSMs: Cardiovascular system medicines.

DISCUSSION

In this study, the demographic characteristics of the pregnant women and pregnancy outcomes who exposed to CVMs during their pregnancies were examined. Although most of the pregnancies resulted healthy live births, two (4.3%) pregnancies ended in miscarriage and three (6.4%) pregnancies were terminated electively. The rates of miscarriage and elective termination in this study are similar to the general population.[7,8]

Cardiac diseases are complicated by approximately 1% of all pregnancies.[9] Pregnant women with or without underlying cardiovascular disease may need to use CVMs due to the physiological changes during pregnancy. This need may be caused by worsening of an existing disease or by a newly developing condition. In general, medications used to treat cardiovascular conditions are antihypertensives, diuretics, antiarrhythmics, anticoagulants and antilipidemics. Moreover, CVMs are preferred in other indications such as migraine, tremor, hyperthyroidism, and anxiety disorders.[9] However, the effects of CVMs on the developing fetus have not been fully understood, yet. Pregnant women need a careful assessment and counselling for CVMs use and their maternal/fetal effects, as well as expert cardiac care in pregnancy. Teratogenicity Information Services are specialized units providing information on the use of medication/substance during pregnancy and lactation period. The TIS of Dokuz Eylul University is a regional unit dedicated to provide information about medication/substance use during pregnancy and/or lactation period since 2011.

Epidemiological data on CVMs exposures during pregnancy are limited. In a study carried out in Germany on drug prescriptions in pregnancy, CVMs accounted for 17% of the medicines prescribed during pregnancy.[10] In another study conducted by Demir et al.,[11] CVMs were responsible for 9.5% of all exposures among the pregnant women admitted to TIS. Göker et al.[12] also reported that the use of CVM ratios were 1.14% and 8.17% in a study evaluating pregnants admitted to two reference hospital in our country. In this study, this rate was 12.6% of the patients applied to the TIS of our institution.

The increasing prevalence of women with adverse pregnancy outcomes (stillbirth, fetal malformations or abortus) due to the increasing maternal age of first pregnancy remains as a challenging issue. Advanced maternal age, particularly over 35 years of age, poses a greater risk of pregnancy complications.[13] Almost 7% of stillbirths are attributed to advanced maternal age (>35 years) worldwide. Also, adolescent pregnancy (<16 years) is associated with an increased risk of adverse pregnancy outcomes.[1,14] In this study, the mean age of pregnant women was 34.0±5.5 years. Additionally, it is noteworthy that four (80%) of five pregnancies ended in miscarriage or elective termination were older than 35 years old (31 to 40 years).

The pregnancy termination rates in consanguineous marriages may be higher due to the increased risk for recessively inherited congenital diseases.[14] In a study carried out in our country, the rate of consanguineous marriage was found to be 12.7%.[11] In this study, the rate of consanguineous marriage was found as 6.4% and all pregnancies with consanguineous marriages resulted in a healthy infant.

On the other hand, the presence of chronic diseases during pregnancy also poses a risk for adverse pregnancy outcomes. The most common chronic diseases in pregnant women are epilepsy, hypertension, diabetes mellitus, psychiatric diseases, and thyroid dysfunctions.[15] In this study, approximately 90% of the mothers had a chronic disease, consistent with the previous reports, and hypertension, diabetes mellitus, and hypothyroidism were the most common diseases. Furthermore, 60% of the mothers whose pregnancies ended in miscarriage or terminated electively had an underlying maternal chronic disease such as hypothyroidism, hypertension, or diabetes mellitus.

Beta-blockers are the most commonly used drugs in the treatment of hypertension in pregnancy and are also frequently used in the management of conditions, such as thyrotoxicosis, hypertrophic cardiomyopathy, and mitral stenosis.[16-19] In this study, in line with the previous reports, the most commonly used CVMs during pregnancy were beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and angiotensin receptor blockers, respectively. In addition, 80% of the mothers whose pregnancies ended in miscarriage or elective termination used beta-blockers. Beta-blockers can cross the placenta and may cause potential physiological changes in the fetus.[20] Although there are inconsistent data about the relationship between

the use of beta-blockers in pregnancy and the risk of fetal growth restriction, preterm birth, cardiac malformations, and perinatal mortality, there are some reports indicating that direct relationship could not be established due to methodological limitations in the interpretation of available data and presence of confounding factors. However, it is also reported that uncontrolled hypertension during pregnancy may increase the risk of maternal and fetal adverse events such as preeclampsia, premature birth, gestational diabetes, fetal growth restriction, and intrauterine demise.[21-25]

In the current study, amiodarone with concomitant medications was used in a pregnancy ended in miscarriage. Amiodarone and desethylamiodarone, its major metabolite, can cross the placenta and reach 9 to 14% of maternal serum concentrations in fetus.[25] The available data are limited to identify the fetal risk related to amiodarone use in pregnancy. Amiodarone use during pregnancy may also increase the risk of neonatal hypothyroidism with or without goiter and predisposes to neonatal hyperthyroxinemia. It may be also associated with fetal bradycardia, long QT syndrome, ventricular septal defect, prematurity, and death. Amiodarone can be used during pregnancy, if the potential benefit to the mother justifies the possible risk to the fetus. Neonatal electrocardiogram and thyroid functions monitoring are also recommended.[25]

To the best of our knowledge, previous reports are usually limited to the use of CVMs alone during pregnancy, and are lacking the information regarding pregnancy outcomes related to their use with concomitant medications. Furthermore, other confounding factors that may affect pregnancy outcomes such as maternal age, smoking or alcohol use, radiation exposure, and chronic disease should be considered. Our relatively low sample size is the main limitation of this study. Although the number of the cases in this study is limited, our results may contribute to the literature. To achieve more accurate results, further large-scale, prospective studies are needed investigating specific CVMs groups.

In conclusion, based on our study results, it is not possible to establish a definite causality relationship between pregnancy outcomes and CVMs exposure. Nevertheless, we believe that the results of this study can contribute to the existing body of knowledge in this field and provide additional information to the physicians regarding the teratogenic risks of CVMs exposures during pregnancy.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):28-34
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1050
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Cardiovascular Surgery and Interventions

Original Article Open Access

Evaluation of factors increasing the risk of silent brain infarction using multidetector computed tomography in patients undergoing carotid artery stenting

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Received: January 09, 2021 ***Accepted:*** February 22, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: This study aims to identify the factors increasing the risk of silent brain infarction using multidetector computer tomography (MDCT) in patients undergoing carotid artery stenting (CAS).

Patients and methods: Medical data of a total of 24 patients (12 males, 12 females; mean age: 65.4±74 years; range, 50 to 76 years) who underwent CAS between December 2017 and July 2019 were retrospectively analyzed. The plaque characteristics of carotid arteries and the aortic arch structures were determined using MDCT before the procedure. The patients were divided into two groups based on the diffusion-weighted images after the procedure. Those with and without silent brain infarction were in Group 1 (n=10) and Group 2 (n=14), respectively. Both groups were compared in terms of aortic arch structures and the plaque characteristics.

Results: There was a significant difference between the groups in terms of plaque in the aortic arch (n=8 vs. n=5, respectively, p=0.047). The number of irregular plaque surfaces, plaque length, and plaque volume were significantly higher in Group 1 than Group 2 (8 vs. 5, respectively; p=0.047; 21.8 vs. 17.6, respectively; p=0.045, and 991.1 vs. 740.3, respectively; p=0.015). The percentages of lipid components in total plaque volume were significantly higher in Group 1 (p=0.026). The receiver operating characteristic analysis revealed that 17.8% of lipid components in total volume had 64.3% sensitivity and 90% specificity in the differentiation of the groups.

Conclusion: Evaluation of aortic arch structures and the plaque characteristics in carotid arteries using MDCT may be useful for predicting the risk of silent brain infarction after CAS.

Keywords: Aortic arch, carotid stenting, computed tomography, plaque.

Carotid artery stenting (CAS) has been widely used to treat patients with carotid artery stenosis since the 2000s.[1] The technical success rates of CAS have been reported to be similar to carotid endarterectomy (CEA); however, the risk of silent brain infarction (SBI) in the post-procedural period is higher in patients undergoing CAS.[1-3] Silent brain infarction is defined as a vascular brain lesion of embolic origin. Although SBI is asymptomatic in the acute phase, it has a negative effect on cognitive functions in the long-term. Therefore, in CAS planning, patients at high risk of developing SBI should be detected prior to the procedure and referred for CEA treatment, instead of CAS.[3,4] Although there is no clear consensus yet, a few studies have recently provided evidence that characteristics of the aortic arch and its branches may be associated with the development of ipsilateral SBI during the post-procedural period. Therefore, it may be important to identify the characteristics of the aortic arch and its branches in planning CAS.[5,6]

Recent technological advances have enabled the high-spatial resolution images to be obtained using multidetector computed tomography (MDCT). Thus, anatomical variation and pathological changes of vessels can be much better demonstrated with three-dimensional imaging.[7,8] In addition, on post-processing analysis, structure characteristics of

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Citation:
Onan H, Pişkin F, Demir T, Ballı H. Evaluation of factors increasing the risk of silent brain infarction using multidetector computed tomography in patients undergoing carotid artery stenting. Cardiovasc Surg Int 2021;8(1):28-34.

atheromatous plaque in vessels can reveal using specific software.[7,8]

In the present study, we aimed to analyze images obtained in MDCT before CAS and to identify differences in the vascular structures of patients having SBI after the procedure.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Çukurova University Faculty of Medicine, Department of Interventional Radiology between December 2017 and July 2019. Data of the patients who underwent CAS were analyzed retrospectively. Of a total of 108 patients, 24 (12 males, 12 females; mean age: 65.4±74 years; range, 50 to 76 years) who met the inclusion criteria were recruited. Inclusion criterion was undergoing imaging of the carotid arteries using MDCT within the last month before CAS. Neurological and general physical examinations were performed by an experienced neurologist before and after procedure. Patients with newly developed neurological symptoms after the procedure were excluded from the study. The medical history of the patients was obtained from the institutional database. A written informed consent was obtained from each patient. The study protocol was approved by the Çukurova University Faculty of Medicine Clinical Research Ethics Committee (No: 09/2019-91). The study was conducted in accordance with the principles of the Declaration of Helsinki.

MDCT image analysis

All MDCT scans were performed on a 160-detector CT scanner (Toshiba Aquilion™ PRIME; Otawara, Japan). The scanning area was determined to cover the lower limit of the heart and cerebral cortex. Post-processing of the data was evaluated using a dedicated workstation (Vitrea®; Vital Images Inc., MN, USA) by an experienced vascular radiologist.

The aortic arch was grouped according to anatomical variation and elongation (Figure 1). The aortic arch variation was defined according to the arch vessels' origin. The aortic arch elongation was defined according to the vertical distance from the origin of the innominate artery to the top of the arch (elongated aortic arch: >1 cm in diameter).[9,10]

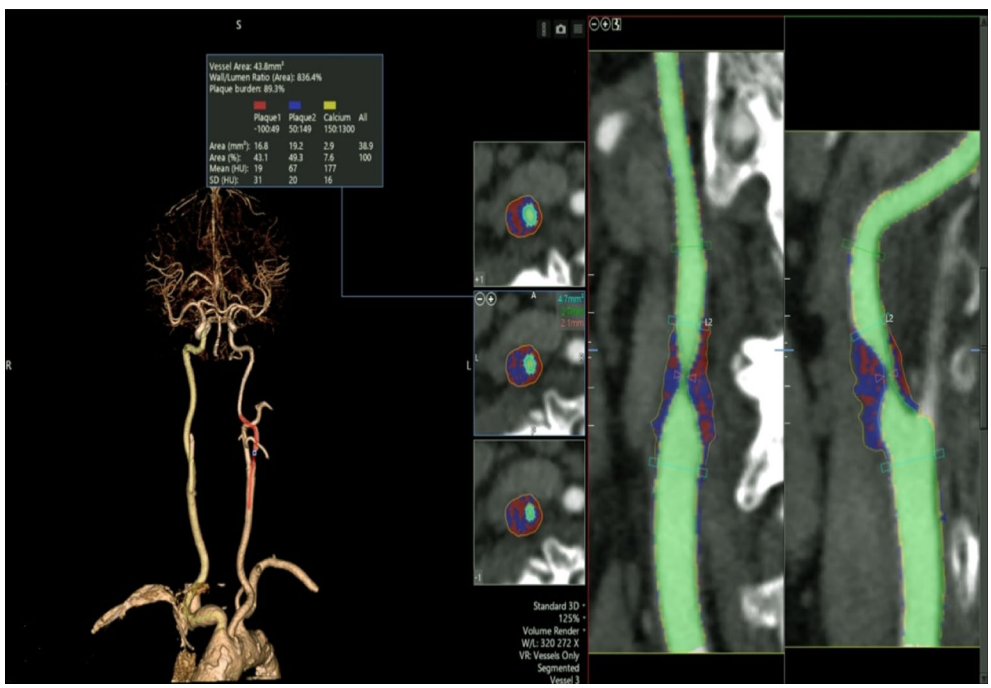

Figure 1. The images of a 54-year-old female case with the left internal carotid artery stenosis due to atheroma plaques. The post-processing images (volume rendering and curved reformat) show the plaque components with the Hounsfield Unit values and the aortic arch structures.

The degree of carotid artery stenosis was measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[11] The plaque length was defined as the distance from the proximal to the distal of the plaque. Plaque surface morphology was as a regular or irregular surface. The total volume of plaques and the percentages of plaque components in total volume was automatically calculated according to Hounsfield unit (HU) using the SurePlaque™ software (Toshiba Medical Systems Co., Tokyo, Japan).[8] Plaque components were classified as lipid (-100-49 HU), fibrous (50-149 HU), and calcific (150-1300 HU) (Figure 1).[7]

CAS procedure

The CAS was administered to symptomatic patients (having an ischemic stroke or transient ischemic attack within the last six months) and angiographically found to have >50% stenosis in the carotid artery or asymptomatic and >70% stenosis in the carotid artery. All patients were pretreated with a combination of acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) for at least seven days before CAS. During the procedure, intravenous heparin was administered to maintain an activated clotting time of whole blood of 250 to 300 sec. Following local anesthesia administration to the inguinal region, the carotid artery was selectively catheterized with a 6F, 90-cm catheter sheath. After an embolic protection device (EPD) (FilterWire EZ™; Boston Scientific Inc., CA, USA) was placed, the internal carotid artery, open-cell stents (PROTÉGÉ™ RX; eV3 Covidien, CA, USA) was implanted on the carotid artery. Balloon dilatation was performed for all patients after stenting. Once significant bradycardia was noted during the dilatation, the required amount of atropine was injected. Finally, an angiogram of the carotid artery and intracranial circulation were performed to rule out embolic complications. The same experienced neuro-interventional radiologist performed all CAS procedures. All patients were followed in the neurocritical care unit for 24 h after the CAS procedure. The modified Rankin scale (mRS) was used for neurological examination by an experienced neurologist.[12]

Magnetic resonance imaging (MRI)

For detecting symptomatic or asymptomatic ischemic lesions, cranial MRI was performed in all patients using a 1.5 T device (Signa, GE Medical Systems; WI, USA) at 12 to 24 h after the CAS. Newly developed ischemic lesions were detected on the diffusion-weighted images (DWIs). The lesions were classified as ipsilateral or contralateral according to the distribution of the treated carotid artery. The patients were divided into two groups: Group 1 (n=10) consisted of patients with a newly developed ipsilateral ischemic lesions, while the remaining patients with contralateral lesions were included in Group 2 (n=14).

After the CAS, the patients were prescribed a combination of acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) for the first six months, followed by acetylsalicylic acid throughout their life.

Statistical analysis

Statistical analysis was performed using the TURCOSA version 1.0 software (Turcosa Analytics Solutions Ltd. Co., Kayseri, Turkey). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and percentage for categorical variables. The chi-square and Fisher's exact tests were used to compare the groups. The Student's t-test was used to compare the quantitative data. The threshold values for differentiation of the groups were obtained via the receiver operating characteristic (ROC) analysis. A p value of <0.05 was considered statistically significant.

Table 1
Baseline demographic and clinical characteristics of patients

	Total (n=24)			Group 1 (n=10)			Group 2 (n=14)			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			65.4±7.4			64.1±4.8			67.2±8.1	0.313
Sex										
Female	12	50		6	60		6	42.8		
Cardiovascular risk factors	10	41.6		6	60		4	28.5		0.211

SD: Standard deviation; Cardiovascular risk factor: Diabetes mellitus, hypertension, and smoking.

Table 2
Structures of aortic arch

	Group 1 (n=10)		Group 2 (n=14)		
	n	%	n	%	*p*
Anatomical variations					
Type 1	7	70	11	78.5	0.665
Type 2	3	30	3	21.4	
Elongation	7	70	11	78.5	0.665
Presence of plaque	8	80	5	35.7	0.047

RESULTS

All CAS procedures were successfully performed, and all patients were neurologically intact (mRS 0) after the CAS. However, DWI images revealed acute SBI in 13 (54.1%) patients. The anatomical distribution of the SBI lesions was as follows: ipsilateral lesions in 10 (41.6%) patients and contralateral lesions in three (12.4%) patients. According to the presence or absence of ipsilateral acute SBI, there were 10 (41.6%) patients in Group 1 and 14 (58.3%) patients in Group 2. There was no significant difference between the groups in terms of age and cardiovascular risk factors (p=0.313 and p=0.211, respectively). Baseline demographic and clinical characteristics of the patients are summarized in Table 1.

Type 1 and Type 2 anatomical variations of the aortic arch were present in both groups. Type 1 aortic arch was present in seven (70%) patients in Group 1 and 11 (78.5%) patients in Group 2. No significant difference was detected between the groups regarding the anatomic variations of the aortic arch (p=0.665). Aortic arch elongation was seen in seven (79%) patients in Group 1 and 11 (78.5%) patients in Group 2, indicating no significant difference between the groups (p=0.665). An aortic arch plaque was detected in eight (80%) patients in Group 1 and five (35.7%) patients in Group 2, indicating a significant difference between the groups (p=0.047). Table 2 shows the features of the aortic arch of the patients.

The degree of carotid artery stenosis was ≥70% in five (50%) patients in Group 1 and seven (50%) patients in Group 2, indicating no significant difference between the groups (p>0.05). The plaque surface morphology was irregular in eight (80%) patients in Group 1 and five (35.7%) patients in Group 2, indicating a higher rate of irregular morphology in Group 1 (p=0.047). The mean plaque length was 21.8±5.9 mm in Group 1 and 17.6±3.7 mm in Group 2. The mean plaque length of Group 1 was significantly higher than that of

Table 3
Plaque characteristics in carotid arteries as assessed by multidetector computed tomography

	Group 1 (n=10)				Group 2 (n=14)				
	n	%	Mean±SD	UL-LL	n	%	Mean±SD	UL-LL	*p*
Stenosis degree ≥70%	5	50			7	50			1.0
Irregular surface	8	80			5	35.7			0.047
Length (mm)			21.8±5.9	17.6-26.1			17.6±3.7	15.5-19.8	0.045
Total volume (mm^3)			991.1±279.2	791-1190			740.3±190	630-850	0.015
Percentage of components									
Lipid component			27.3±11.2	11.3-35.4			17.3±9.3	11.9-22.7	0.026
Fibrous component			41.6±10.1	34.3-48.9			45.9±15.2	37.1-54.8	0.442
Calcific component			30.9±19.7	16.8-45.1			36.6±21.9	24.0-49.3	0.519

SD: standard deviation; UL: Upper limit; LL: Lower limit.

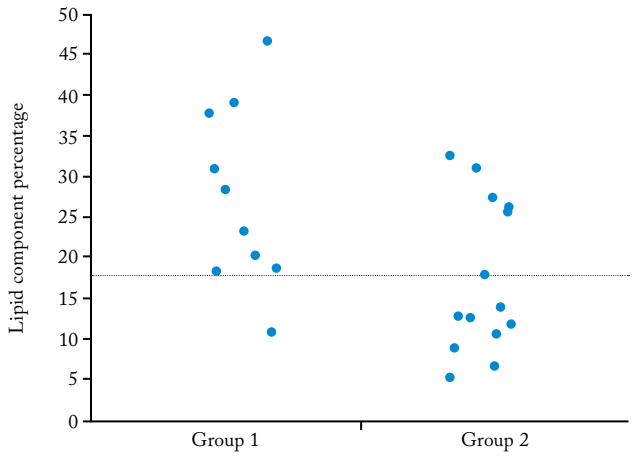

Figure 2. Distribution chart for the percentage of lipid components.

Group 2 (p=0.045). The mean total plaque volume was 991.1±279.2 mm^3 in Group 1 and 740.3±190 mm^3 in Group 2, indicating a significantly higher mean total plaque total volume in Group 1 (p=0.015).

The percentages of plaque components in total volume were as follows: the mean percentage of lipid components was 27.3±11% in Group 1 and 17.3±9.3% in Group 2. The mean percentage of fibrous components was 41.6±10.1% in Group 1 and 45.9±15.2 in Group 2. The mean percentage of calcific components was 30.9±19.7% in Group 1 and 36.6±21.9 in Group 2. The comparison of the percentages of plaque components in total volume showed that the percentage of lipid components of Group 1 was higher than that of Group 2 (p=0.026). However, no significant difference was observed between the groups in terms of the percentages of fibrous and calcific components (p=0.442 and p=0.519). The plaque characteristics in carotid arteries are shown in Table 3.

In the ROC analysis, an optimal cut-off value of percentages of lipid component in a total volume of 17.8% had a sensitivity of 64.3% and a specificity of 90% for the prediction of ipsilateral SBI after CAS with an area under the curve (AUC) of 0.75 (Figure 2).

DISCUSSION

Carotid artery stenting is an alternative treatment method to CEA for carotid artery stenosis. However, it has a serious disadvantage due to the high incidence of SBI after the procedure.[13,14] Silent brain infarction has adverse effects on the patients' cognitive functions in the long-term; therefore, it is important to identify patients with a high risk of SBI during CAS planning.[15] In this study, the patients were evaluated with MDCT during CAS planning. A significant difference was found in the aortic arch structure and plaque characteristics of the carotid artery between the patients with and without SBI after CAS.

In a study, Kastrup et al.[16] reported ipsilateral SBI after CAS with and without EPD as 49% and 67%, respectively. In this study, EPD was used for all procedures, and the ratio of ipsilateral SBI after CAS was similar to Kastrup et al.[16] Acute SBI was determined in 13 (54.1%) patients and, according to treated carotid artery distribution, ipsilateral SBI was observed in 10 (41.6%) patients and contralateral SBI was observed in three (12.5%) patients.

In another study, Wyers et al.[17] detected that anatomical variation or elongation of the aortic arch negatively affected the technical success and increased the risk of SBI. In this study, the presence of plaque in the aortic arch was significantly more frequent in the patients who developed SBI after CAS (p=0.047). However, there was no significant difference between the groups in terms of anatomical variation and elongation of the aortic arch. This may be due to the limited sample size of our study. Anatomical variations and degenerative changes (elongation and atherosclerosis) in the aortic arch lead to prolonged catheter manipulation time and predisposition to SBI during the procedure.[18] Wyers et al.[17] suggested that evaluation of aortic arch structure using MDCT for CAS planning and that patients having anatomical variation or significant elongation in the structure of aortic arch should be referred to other treatments.

Furthermore, Krapf et al.[19] investigated the effects of carotid artery plaque length and the degree of stenosis on the development of SBI after CAS. A significantly high correlation was found between the plaque length and development of acute SBI; however, no significant correlation was observed between the degree of stenosis and the development of SBI. In the present study, carotid artery plaque length was significantly higher in the group in which ipsilateral SBI developed after CAS (p=0.045). The contact between the long plaque and the catheter used in the procedure is greater than the short plaque, which increases the risk of ruptured plaque capsule and distal embolism of its components.[19]

In their study, Rosenkranz et al.[20] evaluating the effect of surface morphology of carotid artery plaque on the development of SBI after CAS measured the number of microembolism during CAS by dual-frequency Doppler ultrasound. The number of microembolism was higher in plaques with an irregular surface than other plaques (p=0.030). Our study revealed that the surface morphology of carotid artery plaque in Group 1 was significantly more frequently irregular, compared to Group 2 (p=0.047). The irregular surface morphology is a sign of the defect in the plaque capsule. The plaques are more vulnerable due to high blood levels of pro-inflammatory markers. Therefore, catheter contact more often causes distal embolism of plaque components.[21]

Moreover, Matsumoto et al.[22] found that the amount of development SBI during CAS was positively correlated with the total volume of plaque and proportion of lipid component in total volume (r=0.480, p=0.015 and r=0.561, p=0.001, respectively). Uchiyama et al.[23] found that lipid component-weighted plaques, with a mean HU value of <0, were found to be more prone to the development of SBI after CAS. In the present study, the total volume of plaque and percentage of lipid component was significantly higher in patients who developed SBI than the others (p=0.015 and p=0.026, respectively). For differentiation of the patients with and without SBI after CAS, the percentage of lipid component in total volume of >17.8% was found to be a selectivity cut-off value. As the total volume of plaque and proportion of lipid component in total volume increase, plaque resistance to mechanical stress decreases and a predisposition to microembolism occurs due to the catheter contact.[24]

In the current study, we found no significant differences in the percentages of calcific components between the groups (p=0.519). Rather than the percentage of the calcific components, the localization of the calcific components appears to be the factor affecting the development of SBI. The calcific component can be located in the blood vessel wall in two different locations: tunica intima and tunica media/adventitia. Peripheral calcific plaques located on tunica media/adventitia are larger and less elastic and, therefore, the risk of development SBI is higher in such plaques.[25]

Nonetheless, there are several limitations to this study. First, this study has a retrospective design with a small sample size which may have affected the statistical results. Unfortunately, most of the patients who underwent CAS in our hospital were advanced age and prone to contrast nephropathy and, therefore, the number of patients evaluated using MDCT was limited. Second, we did not include intraplaque hemorrhage in plaque component classification. Intraplaque hemorrhage cause plaque instability and predisposition to SBI. Third, the study included only a single observer, inter-observer agreement was unable to be measured.

In conclusion, in CAS planning, it is of utmost importance to identify patients at high risk of developing SBI after CAS. Structures of the aortic arch and characteristics of carotid artery plaque may be useful markers to predict the risk of development of SBI. Post-processing analysis of high-spatial resolution images obtained using MDCT may be helpful to determine these properties successfully.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):35-43
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1041
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Cardiovascular Surgery and Interventions

Original Article Open Access

Are systemic diseases a risk factor for post-implantation syndrome? A systematic review and meta-analysis

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Received: December 23, 2020 ***Accepted:*** February 22, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: Endovascular aneurysm repair (EVAR) causes less perioperative morbidity versus the open surgical technique. In this review, we discuss whether systemic diseases have a role in the development of post-implantation syndrome (PIS).

Patients and methods: Literature search was performed using the PubMed, Scopus, and Web of Science electronic databases without date limitation and manually from the references of the related articles. Only English-language studies were included in which PIS developed after EVAR and systemic diseases were preoperatively recorded. The results of analysis were evaluated with random or fixed effect models according to the presence of heterogeneity (I^2>25%).

Results: A total of 1,894 articles were reached. After reviewing the titles and abstracts, six articles including 947 patients which met the inclusion criteria were included in the meta-analysis. Coronary artery disease (odds ratio [OR]: 0.6, 95% confidence interval [CI]: 0.42-0.86; p=0.006), chronic obstructive pulmonary disease (OR: 0.67, 95% CI: 0.46-0.98; p=0.041), and heart failure (OR: 0.53, 95% CI: 0.31-0.92; p=0.02) increased the possibility of PIS development. The studies were heterogeneous for chronic obstructive lung disease and renal failure (I^2>25%). Publication bias according to the Begg's test was significant, except for the studies including renal failure (tau^2<0.05).

Conclusion: Based on our meta-analysis, coronary artery disease, chronic obstructive pulmonary disease, and heart failure are important factors for development of PIS after EVAR.

Keywords: Endovascular aneurysm repair, meta-analysis, post-implantation syndrome, systemic disease.

Inflammation plays an important role in endovascular aortic aneurysm repair (EVAR) process.[1] Post-implantation syndrome (PIS), defined as a systemic inflammatory response, is frequently observed after EVAR. Following the intervention, PIS development is at high rates up to 60%, with the generally accepted PIS diagnostic criteria including increased leukocytosis (white blood cell [WBC] >12,000 µL), increased C-reactive protein (CRP >10 mg/mL), and fever (>38°C).[2,3] However, despite this definition, differential diagnosis is not made in cases for signs and symptoms such as fever, leukocytosis, or high CRP levels. Thus, important factors appear to be the lack of differential diagnosis for fever observed after the intervention and the lack of agreed diagnostic criteria. Post-implantation syndrome is believed to be transient and harmless in most cases, although it can increase the length of hospital stay and cost of treatment.

Literature research reveals information related to systemic diseases including diabetes mellitus, hypertension, coronary artery disease (CAD), renal failure, hyperlipidemia, heart failure, and chronic obstructive pulmonary disease (COPD) in patient records. However, at the time of our literature research, there was no information available as to whether the systemic diseases were each a factor in the formation of PIS in the postoperative period after EVAR. In the

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Citation:
Öztürk S, Kavasoğlu K, Kısa U, Koçoğulları CU, Öztürk İ. Are systemic diseases a risk factor for post-implantation syndrome? A systematic review and meta-analysis. Cardiovasc Surg Int 2021;8(1):35-43.

present study, therefore, we aimed to investigate which comorbid diseases were effective in the development of PIS.

PATIENTS AND METHODS

Database search

We performed a database screening in accordance with the guidelines published by Moher et al.[4] in 2015. Our goal was to determine which coexisting diseases were significant risk factors for development of PIS after EVAR procedure. The database was searched until the date of 12.10.2020 without any publication date limitation. Electronic screening performed on PubMed, Scopus, and Web of Science. We did not use manual research screening, apart from the electronic database. Possible relevant articles in the reference sections of the articles were investigated. The following keywords or different combinations of words were used: "endovascular aortic aneurysm repair", "post-implantation syndrome", "EVAR", "inflammatory response", and "TEVAR". Articles reported in the languages other than English were not included.

Selection of trials

The authors described both inclusion and exclusion criteria before database screening. All studies (whether retrospective or prospective) were included without attention to the sample sizes. Inclusion criteria were as follows: *(i)* clinical human studies, *(ii)* endovascular intervention for aortic aneurysm trials, *(iii)* articles in only English language, *(iv)* randomized or non-randomized studies, *(v)* cohort studies, and *(vi)* case-control studies. Exclusion criteria were as follows: *(i)* experimental studies, *(ii)* case reports, case series, editorials and reviews, *(iii)* surgical interventions, and *(iv)* studies without control groups. Studies that did not provide information about comorbid diseases in the preoperative period were not included. The articles presented the relevant data as figures or graphs were also excluded from the analysis.

Data for analysis

The researchers independently recorded data (first author name, year of publication, sample and coexisting diseases numbers for PIS and control groups, research design) from the articles. Disagreements related to data and inclusion/exclusion of articles were resolved by agreement.

Statistical analysis

For statistical analysis, Open MetaAnalyst® (Brown University, Rhode Island, USA) program was used. The results were presented as odds ratio (OR) and 95% confidence interval (CI). Heterogeneity of the trials was assessed with the I^2 statistics. Heterogeneity was accepted as significant, if I^2 ≥25% and, the cause of heterogeneity was evaluated with analysis of moderators. In evaluation of the results of meta-analysis, we used fixed effect or random effect models. In the presence of heterogeneity (I^2 >25%), the random effects model was used and, in the absence of heterogeneity (I^2 <25%), the fixed effects model was applied. A p value of <0.05 was considered statistically significant. DerSimonian and Laird method for random effects model and Peto's method for fixed effects model were used. Publication bias for

Table 1
Trial characteristics

	Date	PIS (n)	Patients (n)	Trial design	Effect of PIS on hospital stay	Effect of PIS on intensive care stay	Anethesia type	Mortality (PIS) (n)	Mortality (control) (n)
Arnaoutoglou et al.[5]	2010	49	162	P	NA	NA	GA	NA	NA
Arnaoutoglou et al.[6]	2015	77	214	P	Prolonged	Prolonged	GA	NA	NA
Arnaoutoglou et al.[7]	2016	65	182	P	Prolonged	No difference	GA	3	1
Gorla et al.[8]	2016	21	133	R	NA	NA		0	7
Kwon et al.[9]	2016	64	204	R	Prolonged	NA	GA (129) RA (75)	14	32
Sartipy et al.[3]	2014	12	52	P	Prolonged	NA	NA	NA	NA

PIS: Post-implantation syndrome; NA: Not available; P: Prospective; R: Retrospective; GA: General anesthesia; RA Regional anesthesia.

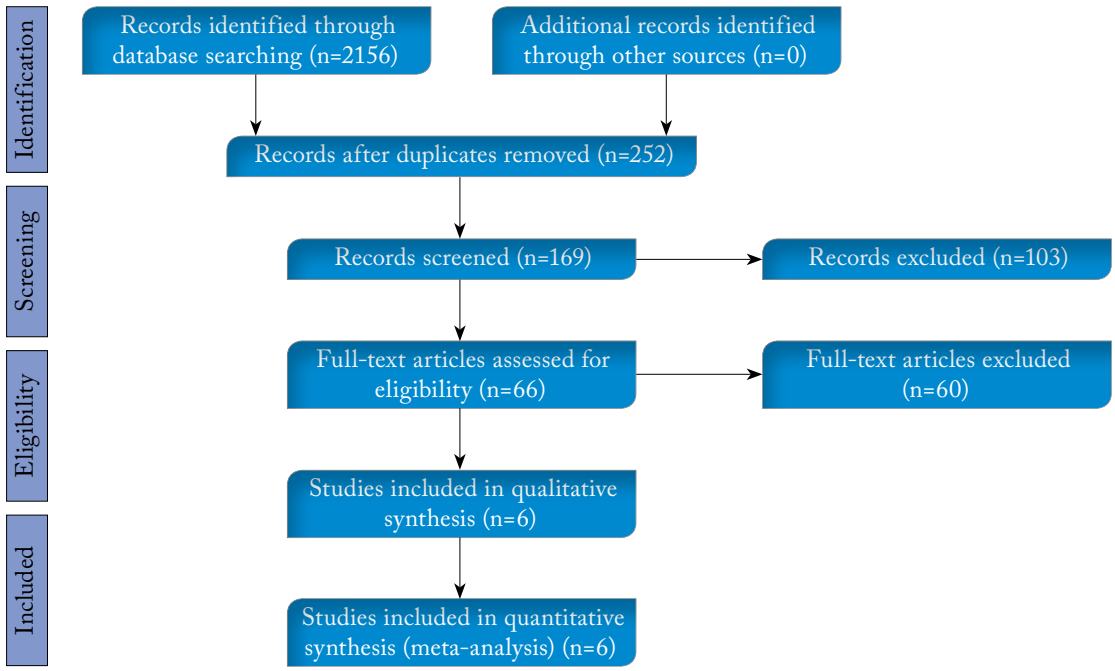

Figure 1. Flow diagram of database search.

reported articles was assessed with the Begg's test and funnel plot. Metalight® (V.1.2.0) (University College London, London, Great Britain) program was used to get funnel plots.

RESULTS

A total of 2,156 articles were reached based on the electronic database screening. After the review of duplications between the databases, 252 articles remained. The abstracts and titles of remained articles were reviewed in the context of PIS development and coexisting diseases and 169 articles that were irrelevant to the aim of our investigation were excluded from the study. Full texts of a total of 66 articles were examined for convenience. Sixty articles were eliminated, as they were not eligible. A total of six research articles consisting of 947 patients were included in quantitative synthesis.[3,5-9] The demographic data and features of the articles were reviewed (Table 1). We found the PIS development rate to be 30.41% from six studies included the analysis (288 cases out of 947). Flow diagram for screening according to the guideline is shown in Figure 1.

During the examination of trials, we recorded data about seven coexisting diseases: COPD, diabetes mellitus, CAD, heart failure, hypertension, hyperlipidemia, and renal failure. First, we analyzed heterogeneity of included studies. We found research articles including COPD (I^2: 30%) and renal failure (I^2: 32.6%) were heterogeneous and, thus, the random effects model was used for these diseases. The fixed effects model was used for the others (diabetes mellitus, CAD, heart failure, hypertension, and hyperlipidemia; I^2<25%). As a result, CAD, COPD, and heart failure were the risk factors for the development of PIS after EVAR ($p<0.05$), while the others (diabetes mellitus, hypertension, hyperlipidemia, and renal failure) were not ($p>0.05$). The results obtained are presented as figures and tables (Figures 2 and 3; Table 2).

When we analyzed clinical or methodological variations between the studies, heterogeneity was observed in articles including COPD (I^2: 30%) and renal failure (I^2: 32.6%). When the cause of heterogeneity was investigated with the subgroup analysis, the research design (retrospective or prospective) appeared as a factor for COPD. Subgroup analysis for renal failure could not be performed, since there were only two studies in total. The results related to heterogeneity analysis are summarized in Table 2. When we evaluated publication bias, we observed that it was significant in all studies (tau^2 <0.05) except

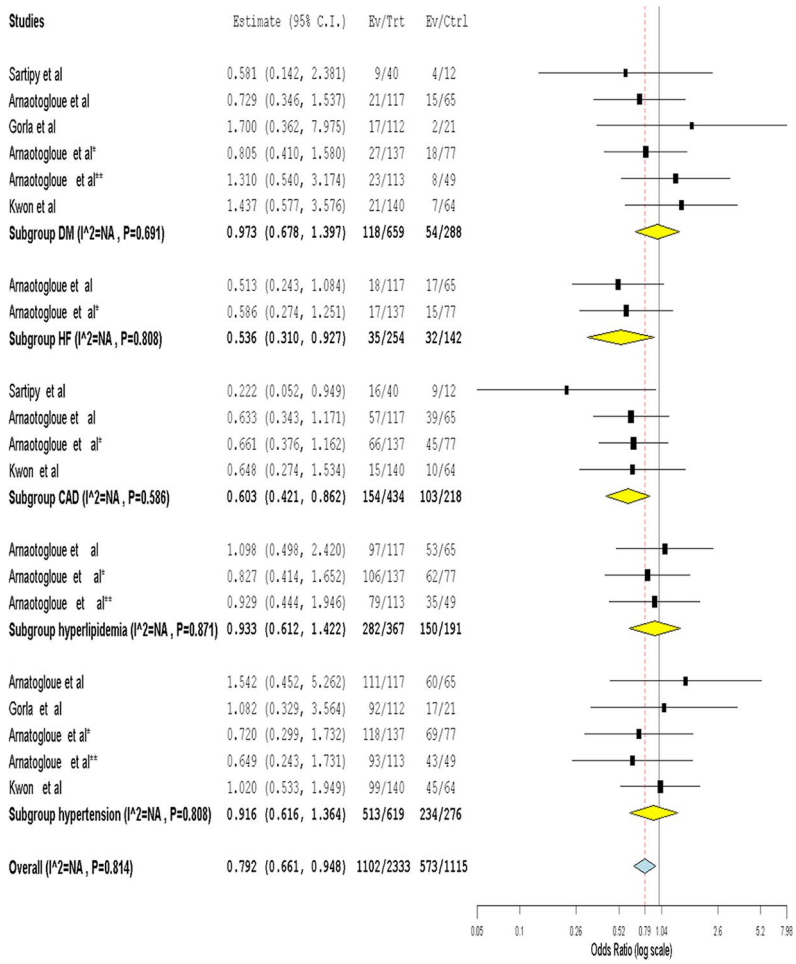

Figure 2. Forest plot of analysis for diabetes mellitus, heart failure, coronary artery disease, hyperlipidemia, and hypertension.

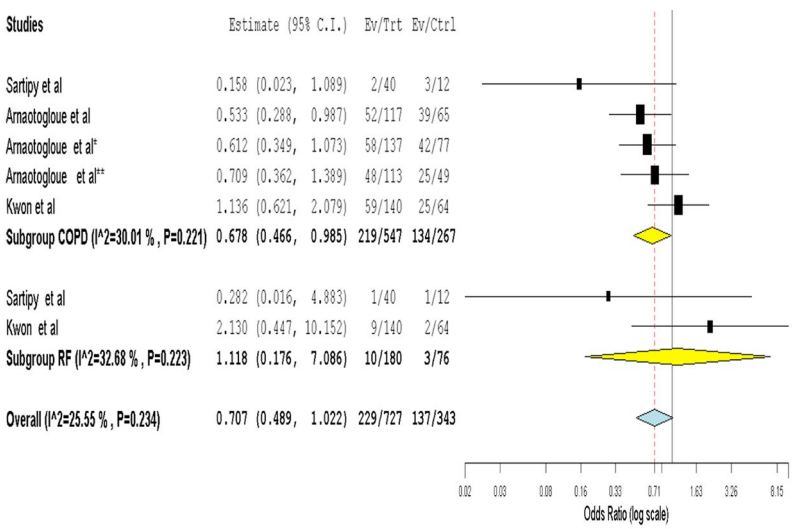

Figure 3. Forest plot of analysis for chronic obstructive lung disease and renal failure.

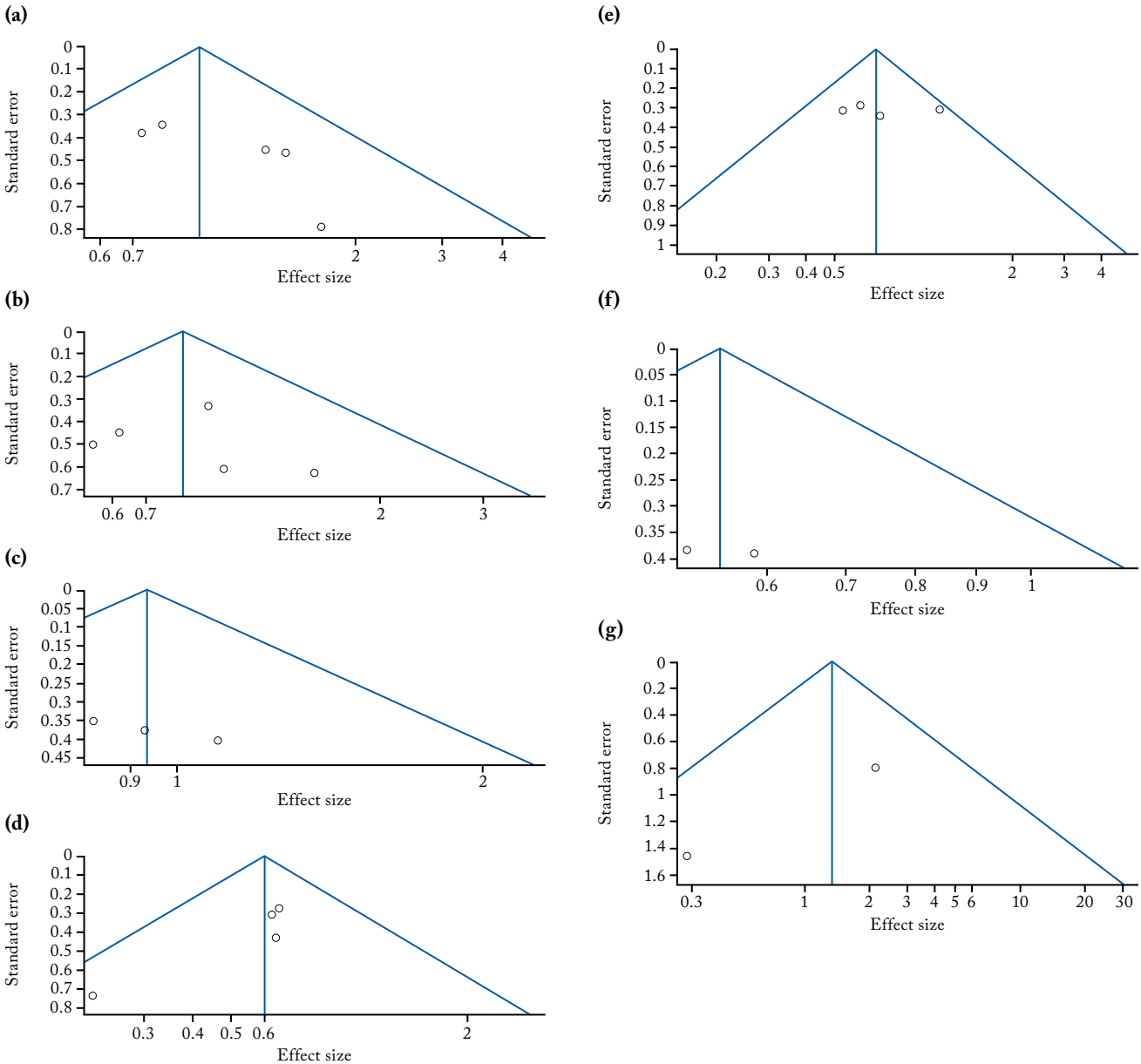

Figure 4. **(a)** Funnel plot for diabetes mellitus. **(b)** Funnel plot for hypertension. **(c)** Funnel plot for hyperlipidemia. **(d)** Funnel plot for coronary artery disease. **(e)** Funnel plot for chronic obstructive lung disease. **(f)** Funnel plot for heart failure. **(g)** Funnel plot for renal failure.

the articles for renal failure (tau^2=0.66). On the other hand, we found fail safe number analysis (potentially missed articles during database screening) significant only for CAD (n=4) and COPD (n=3). For visual detection of bias the funnel plots for each diseases are shown in figures 4a-g.

The effect weights of each study on the results obtained from the analysis are summarized in Table 3.

DISCUSSION

In this study, we investigated the association between coexisting systemic diseases and PIS development after EVAR. The results showed that CAD, heart failure, and COPD were significant risk factor for PIS. We also observed that other systemic diseases, such as hypertension, renal failure, diabetes mellitus and hyperlipidemia, that are likely to be found

Table 2
Results of analysis

	Results				Heterogeneity				Publication bias
	OR	95% CI		*p*	Q	df	*p*	I^2	Tau^2
Hypertension	0.91	0.61	1.36	0.66	1.60	4	0.80	0	0.00
Hyperlipidemia	0.93	0.61	1.42	0.74	0.27	2	0.87	0	0.00
Diabetes mellitus	0.97	0.67	1.39	0.88	3.05	5	0.69	0	0.00
Coronary artery disease	0.60	0.42	0.86	0.006	1.93	3	0.58	0	0.00
Chronic obstructive pulmonary disease	0.67	0.46	0.98	0.04	5.71	4	0.22	30	0.00
Heart failure	0.53	0.31	0.92	0.02	0.05	1	0.80	0	0.00
Renal failure	1.12	0.17	7.08	0.9	1.48	1	0.22	32.6	0.66

OR: Odds ratio; COPD: Chronic obstructive pulmonary disease.

Table 3
Weight of trials on the results (%)

	Hypertension	Hyperlipidemia	Coronary artery disease	COPD	Diabetes mellitus	Heart failure	Renal failure
Arnaoutoglou et al.[5]	19.09	33.17		19.87	18.11		
Arnaoutoglou et al.[6]	22.49	38.66	41.31	28.77	27.99	49.11	
Gorla et al.[8]	10.85				7.42		
Kwon et al.[9]	37.74		15.86	24.95	17.79		68.13
Sartipy et al.[3]			7.85	1.91	6.01		31.87
Arnaoutoglou et al.[7]	9.83	28.17	34.99	24.51	22.69	50.89	

COPD: Chronic obstructive pulmonary disease.

in patients with aortic aneurysms were not related to PIS. Although the lack of randomized controlled trials and the low number of patients make the findings argumentative, this controversy is decreasing due to the fact that the number of researches is increasingly, particularly in COPD, hypertension, and diabetes mellitus compared to other coexisting diseases.

Due to the older ages of patients undergoing EVAR, it seems to be reasonable that this age group would have many coexisting diseases. Researches included in our study did not found a significant difference between developed and undeveloped PIS groups in terms of systemic coexisting diseases, other than one study. In terms of ischemic heart disease and COPD, Sartipy et al.[3] observed a significant difference between the groups, contrary to the other studies. Additionally, the differences for diabetes mellitus and renal failure were not significant in this study. No additional statistical analysis (univariate or multivariate analysis) was performed in this research other than comparisons between the groups. Kwon et al.[9] evaluated diabetes mellitus and hypertension as variables in univariate and multivariate analysis; however, results were not significant. Contrary to the findings of five researches[5-9] which did not observe a significant difference between the groups in terms of CAD, COPD, and heart failure, we found that these three systemic diseases were closely associated with the development of PIS.

In 1992, the systemic inflammatory response syndrome (SIRS) was defined at the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[10] This old definition consisted of the following criteria: a body temperature of >38°C or <36°C, heart rate of >90 bpm, respiratory rate of >20 breath/min, and WBC of >12,000 cells/mm^3 or <4,000 cells/mm^3. Current sepsis guidelines have abandoned the SIRS definition.[11] In spite of this,

PIS is usually accepted as a systemic inflammatory response occurring after EVAR. The published studies defined PIS as fever and leukocytosis in conditions without an infection.[12] This definition is different to the diagnostic criteria for SIRS.[13] While the criteria for SIRS have four points, PIS only encompasses leukocytosis and fever from these criteria. Respiration or heart beats per minute are outside the definition of PIS. The remaining leukocytosis and fever appear to be findings that may be confused with other causes. As a result, Spanos et al.[14] were of the opinion that there was a need to consider anaphylaxis, particularly in the differential diagnosis.

There are three criteria used as the general definition for PIS: fever, leukocytosis, and elevated CRP. However, although all of the studies included in our study agreed fever and leukocytosis as the main criteria, CRP was added to the definition only by Gorla et al.[8]

Diabetes mellitus, frequently encountered in those with cardiovascular diseases, increases the risk of infection and sepsis. Also, up to 22% of all sepsis patients are known to have diabetes mellitus.[15,16] The main reason for this susceptibility toward infection can be attributed to the effect of hyperglycemia and is considered to be related to defects in adhesion, neutrophil chemotaxis, and intercellular death.[17] Although there is a direct correlation between the inflammatory process and sepsis with diabetes mellitus, the cause of the lack of a significant link between PIS and diabetes mellitus in our analysis is not consistent with this situation. However, we believe that, at this point, it is necessary to investigate whether other comorbid disease are the risk factors. Also, other variables related to diabetes mellitus such as duration and antidiabetic medications should be analyzed. Investigation of patients in subgroups according to years of diabetes mellitus, type of diabetes mellitus, and treatment options may reveal the correlation between PIS and diabetes mellitus more clearly.

Inflammation is shown to be effective in the development of many cardiac diseases including atherosclerosis and CAD and in the formation of complications.[18] In atherosclerotic lesions, a chronic inflammatory process, balloon angioplasty administration induces inflammation, leading to the release of inflammatory biomarkers by the interleukin-6 and tumor necrotizing factor-alpha.[19]

Inflammation and heart failure are strongly linked with each other.[20] Indeed, they often mutually strengthen each other. This situation supports our results about that there is a relationship between PIS with both CAD and heart failure. A similar situation for heart disease exists in COPD which is associated with chronic inflammation affecting pulmonary parenchyma and peripheral airways, resulting in inflammation characterized by increased alveolar macrophages, neutrophils and T-lymphocytes.[21] This relationship shows positive correlation, reaching the highest points during acute exacerbations.[21]

The exact etiology of PIS still remains to be elucidated. Endograft material, bacterial translocation, contrast use, and thrombus are thought to be the potential factors.[22] Endograft material (polyester and polytetrafluoroethylene) is the most investigated factor. Kakisis et al.[23] found that polyester-based endograft was an independent risk factor for PIS according to the multivariable model. On the contrary, Moulokakis et al.[24] were unable to find any difference between these two materials.

In particular, considering the patient group to which EVAR would be applied, accompanying systemic diseases constitute an important clinical situation. Therefore, it is important to identify and control coexisting diseases before the procedure. At the same time, identification of diseases that may be a risk factor for PIS would form the basis for the measures to be taken. Thus, factors that increase the cost of treatment such as complications and length of hospital stay can be prevented.

There are some limitations to this meta-analysis. First, PubMed, Scopus, and Web of Science were used for database screening. Since the other databases were not examined, the number of articles available remained low. Second, only English publications were selected. Third, a population of 947 patients was reached, which may be an insufficient sample size. Finally, we were unable to evaluate syndromes such as Marfan. In the literature, EVAR in patients with connective tissue disorders has been shown to be associated with a high risk of early and mid-term complications and reinterventions and an open surgical approach should be reserved for patients with acceptable risks.[25]

In conclusion, there is a significant correlation between PIS with CAD, heart failure, and COPD. Although the endograft material is the most known

etiological factor for PIS, coexisting diseases should be also considered. This may be helpful for planning the preventive therapies of PIS. Nevertheless, further large-scale, prospective, randomized-controlled studies are warranted to reveal the possible relationship between other frequently encountered diseases such as diabetes mellitus.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):44-52
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1075
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Cardiovascular Surgery and Interventions

Original Article Open Access

The influence of left ventricular pacing polarity on ventricular repolarization parameters in cardiac resynchronization therapy and its clinical reflections on ventricular tachyarrhythmias

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Received: February 08, 2021 ***Accepted:*** February 20, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: This study aims to investigate the effects of the left ventricular (LV) pacing polarities on ventricular repolarization patterns and to examine novel parameters taking depolarization into account.

Patients and methods: This prospective study included a total of 54 patients (39 males, 15 females; mean age: 65.2±11.6 years; range, 40 to 89 years) with successful cardiac resynchronization therapy using quadripolar LV leads between January 2014 and February 2017. The patients were divided into two groups as the true bipolar group (n=25) and the unipolar/extended bipolar group (n=29). Ventricular repolarization parameters and novel markers, i.e., TpTe/QRS, Tpec/QRS, TpTe/(QRS × QTc) and Tpec/(QRS × QTc), were measured before implantation within 48 h following the procedure and at six months. Evaluation of ventricular tachyarrhythmias was performed using device records during follow-up.

Results: The median follow-up was 17.7 (range, 12.6 to 31.2) months. The mean ejection fraction was 23.3±5.5% in the bipolar group and 23.62±6.24% in the unipolar/extended bipolar group. Bipolar LV pacing was associated with higher Tpec/QTc values (acute, bipolar vs. unipolar, +0.011 vs. -0.0008, p=0.019; long-term, bipolar vs. unipolar, +0.005 vs. - 0.015, p=0.005, respectively). There was no significant difference between the groups in terms of other repolarization parameters. Bipolar pacing was associated with significantly higher novel markers values and more frequent sustained and non-sustained ventricular tachyarrhythmias.

Conclusion: The LV pacing polarity significantly affects Tpec/QTc, but not the other ventricular repolarization parameters. Novel arrhythmia predictors, i.e., TpTe/QRS, Tpec/QRS, TpTe/(QRS x QTc), and Tpec/(QRS x QTc), are more influenced in bipolar pacing associated with more frequent ventricular tachyarrhythmias.

Keywords: Cardiac resynchronization therapy, depolarization, pacing polarity, tachycardia, ventricular.

Despite enormous advances in pharmacological treatments in recent years, heart failure (HF) continues to occupy an important place among the leading causes of morbidity and mortality. Cardiac resynchronization therapy (CRT), which has created an important glimmer of hope in this regard, has become an established treatment procedure to improve clinical complaints and exercise tolerance, and to reduce all-cause mortality and hospitalizations in patients with mild-to-severe HF, reduced left ventricular (LV) systolic functions, and wide QRS complex, particularly with left bundle branch block (LBBB) morphology.[1] Reverse remodeling and ventricular resynchronization are mechanisms of action of CRT. To correct these intra- and interventricular contraction disorders, three leads are placed in the right atrium, right ventricular apex, and LV epicardial surface (either retrograde via the coronary sinus [CS] or surgically). Consequently, cardiac output increases, pulmonary capillary wedge pressure decreases, and contractility is improved.[2,3]

Providing different vector activation of different pacing configurations can affect ventricular

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Citation:
Abusharekh M, Yılmaz A, Alak Ç, Ertürk E, Özcan EE, Göçer H, et al. The influence of left ventricular pacing polarity on ventricular repolarization parameters in cardiac resynchronization therapy and its clinical reflections on ventricular tachyarrhythmias. Cardiovasc Surg Int 2021;8(1):44-52.

repolarization patterns. Quadripolar LV leads exhibit 10 variant pacing configurations in the clinical practice, although LV lead pacing polarity is mostly a modifiable parameter. Preference of pacing configuration is made taking into account the branch of the available CS, the risk of phrenic nerve stimulation, and optimization of LV pacing thresholds, whereas unipolar stimulation can be placed between the tip and generator, or between the pacing tip and the right ventricular coil or ring electrode (known as extended bipolar), Bipolar stimulation can be between distal and proximal electrodes or vice versa.[4]

Differences in mechanical activation sequence according to pacing polarities have been proven, resulting in different activation between the different layers of the myocardium, and this affect the ventricular repolarization patterns.[5] The difference in intrinsic repolarization between epicardium, midmyocardial M cells, and endocardium varies according to LV pacing polarities. Additionally, as a result of delayed activation and repolarization of midmyocardial M cells during epicardial biventricular pacing, the transmural dispersion of repolarization (TDR) can be significantly increased.[6] In the light of this knowledge, the influences of LV pacing polarity on ventricular repolarization parameters and its relationship with the likelihood of developing ventricular arrhythmias has become a matter of concern.

Potential proarrhythmic effects of CRT are still controversial and various mechanisms have been proposed. One of the main mechanisms is the reversal of the myocardial activation sequence, which increases QT and TDR.[7] Furthermore, it has been suggested that the proarrhythmic mechanism of unidirectional block and re-entry may be corrected by changing the activation sequence within the scar areas.[8] In contrast, antiarrhythmic properties of CRT are advocated by leading to LV reverse remodeling, electrical stabilization of myocyte membranes, and bringing about a decrease in myocardial wall stress.[9]

It has been previously documented that long-term clinical outcomes of different LV pacing polarity, unipolar/extended bipolar configuration are associated with a higher incidence of HF/death, and all-cause mortality in patients with LBBB, compared to true bipolar.[10] Although the effect on ventricular repolarization patterns has not been studied, no significant difference is observed in terms of ventricular tachyarrhythmic (VTA) events.[10] In our study, we aimed to investigate the effects of different LV pacing polarities on ventricular repolarization patterns and to examine the novel arrhythmia predictive parameters taking depolarization into account and its relationship with VTA events.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Dokuz Eylül University, Department of Cardiology and Medical Park Izmir Hospital, Department of Cardiology between January 2014 and February 2017. A total of 54 patients (39 males, 15 females; mean age: 65.2±11.6 years; range, 40 to 89 years) with successful CRT with biventricular pacemaker implantation using quadripolar LV leads according to the conventional CRT indications were included in the study. The only indication for CRT-defibrillator (D) implantation was considered the primary prevention from sudden cardiac death (SCD). Inclusion criteria were as follows: *(i)* patients with a standard indication of CRT according to the New York Heart Association (NYHA) Class II-IV despite optimal medical therapy with a LV ejection fraction (LVEF) of ≤35% and a QRS duration of >130 msec, irrespective of the QRS morphology; and *(ii)* patients with a LVEF of ≤35% regardless of the NYHA functional class who required ventricular pacing and had a CRT indication due to a QRS duration of >130 msec, irrespective of the QRS morphology. Exclusion criteria were as follows: patients with a QRS duration of <130 msec, a history of ventricular arrhythmia event or SCD according to medical history and Holter electrocardiographic [ECG] records, Wolff-Parkinson-White (WPW) syndrome, arrhythmogenic right ventricular dysplasia, Brugada syndrome, or a history of channelopathy, failure of the CS cannulation or implantation procedure. A written informed consent was obtained from each patient. The study protocol was approved by the Dokuz Eylül University, School of Medicine, Ethics Committee (date/no: 16.11.2016-61804747000/1056). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The CRT-D device implantation and identifying the LV pacing configurations in terms of polarity were performed in the cardiac catheterization laboratory using standard transvenous approach of CRT device implantation techniques. Following an apically right ventricular shock lead implantation, a quadripolar LV (The Quartet Model 1458Q, St. Jude Medical, St.

Paul, Minnesota, USA) and the right atrium leads were implanted, respectively, and capture thresholds were recorded simultaneously. The identification of LV electrodes was determined as the Distal 1(D1), Mid 2(M2), Mid 3(M3), and Proximal 4(P4), respectively, starting from the distal tip electrode. Then different pacing configurations offered by the quadripolar LV lead were defined as follows: True Bipolar: D1 to M2, D1 to P4, M2 to P4, M3 to M2, M3 to P4 and P4 to M2 configurations; Unipolar (or extended bipolar): D1 to RV coil, M2 to RV coil, M3 to RV coil and P4 to RV coil configurations (Figure 1). The patients were divided into two groups as the true bipolar group (n=25) and the unipolar/extended bipolar group (n=29).

The 12-lead ECGs were recorded before CRT device implantation within 48 h following the procedure and six months after the procedure. All ECGs were scanned digitally and evaluation was made at 400% magnification. The measurements were performed by a blinded cardiologist. The onset of the QT interval was determined as the first portion (deflection) of the QRS complex, and the end was identified as the point where the isoelectric line intersected the tangent slope of the T wave. The longest interval of entire leads wherein the T wave was obviously selected (usually V2 or V3) was regarded to be the QT interval. The acquired QT value was corrected to heart rate using the Bazzet formula (QTc). The QT peak interval was defined as the interval from the onset of the QRS to the peak of the positive T wave or the bottom of a negative T wave. In case of a biphasic T wave, the first peak was selected as a reference point for measurement. The TpTe interval was calculated by subtracting the QT peak interval from the QT interval. TpTe was averaged after measuring TpTe in all 12 leads. The TpTe value was corrected according to the Bazzet formula and Tpec was obtained. The QT and TpTe dispersions were calculated from the difference between the longest and shortest of the mentioned intervals in 12-lead ECG. The TpTe/QT, Tpec/QTc, TpTe/QRS, Tpec/QRS, TpTe/(QRS × QTc), Tpec/(QRS × QTc) values were also calculated.[11]

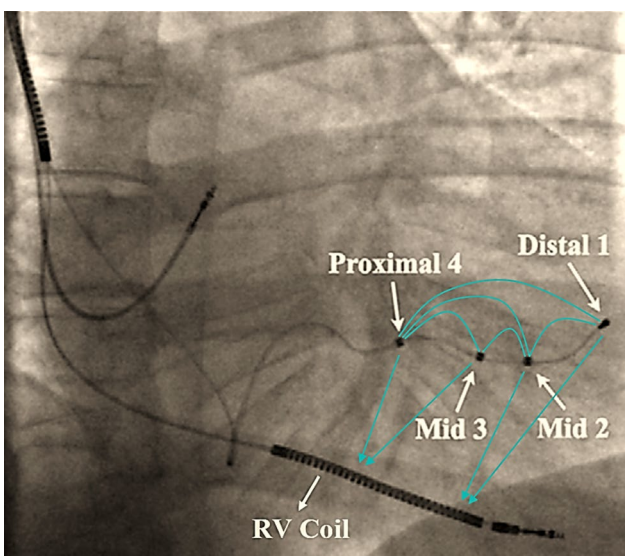

Figure 1. Cardiac fluoroscopic image showing bipolar stimulation.

Evaluation of VTA events was performed based on the recorded ECG readings and clinical records. Device therapies were analyzed in two main categories as anti-tachycardic pacing (ATP) or shock. In case of both ATP and shock delivery in the same arrhythmia episode, the episode was evaluated in the shock category. Ventricular tachyarrhythmia detected by the device and terminated spontaneously without any therapy was recognized as non-sustained ventricular tachycardia (NSVT). Ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes which met the device detection criteria and underwent therapy (ATP or shock) were considered to be sustained VTAs. Electrical storm was defined as ≥3 VTA episodes within 24 h. Tachyarrhythmic events treated by the device as a result of atrial fibrillation (AF) or supraventricular tachycardia (SVT) were identified as inappropriate and not included in the analysis. The VTA detection criteria of the device and therapy settings were programmed in accordance with the nominal settings at the time of implantation and, if necessary, changed only at the discretion of the cardiologist.

Statistical analysis

Statistical analysis was performed using the PASW 17.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (interquartile range [IQR], while categorical variables were presented in number and frequency. For the comparison of independent variables with the dependent variables, the Mann-Whitney U test was used, since non-parametric conditions were provided for numerical variables. The chi-square test was used to compare categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

The median follow-up was 17.7 (range, 12.6 to 31.2) months. The mean age was 64.7±12.3 in the true bipolar group and 65.7±11.2 in the unipolar/extended bipolar group. The mean LVEF was 23.3±5.5% in the true bipolar group and 23.6±6.2% in the unipolar/extended bipolar group. The baseline characteristics of both groups were comparable (Table 1).

To analyze the difference acute effects of CRT on ventricular repolarization parameters and the novel arrhythmia markers between the groups, pre-procedural ECGs were compared to ECGs at 48 h after CRT device implantation. Compared to the pre-procedural values, an increase in the TpTe/QRS, Tpec/QRS, TpTe/(QRS × QT) and Tpec/(QRS x QTc) values in the acute period was more prominent in the bipolar group (p=0.026, p=0.018, p=0.016, and p=0.013, respectively). The TpTe/QT and Tpec/QTc values were found to be acutely increased after the procedure in the bipolar group, while a decrease was observed in the unipolar group (p=0.089 and p=0.019,

Table 1
Baseline demographic and clinical characteristics of study population

	True bipolar (n=25)			Unipolar/extended bipolar (n=29)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			64.7±12.3			65.7±11.2	0.755
LVEF (%)			23.3±5.5			23.6±6.2	0.853
DM	7	28		8	27.58		0.973
HT	8	32		9	31		0.939
Sex							0.565
Male	19	76		20	69		
Female	6	24		9	31		
Etiology							0.542
Ischemic	10	40		14	48		
Non-ischemic	15	60		15	52		
NYHA Class							0.567
I-II	-	-		1	3.44		
II	-	-		1	3.44		
II-III	1	4		3	10.34		
III	22	88		21	72.41		
Ambulatory IV	2	8		3	10.34		
Baseline rhythm							0.499
AF	2	8		4	13.8		
SR	23	92		25	86.2		
QRS morphology							0.560
LBBB	24	96		28	96.55		
RBBB	1	4		1	3.44		
Device							
CRT-D	25	100		29	100		
CRT-P	-			-			
Drugs							
ACE-I/ARB	23	92		26	89.65		0.893
Beta blocker	24	96		28	96.55		1.000
MRA	14	56		17	58.62		0.923
Amiodarone	13	52		8	27.58		0.067
Digoxin	5	20		2	6.89		0.229

SD: Standard deviation; LVEF : Left ventricular ejection fraction; DM: Diabetes mellitus; HT: Hypertension; NYHA: New York Heart Association; AF: Atrial fibrillation; SR: Sinus rhythm; LBBB: Left bundle branch block; RBBB: Bundle branch block; CRT-D: Cardiac resynchronization therapy-defibrillator; CRT-P: Cardiac resynchronization therapy pacemaker; ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; MRA: Mineralocorticoid receptor antagonist.

respectively). We revealed no statistically significant difference in the QRS duration between the groups (median: -18.66 vs. -13.22 msec, respectively; p=0.515). When the early changes in other ECG parameters were compared, no statistically significant difference was revealed according to the LV pacing polarity (Table 2).

Statistically significant differences in the LV pacing polarity between the groups persisted at six months; however, there was a marked decline in the median values of ventricular repolarization parameters and novel markers, compared to the acute phase. Compared to the pre-procedural values, the increase in the TpTe/QRS, Tpec/QRS, TpTe/(QRS × QT) and Tpec/(QRS × QTc) values at six months was higher in the bipolar group (p=0.023, p=0.004, p=0.052, and p=0.006, respectively). Although the median value of Tpec/QTc decreased compared to the acute phase, the increase from baseline persisted at six months in the bipolar group, while a decrease from baseline was observed in the unipolar/extended bipolar group (bipolar vs. unipolar: +0.005 vs. -0.015, respectively; p=0.005). At six months, no statistically significant difference in the QRS duration was revealed between the groups (median: -20.10 vs. -13.59, respectively; p=0.302). When the long-term changes in other ECG parameters were compared, no statistically significant difference was revealed according to the LV pacing

Table 2
Electrocardiographic changes in acute period based on left ventricular pacing polarity

Electrocardiographic measurements	Polarity	Median	Interquartile range	*p**
Δ^{1-2} TpTe interval (ms)	Unipolar	+ 11.08	46.49	0.147
	Bipolar	+ 13.83	22.47	
Δ^{1-2} Tpec (ms)	Unipolar	+ 7.59	41.62	0.125
	Bipolar	+ 16.12	19.85	
Δ^{1-2} TpTe dispersion (ms)	Unipolar	+ 12.95	58.62	0.855
	Bipolar	+ 10.44	49.02	
Δ^{1-2} QTc (ms)	Unipolar	+ 52.00	105.07	0.931
	Bipolar	+ 38.95	54.67	
Δ^{1-2} Tp-Te/QT	Unipolar	- 0.006	0.05	0.089
	Bipolar	+ 0.012	0.04	
Δ^{1-2} Tpec/QTc	Unipolar	-0.0008	0.04	0.019
	Bipolar	+ 0.011	0.03	
Δ^{1-2} QRS duration (ms)	Unipolar	- 13.22	23.66	0.515
	Bipolar	- 18.66	15.12	
Δ^{1-2} QT dispersion (ms)	Unipolar	+ 21.98	46.94	0.391
	Bipolar	+ 33.85	42.42	
Δ^{1-2} (TpTe)/QRS	Unipolar	+0.08	0.25	0.026
	Bipolar	+0.15	0.13	
Δ^{1-2} (Tpec)/QRS	Unipolar	+0.12	0.25	0.018
	Bipolar	+ 0.17	0.18	
Δ^{1-2} (Tpec)/(QRS x QTc) (ms^{-1})	Unipolar	+1*10-4	0.00	0.013
	Bipolar	+2*10-4	0.00	
Δ^{1-2} (TpTe)/(QRS x QTc) (ms^{-1})	Unipolar	+1*10-4	0.00	0.016
	Bipolar	+2*10-4	0.00	

* Mann Whitney U test; Δ^{1-2}: Change between before and after the procedure (within 48 hours); QTc: QT interval corrected according to the Bazzet formula; TpTe: Difference between QT and QT peak interval; Tpec: TpTe interval corrected according to the Bazzet formula.

Table 3
Electrocardiographic changes in long-term based on left ventricular pacing polarity

Electrocardiographic measurements	Polarity	Median	Interquartile range	*p**
Δ^{1-3} TpTe interval (ms)	Unipolar	-6.05	35.63	0.196
	Bipolar	+ 6.21	28.15	
Δ^{1-3} Tpec (ms)	Unipolar	- 3.02	35.04	0.075
	Bipolar	+ 5.71	26.88	
Δ^{1-3} TpTe dispersion (ms)	Unipolar	+ 9.99	57.72	0.472
	Bipolar	+ 0.81	29.81	
Δ^{1-3} QTc (ms)	Unipolar	-1	81.80	0.952
	Bipolar	+4	59.77	
Δ^{1-3} Tp-Te/QT	Unipolar	- 0.014	0.02	0.062
	Bipolar	- 0.004	0.03	
Δ^{1-3} Tpec/QTc	Unipolar	- 0.015	0.02	0.005
	Bipolar	+ 0.005	0.03	
Δ^{1-3} QRS duration (ms)	Unipolar	- 13.59	22.13	0.302
	Bipolar	- 20.10	16.77	
Δ^{1-3} QT dispersion (ms)	Unipolar	- 2.86	31.58	0.788
	Bipolar	+ 2.96	29.43	
Δ^{1-3} (TpTe)/QRS	Unipolar	+0.03	0.13	0.023
	Bipolar	+0.08	0.14	
Δ^{1-3} (Tpec)/QRS	Unipolar	+0.03	0.16	0.004
	Bipolar	+0.12	0.14	
Δ^{1-3} (Tpec)/(QRS x QTc) (ms^{-1})	Unipolar	0	0.00	0.006
	Bipolar	+2*10-4	0.00	
Δ^{1-3} (TpTe)/(QRS x QTc) (ms^{-1})	Unipolar	0	0.00	0.052
	Bipolar	+2*10-4	0.00	

* Mann Whitney U test; Δ^{1-3}: Change between before and long term after the procedure (at 6 month); QTc: QT interval corrected according to the Bazzet formula; TpTe: Difference between QT and QT peak interval; Tpec: TpTe interval corrected according to the Bazzet formula.

polarity (Table 3). Figure 2 shows the acute and long-term difference of CRT's impact on Tpec/QRS according to LV pacing polarity, as an example of novel arrhythmia markers.

Considering VTAs, we observed that both sustained and NSVTs were higher in the true bipolar group. A detailed analysis revealed that sustained VTAs were observed in 22 patients, 14 (63.6%) of which were bipolar and eight (36.4%) were unipolar (p=0.034). Similarly, NSVTs were found to be significantly higher in the true bipolar group (73.7%), whereas 26.3% were in the unipolar group (p=0.003). In terms of VF, there was no significant difference between the groups (p=0.313). Furthermore, there

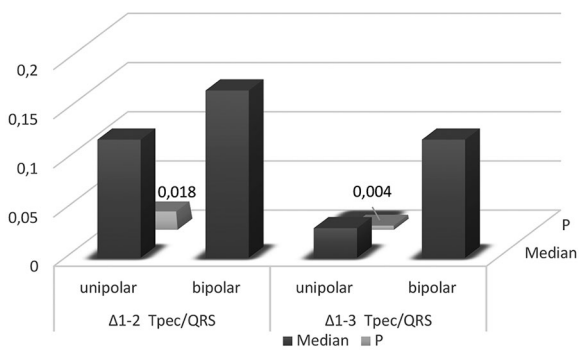

Figure 2. The acute and long-term difference of CRT's impact on Tpec/QRS according to left ventricular pacing polarity.

* Δ1-2: Change between before and after the procedure (within 48 h); Δ1-3: Change between before and long term after the procedure (at 6 month); Tpec - TpTe interval corrected according to the Bazzet formula.

Table 4
Comparison of ventricular arrhythmia events based on different left ventricular pacing polarity

	Polarity	n	%	p^*
Sustained VTA	Unipolar	8	36.4	0.034
	Bipolar	14	63.6	
Ventricular fibrillation	Unipolar	5	71.4	0.313
	Bipolar	2	28.6	
NSVTA	Unipolar	5	26.3	0.003
	Bipolar	14	73.7	
VTA with shock delivery	Unipolar	4	66.7	0.499
	Bipolar	2	33.3	
VTA terminated with ATP	Unipolar	6	75	0.191
	Bipolar	2	25	

* Pearson chi-square; VTA: Ventricular tachyarrhythmia; NSVTA: Non-sustained ventricular tachyarrhythmia; ATP: Anti-tachycardia pacing.

was no significant difference between the two groups in respect of shock delivery and ATP (p=0.499 and p=0.191, respectively). A comparison of ventricular arrhythmias between the groups is summarized in Table 4. Electrical storm was observed in five (9.25%) patients, including four in the bipolar group and one in the unipolar group. Four of them (80%) occurred within the first 100 days.

DISCUSSION

The CRT considered a crucial treatment modality for HF may be pro-arrhythmic, since pacing from epicardium increases TDR.[7] In responders to CRT, this early increase has been shown to decrease in the long-term, presumably as a result of reverse remodeling.[12] In the present study, our objective was to investigate the impact of CRT on conventional and recently defined ventricular repolarization parameters from the perspective of different LV pacing polarities in both acute and long-term and to examine novel arrhythmia predictive parameters taking depolarization into account. We also attempted to identify whether there were reflections on arrhythmic events.

Different pacing polarities lead to different distribution of activation in the ventricle. The activation wave of a bipolar depolarization detracts with the third force of the distance, while a unipolar wave attenuates with the square of the distance.[13] This difference caused by polarity particularly influences the initiation of the re-entry mechanism in the scar tissue. Although the first capture point in the epicardium can be the same, the subepicardial layers captured by the virtual electrode may differ. Additionally, the presence of scar tissues may affect the conduction vectors and can change the transmural activation sequence within such heterogeneous myocardium.[14] Yang et al.[5] reported a higher basal endocardial strain with bipolar pacing and found more uniform global strain compared to unipolar pacing. They also revealed that there were differences in the mechanical activation sequence in terms of LV pacing polarity, probably affecting vectoral activation and ventricular repolarization patterns.

Myocardial activation sequence reverses during biventricular pacing in conventional CRT patients. As a consequence of this reverse activation, early repolarization of epicardium, delayed activation and repolarization of midmyocardial M cells lead to a significant increase in TDR.[7] The Increased TDR can be measured non-invasively using parameters, such as Tpeak-Tend (TpTe or Tpe) and Tp-Te/QT.[15] Furthermore, it was shown that the QT dispersion which reflects regional heterogeneity in myocardial repolarization is associated with life-threatening arrhythmias and SCD. However, TpTe has been demonstrated to be superior to QT and QT dispersion in predicting VTs.[16] The TDR seems to play a key arrhythmogenic role not only in CRT's HF patients, but also in those with SCD, myocardial infarction, long QT syndrome, and Brugada syndrome.[17] Recently,

Tpec (TpTe corrected according to the Bazett formula) was suggested to be more sensitive measurement in predicting the risk of SCD and Tpec of more than 90 msec was determined to be associated with an approximately three-fold increased risk.[18] In the light of these data, we investigated both Tpec and Tpec/QTc value that, to the best of our knowledge, has not been evaluated previously.

In our study, Tpec/QTc showed a significant post-procedural increase in the true bipolar group, while a decrease was observed in the unipolar/extended bipolar group. The difference between the two groups decreased in the long-term, but remained statistically significant. There was no significant difference in the remaining ventricular repolarization parameters between the groups. As a clinical reflection of this observation, four of five patients with electrical storm were in the true bipolar LV configuration. Sustained and NSVTs were observed more frequently in the bipolar group. The greater influence of Tpec/QTc in the early period after CRT supports that a significant part of the increase in TDR is temporal. The point that draws our attention in this regard is that electrical storm occurred in four (80%) of our five patients within the first 100 days.

In another aspect, TDR does not take into account depolarization and action potential in HF patients whose myocardium are electrically and mechanically heterogeneous and transmural activation sequence is abnormal due to scar tissues. Recently, it has been suggested that, in arrhythmogenic right ventricular dysplasia and Brugada syndrome, QT/QRS ratio defined as cardiac electrophysiological balance index can be used to predict arrhythmia, as it takes depolarization into consideration.[19] In this context, it was recommended that TpTe/QRS and TpTe/(QRS × QT) parameters may be used, since the TpTe interval has been shown to be more precise in predicting arrhythmic risk rather than the QT interval.[20] In the present study, we evaluated Tpec/QRS and Tpec/(QTc × QRS) as well as aforementioned novel markers. To the best of our knowledge, this was not previously evaluated in CRT patients.

The LV pacing polarity has also a substantial role in the pathophysiology of arrhythmogenesis other than TDR. Asvestas et al.,[21] in a patient who presented with a monomorphic electrical storm two years after CRT, completely terminated the storm by changing the LV pacing configuration from the true bipolar to the extended bipolar (unipolar). The authors suggested that the bipolar configuration (D1-M2) caused the initiation of the one-way block and re-entry circuit due to its proximity to the critical isthmus in the scar tissue, and they prevented the onset of the re-entry circuit by pacing from extended bipolar. Considering the novel arrhythmia markers along with depolarization and TDR in our study, we observed that, in the bipolar group, where electrical storm and sustained VTAs were predominantly observed, the TpTe/QRS, Tpec/ QRS, Tpec/QRS × QTc, TpTe/QRS × QTc values increased more than the unipolar group. We persuaded that these markers may be used to predict arrhythmia, if supported by larger studies.

The main limitation of the present study is its relatively small sample size. The second limitation is the relatively high ischemic etiology (44.4%). The presence of ischemic scar tissues, as well as the heterogeneity of myocardium may have influenced the transmural activation sequence and VTAs. However, it should be kept in mind that the CRT patient population in daily practice is quite heterogeneous, as in this study. Bias in choosing the LV pacing configuration can be also considered a limiting factor; many factors, such as the branch of the existing CS, the risk of phrenic nerve stimulation, avoiding anodal capture, and optimization of LV pacing thresholds are taken into consideration in the decision-making process. Furthermore, given the nature of the study, we cannot ignore the impact of extrinsic and intrinsic variables, such as use of antiarrhythmic agents, coronary anatomy, and LV lead position on the outcomes.

In conclusion, left ventricular pacing polarity significantly affects Tpec/QTc, but not other ventricular repolarization parameters. Novel arrhythmia predictors (TpTe/QRS, Tpec/QRS, TpTe/(QRS × QTc) and Tpec/(QRS × QTc)) are more influenced in bipolar pacing associated with more frequent ventricular tachyarrythmias.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):53-57
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1080
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Cardiovascular Surgery and Interventions

Original Article Open Access

The role of inflammation in the epicardial adipose tissue on coronary artery disease pathogenesis

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Received: February 15, 2021 ***Accepted:*** February 22, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Objectives: In this study, we aimed to investigate the potential relationship between inflammation of the epicardial adipose tissue (EAT) and coronary artery disease (CAD).

Patients and methods: Between September 2017 and March 2018, a total of 38 patients (31 males, 7 females; mean age: 55 years; range, 46 to 64 years) who underwent elective open heart surgery were prospectively analyzed. The patients were divided into two groups according to the procedure type as those without CAD (n=15) and those with CAD (n=23) as the control group. The CAD group underwent isolated coronary artery bypass grafting, while the control group underwent open heart surgery and had normal coronary arteries as assessed by coronary angiography. The EAT samples were taken intraoperatively from peri-arterial and right atrial appendage in the CAD patients, while the samples were taken from only right atrial appendage in the control group. Specimens were stained and the presence and amount of inflammatory cell infiltrates were examined. More than 50 inflammatory cell counts in the pathological examination were accepted as significant inflammation.

Results: The mean white blood cell (7.5±2.3 vs. 7.1±2.2, respectively; p=0.842) and mean C-reactive protein (0.4±1.0 vs. 0.5±0.8, respectively; p=0.755) values were similar in both groups. In the CAD group, inflammatory cell infiltration in the atrium was more frequent than the control group (43% vs. 6.6%, respectively; p=0.036). Peri-arterial infiltration was also high similar with RAA in the CAD group.

Conclusion: Our study shows that both peri-arterial and atrial EAT inflammation significantly increase in patients with CAD, suggesting that inflammation in EAT may have a significant relationship with the CAD's pathogenesis.

Keywords: Atherosclerosis, coronary artery disease, epicardial adipose tissue, inflammation.

The pathological mechanism of atherosclerosis includes certain processes such as lipid accumulation, neo-intima and fibrous cap formation, and inflammation in the arterial wall.[1] Previously, it was thought that inflammation in the arterial wall developed in response to intimal injury, and peri-arterial epicardial inflammation occurred due to a close neighborhood relationship.[2] In recent studies, it has been proposed that adipose tissues act as a paracrine organ rather than an energy store and have proinflammatory effects.[3] However, in addition to the close relationship between cardiovascular diseases and obesity, the absence of coronary artery disease (CAD) at the same level in every patient with obesity suggests that there may be another mechanism different from the amount of adipose tissue.

Some mediators called adipokines secreted from adipocytes have been shown to be responsible for inflammatory responses occurred after intimal injury.[4] Therefore, the possible relationship between inflammation levels of epicardial adipose tissue (EAT) and atherosclerosis may lead to investigate different treatment strategies for CAD. In the present study, we

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Citation:
Özer T, Doğan C, Şengör M, Çoban Kökten S, Altaş Yerlikhan Ö, Çağan Efe S, et al. The role of inflammation in the epicardial adipose tissue on coronary artery disease pathogenesis. Cardiovasc Surg Int 2021;8(1):53-57.

aimed to examine the presence of inflammation of the EAT and its relationship with CAD.

PATIENTS AND METHODS

This single-center, prospective cohort study was conducted at Health Science University, Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital, Department of Cardiovascular Surgery between September 2017 and March 2018. A total of 38 patients (31 males, 7 females; mean age: 55 years; range, 46 to 64 years) who underwent elective open heart surgery were included. The patients were divided into two groups according to the procedure type as those without CAD (n=15) and those with CAD (n=23) as the control group. The CAD group underwent isolated coronary artery bypass grafting, while the control group underwent open heart surgery and had normal coronary arteries as assessed by coronary angiography. Inclusion criteria were as follows: having coronary artery disease and valvular disorder scheduled for elective coronary artery bypass graft (CABG) implantation, valvular replacement, or valvuloplasty. Those undergoing acute cardiac and aortic surgical procedures and those who were unwilling to give a consent were excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Health Science University, Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital Ethics Committee (date/no: 2018/1-42). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Adipose tissue sampling

Due to ethical reasons, EAT samples were obtained only from routine dissection by avoiding making additional dissections which were out of procedural steps. Epicardial adipose tissue samples were taken from the right atrial appendage (RAA) in both groups before cardiopulmonary bypass (CPB). In the

Table 1
Baseline demographic and clinical characteristics of study population

	All patients (n=38)			CAD group (n=23)			Control group (n=15)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			54.1±12.9			57.8±8.9			48.3±2	0.024
Sex										
Male	31	81		19	8		12	80		0.051
Hypertension	16	42		11	47		5	33		0.060
Smoking	18	47		13	56		5	33		0.082
Diabetes mellitus	11	28		5	21		6	40		0.751
Dyslipidemia	23	60		16	69		7	46		0.671
LVEF %			56.5±9.9			56.5±10.1			56.3±10.1	0.954
Laboratory parameters										
WBC (10^3/μL)			7.3±2.3			7.5±2.3			7.1±2.2	0.842
Hg (g/dL)			13.5±1.7			13.3±1.9			13.8±1.5	0.404
Hct (%)			40.7±5.1			40.0±5.5			41.9±4.2	>0.999
Platelet (10^3/μL)			239.2±48.9			238.7±55.6			240±38.3	0.939
Glucose (mg/dL)			138.1±74.8			144.5±77.7			128.1±71.6	0.516
Urea (mg/dL)			35.7±11.2			35.5±12.5			35.9±9.1	0.913
Creatinine (mg/dL)			0.9±0.3			1.0±0.4			0.9±0.3	0.511
Uric acid (mg/dL)			5.9±1.7			6.0±2.0			5.7±1.3	0.550
TC (mg/dL)			187.3±49.1			179.9±46.0			203.2±50.3	0.149
LDL-C (mg/dL)			117.7±43.3			107.0±43.3			132.1±40.3	0.080
HDL-C (mg/dL)			37.4±9.7			35.4±5.9			40.1±13.1	0.139
Triglyceride (mg/dL)			164.3±67.4			178.7±81.2			144.3±34.6	0.130
CRP (mg/L)			0.4±1.7			0.4±1.0			0.5±0.8	0.755
ESR (h)			20±5.1			21±3.8			19±7.3	0.904

CAD: Coronary artery disease; SD: Standard deviation; LVEF: Left ventricular ejection fraction; WBC: White blood cell; Hg: Hemoglobin; Hct: Hematocrit; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 2
Inflammatory grading of samples

	CAD group (n=23)				Control group (n=15)	
	Samples taken from RAA		Samples taken from peri-arterial		Samples taken from RAA	
	n	%	n	%	n	%
Grade 0	13	56	18	78	14	93
Grade 1	3	13	3	13	1	6.6
Grade 2	0	0	0	0	0	0
Grade 3	7	30	2	8	0	0

CAD: Coronary artery disease; RAA: Right atrial appendage.

CAD group, additional EAT samples were obtained from anterior interventricular sulcus during the left anterior descending (LAD) artery exploration under CPB support to explore the extent of inflammation (peri-arterial).

Histopathological examination

The tissue samples were fixed in 10% buffered formalin. Paraffin-embedded tissues were cut into 3-µm sections. A digital light microscope (Olympus BX53; Olympus Optical Co., Ltd., Tokyo, Japan) was used to evaluate the specimens by a pathologist blinded to the group allocation. Specimens were stained with hematoxylin and eosin (H-E) and the presence and amount of inflammatory cells (mainly macrophages and, lesser amount, T and B lymphocytes) infiltrates (ICIs) were examined. In the presence of more than one focus, the largest ICIs focus was taken into consideration. According to the amount of inflammatory cells, the specimens were scored as follows: (Grade 0): 0-50 cells, (Grade 1): 51-100 cells, (Grade 2): 101-200 cells, and (Grade 3): >200 cells.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism version 8.4.2 software (GraphPad Software Inc., CA, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (25^{th}-75^{th} percentiles), while categorical variables were expressed in n and frequency. Univariate comparisons between two groups were performed using the chi-square or Fisher's exact tests for categorical variables or Wilcoxon rank sum test for continuous variables. The Spearman or Pearson correlation test was used to assess the association between lymphocytes and other measured parameters. A p value of <0.05 was considered statistically significant.

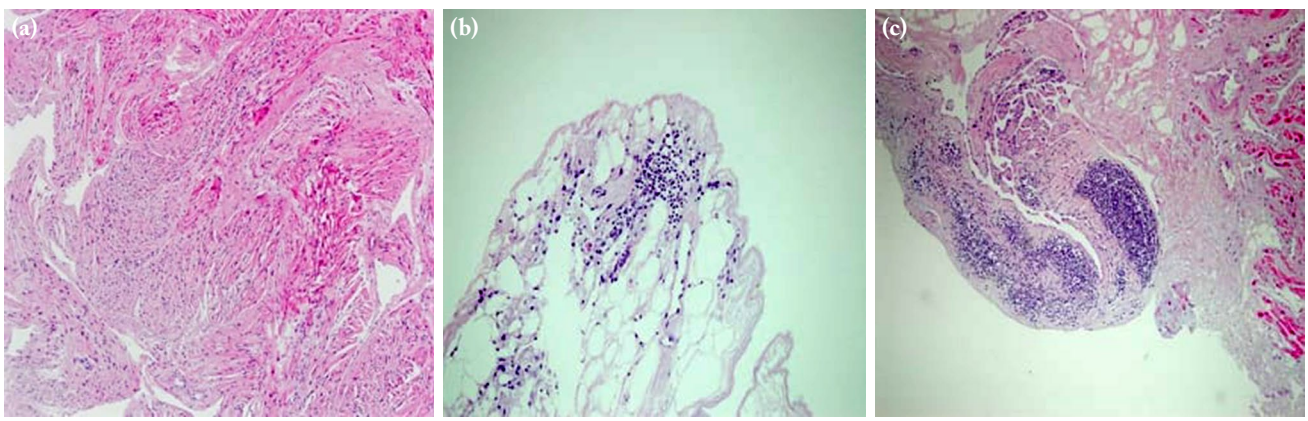

Figure 1. Histopathological examination showing inflammatory cell accumulations. Specimens were stained with H-E with ×100 magnification. Any of the specimens showed Grade 2 inflammation. **(a)** Grade 0, **(b)** Grade 1, **(c)** Grade 3.
H-E: Hematoxylin and eosin.

RESULTS

Baseline demographic and clinical characteristics of the patients with and without CAD are shown in Table 1. There were no significant differences in these characteristics between the groups (p>0.05). However, the prevalence of hypertension and smoking was higher in patients with CAD than in those without CAD. While the number of patients with dyslipidemia was significantly higher in the CAD group, the mean cholesterol levels were higher in the control group. Preoperative laboratory parameters including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were similar in both groups (p>0.05).

In the CAD group, ICI using the samples taken from the RAA was more frequent than the control group (43% vs. 6.6%, respectively; p=0.036) (Table 2). Seven patients in the CAD group demonstrated Grade 3 ICI at the RAA samples compared to two patients in the control group. Grade 2 inflammation was not detected in any of samples (Figure 1). The ICI was not statistically different between the RAA samples and peri-arterial samples in the CAD group (RAA Grade 0, n=13 vs. peri-arterial Grade 0, n=18, respectively).

There was significant correlation between inflammation grade and the existence of CAD (r=0.44, p=0.006).

DISCUSSION

The role of inflammation in atherosclerosis has been a topic of interest in recent years. Many studies have shown that inflammation in plaque formation, in addition to intimal damage and lipid accumulation, plays a key role in the mechanism of atherosclerosis. The accumulation of cellular and humoral structures involving in the mechanism of inflammation has become a guide for these studies.[1,2] Later studies have attempted to identify the proinflammatory structures having paracrine or endocrine effects on the inflammation to discover novel treatment strategies to overcome plaque formations in the arterial wall.[3] In our study, we mainly observed the numerical increase in the inflammatory cells in EAT of the patients having CAD.

Epicardial adipose tissue was initially thought to be responsible for the storage of energy substrates and behaving as a guard for myocardium; however, later studies showed several soluble products produced by adipocytes in the EAT.[5,6] During any inflammatory process, inflammatory cells and several cytokines increase in the tissues nearby the culprit lesions.[7] Mazurek et al.[8] showed in their study that inflammatory cells and markers were significantly higher in the EAT samples of patients with CAD. In our study, similarly, we found a significantly higher accumulation of inflammatory cells in the EAT tissue samples of CAD group than the control group.

In another study of İzgi,[9] EAT was described as a local player of atherosclerosis in the coronary artery walls with its neighborhood. In this study, the author emphasized by referring several studies that the increase of the inflammatory cells and markers in the EAT samples were not seen in the serum samples of the same patients. Additionally, in a study of Erdogan et al.,[10] the decrease in coronary flow was associated with the increased epicardial adipose tissue thickness, independent of serum CRP levels.[10] Similarly, in our study, the measurement of inflammatory cells and markers (CRP and ESR) in the serum samples did not show any significant increment. Moreover, in the study of Yeşilkaya,[11] no significant relationship was found between systemic inflammation and mortality after CABG. This result may suggest a consideration about the interaction of solely local inflammatory of EAT with coronary arterial atherosclerosis.

Beside the increase of inflammatory cells in the EAT taken from the RAA in the CAD patients compared to those without CAD, the increment of inflammatory cells was also similar in the peri-arterial EAT in the CAD patients. In addition to our findings, Moos et al.[12] observed the inflammatory cells accumulation in the adventitia rather than the intima. Taken together, these findings indicate that the EAT may have a proinflammatory effect on atherosclerosis, rather than the inflammatory process in the EAT occurred secondary to intimal injury.[13]

The main limitation of this study was its small sample size. In addition, although sample collections were made prospectively, preoperative data were obtained retrospectively.

In conclusion, our study showed that both peri-arterial and atrial EAT inflammation significantly increased in patients with CAD. This result may suggest that inflammation in EAT have a significant relationship with the CAD's pathogenesis. However, further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):58-62
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.927
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Cardiovascular Surgery and Interventions

Case Report Open Access

Relapsing polychondritis with aortic involvement in fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography: A case report

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Received: August 04, 2020 ***Accepted:*** February 14, 2021 ***Published online:*** March 29, 2021

ABSTRACT

An 83-year-old male patient presented with recurrent high fever. Vegetation was determined on transesophageal echocardiography, and antibiotic treatment was initiated for infective endocarditis. Despite medical treatment, progressive aortic insufficiency occurred and aortic valve replacement was performed. However, C-reactive protein (CRP) and fever did not decrease. During the clinical follow-up, pharyngolaryngeal pain and hoarseness, swelling, pain in the left auricle and nose increased. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) scan was performed which revealed an increased 18F-FDG uptake in the ascending aorta, left ear, and nose. The patient was diagnosed with relapsing polychondritis (RPC). After the steroid and cyclophosphamide treatment, fever and CRP decreased dramatically. In conclusion, 18F-FDG PET/CT is an important imaging method for demonstrating RPC.

Keywords: Computed tomography, fluorodeoxyglucose F18, inflammatory aortitis, positron emission tomography, relapsing polychondritis.

Relapsing polychondritis (RPC) is a rare autoimmune, inflammatory disease which specifically affects the hyaline cartilage.[1,2] The main challenge in the diagnosis of RPC is its rarity, lack of awareness, and a wide variety of symptoms. Therefore, many patients are diagnosed in advance stages. The most common symptoms are cough, fever, pain in the chest wall, sore throat, and arthralgia. Erythrocyte sedimentation rate, C-reactive protein (CRP), pulmonary function tests, and bronchoscopy are the most commonly used methods in the diagnosis. In recent years, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been widely used as a powerful diagnostic tool.[3,4] In this article, we report a rare case of RPC with ^{18}F-FDG PET/CT findings.

CASE REPORT

An 83-year-old male patient presented with recurrent high fever and hospitalized. He had intermittent fever (38.0 to 38.5°C) every day. There was no bacterial growth in recurrent blood cultures. Serological and biochemical examination revealed fever of unknown origin. Brucella agglutination and human immunodeficiency virus (HIV) tests were all negative. The CRP value was 30.32 mg/dL (reference: <0.5) and white blood cell count was 13.02 K/μL (reference: 4 to 10), which were all elevated. Vegetation and aortic valve insufficiency were determined on transesophageal echocardiography (TE). The patient was evaluated according to the Duke criteria.[5] Possible endocarditis was diagnosed according to the Duke criteria and antibiotic treatment was initiated. However, the patient did not improve clinically. Moreover, aortic valve regurgitation progressed, and laboratory findings of the patient became more severe. A written informed consent was obtained from the patient and aortic valve replacement was performed. No vegetation was detected in the macroscopic examination of the aortic valve during the operation. Due to persistent fever and elevated liver enzymes, antibiotic therapy was

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Citation:
Gültekin A, Kutlu S, Emrecan B, Şengöz T, Yaylalı O. Relapsing polychondritis with aortic involvement in fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography: A case report. Cardiovasc Surg Int 2021;8(1):58-62.

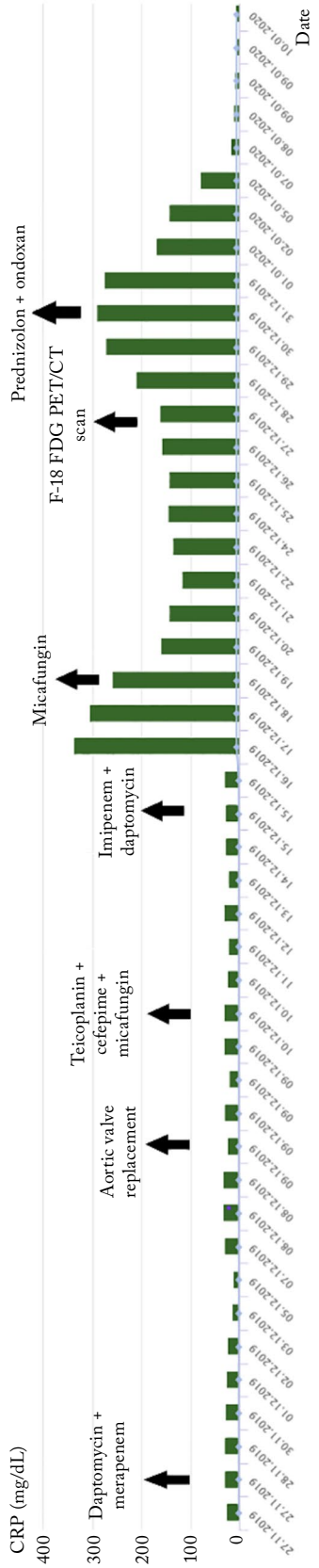

Figure 1. The CRP level-date graph. Treatments applied to the patient are shown in the graph.
CRP: C-reactive protein; ^{18}F-FDG PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography;

switched from teicoplanin and cefepime to imipenem and daptomycin (Figure 1). During follow-up, left ear pain, edema and erythema, nasal sensitivity, and redness of the nose and eye developed (Figure 2). Due to new-onset clinical findings, postoperative persistent fever, and elevated CRP levels, ^{18}F-FDG PET/CT scan was performed after the two weeks of surgery. The increased ^{18}F-FDG uptake was observed in the left ear, nose, eustachian tubes, and aorta compatible with inflammatory involvement of RPC (Figures 3 and 4). Severe ^{18}F-FDG uptake around the

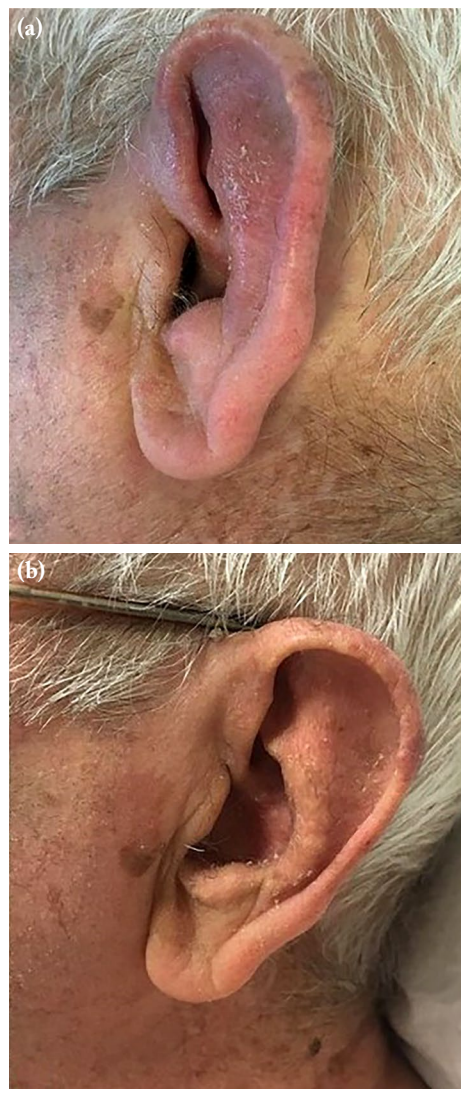

Figure 2. **(a)** During follow-up, edema and erythema developed in the left ear of the patient. **(b)** After treatment, the ear immediately returned to its normal appearance.

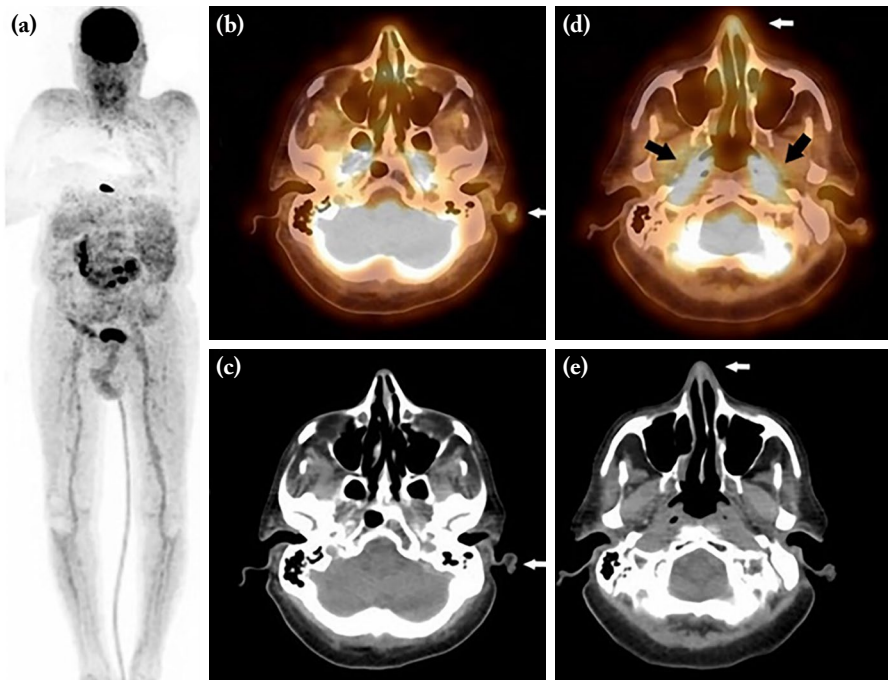

Figure 3. ^{18}F-FDG PET/CT showed increased ^{18}F-FDG uptake in the left auricle, nasal cartilage **(b, d, white arrows)** and bilateral eustachian tube **(d, black arrow)**. The SUV_{max} of the left ear was 2.87 (SUV_{max} of the right ear was 0.97) and the SUV_{max} of the nose was 2.97. CT images showed thickening of the left auricle and nasal cartilage **(c, e, white arrows)**.

18F-FDG PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; SUV_{max}: Maximum standardized uptake value.

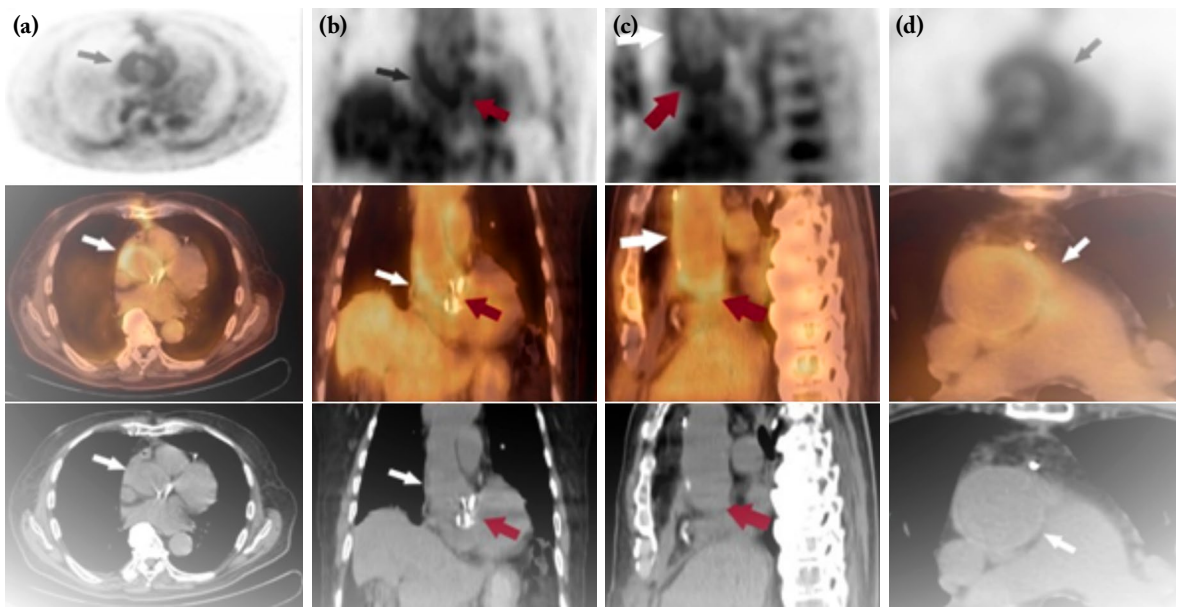

Figure 4. ^{18}F-FDG PET/CT scan showed wall thickening and increased ^{18}F-FDG uptake in the ascending aortic wall (SUV_{max}: 3.91). **(a-d, black and white arrows)**. The FDG uptake around the operating materials was compatible with inflammation secondary to the operation. **(b, c, red arrows)**.

^{18}F-FDG PET/CT: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; SUV_{max}: Maximum standardized uptake value.

aortic valve was interpreted as secondary inflammation related to surgery. A moderate ^{18}F-FDG uptake along with the thickening of ascending aortic wall was evaluated as the aortic involvement of RPC. Due to ^{18}F-FDG uptake in various cartilage tissues, RPC was considered. Steroid and cyclophosphamide treatment was initiated immediately. All of the clinical findings including fever disappeared and serum CRP returned to the normal levels.

DISCUSSION

The most common causes of fever of unknown origin are infections, neoplasms, and non-infectious inflammatory diseases. In this disease group, an individualized diagnosis algorithm is applied after a detailed patient history and physical examination. In our case, comprehensive clinical, biochemical, and microbiological examinations were performed initially to determine the etiology of fever. Intensive antibiotic therapy and aortic valve replacement were performed due to the diagnosis of infective endocarditis as evidenced by TE. Fever did not decrease after the operation and new clinical findings emerged. The ^{18}F-FDG PET/CT was performed which revealed inflammatory aortitis and polychondritis findings.

In the literature, there are some data indicating that immunological diseases are triggered, particularly after heart valve replacement.[6,7] Of note, during the operation, insertion of a rigid prosthesis to the fragile position may cause latent inflammation and stimulate immunological reactions.[7] Relapsing polychondritis is a systemic autoimmune disease characterized by progressive inflammation of hyaline cartilages (ear, nose, peripheral joints, and larynx/trachea/bronchial tree) and proteoglycan-rich structures (eye, inner ear, heart, blood vessels, and kidneys).[1,2] It affects most commonly the nose (90%), ears (54 to 70%),[8] larynx and tracheobronchial tree (11 to 69%), joints (18 to 81%), and cardiovascular system (3 to 27%).[9] The disease usually follows a relapsing-remitting course. However, the destruction of the tracheobronchial cartilage may be complicated by infections. It can cause serious illnesses and even death. There may be an increase in the anti-collagen type II and anti-Matrilin-1 antibody. Computed tomography may be useful in diagnosis. In recent years, the ^{18}F-FDG PET/CT has been increasingly used for diagnostic purposes[3,4,8] and follow-up[4] of RPC. This tool is also useful to localize the biopsy site.[3] The FDG is a radiopharmaceutical that accumulates in cancer tissues due to increased glucose utilization in neoplastic cells. However, the increase in glucose metabolism is not only specific for cancer, but also occurs in inflamed tissues. Respiratory system is affected in approximately 50% of RPC patients. Mortality and morbidity are usually associated with respiratory tree involvement.[10] Cardiovascular complications are the second leading cause of mortality and morbidity in RPC, accounting for about one-third of patients. The rate of aortitis is 6.5%.[11] Relapsing polychondritis is rare and, therefore, it is often overlooked in the differential diagnosis, leading to unnecessary treatment and interventions. Currently, there is no RPC-specific laboratory method or histopathological finding. Relapsing polychondritis is often diagnosed clinically. When ^{18}F-FDG PET/CT findings are evaluated combined with clinical findings, it is helpful to determine the extent of disease and severity of inflammation. In addition, evaluation of the response to treatment is also possible using this method.

In conclusion, open heart operations may trigger autoimmune diseases, such as RPC, or increase the severity of the existing condition. Polychondritis findings are typical on ^{18}F-FDG PET/CT. The Increased uptake of ^{18}F-FDG in cartilages, with clinical suspicion, should suggest RPC.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):63-67
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.1007
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Cardiovascular Surgery and Interventions

Case Report Open Access

Coronary subclavian steal syndrome: A case report

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Received: October 23, 2020 ***Accepted:*** November 08, 2020 ***Published online:*** March 29, 2021

ABSTRACT

Coronary subclavian steal syndrome is characterized by reverse flow of the left internal mammary artery used in the coronary artery bypass grafting (CABG). The stenosis in the proximal segment of the left subclavian artery is the reason which consequently leads to disruption of myocardial perfusion. It may cause myocardial infarction with variety of anginal symptoms in patients. In this article, we present a case who had symptoms of dyspnea and angina pectoris after CABG and was diagnosed with subclavian steal syndrome. In conclusion, physical examination and angiographic evaluation for subclavian artery stenosis in the preoperative period is recommended in patients who are scheduled for CABG.

Keywords: Coronary artery bypass grafting, coronary subclavian steal syndrome, internal mammary artery.

Subclavian steal syndrome (SSS) is a well-described phenomenon characterized by reversal of blood flow in the vertebral artery due to severe stenosis or blockage in the proximal segment of subclavian artery.[1] A special variant of SSS, namely coronary subclavian steal syndrome (CSSS), occurs in cases in whom internal mammary artery (IMA) is used for coronary artery bypass grafting (CABG) in the presence of a narrowed or occluded proximal subclavian artery. This phenomenon leads to a decrease in the IMA blood flow and thus coronary perfusion, possibly leading to myocardial ischemia and angina pectoris.[2] Although most cases are asymptomatic, CSSS has been shown to cause chest pain and effort dyspnea in the postoperative period.[3] In this article, we present a case who had symptoms of dyspnea and angina pectoris after CABG and was diagnosed with SSS.

CASE REPORT

A 77-year-old woman was admitted with a history of CABG 10 years ago in which the left IMA (LIMA) was anastomosed to the left anterior descending (LAD) coronary artery. Other bypasses were saphenous vein graft to the first obtuse marginal and saphenous vein graft to the second obtuse marginal. She had complaints of exertional dyspnea, chest pain, and exhaustion within the last four months. On physical examination, the heart rate was 80 to 95 bpm and systemic arterial blood pressure ranged between 110/70 mmHg and 130/80 mmHg. Compared to the right upper extremity, there was a systolic pressure gradient of 25 mmHg on the left arm. In addition, the left radial and brachial pulses were weaker. Electrocardiogram showed sinus rhythm without findings indicating myocardial ischemia. Coronary angiography showed that all saphenous grafts were patent. The LIMA filling was not observed in the selective subclavian artery injection (Video 1). However, there was no stenosis in the LIMA during retrograde filling. A 90% stenosis in the proximal region of the subclavian artery was detected. In her dynamic angiography examination, a critical stenosis at the proximal segment of left subclavian artery in a length of 40 mm was detected (Video 2). A 7- and 6-Fr sheaths were placed in the right and left femoral arteries, respectively, using the percutaneous Seldinger technique under local anesthesia. Subsequently, a pigtail catheter was placed at the level of the aortic

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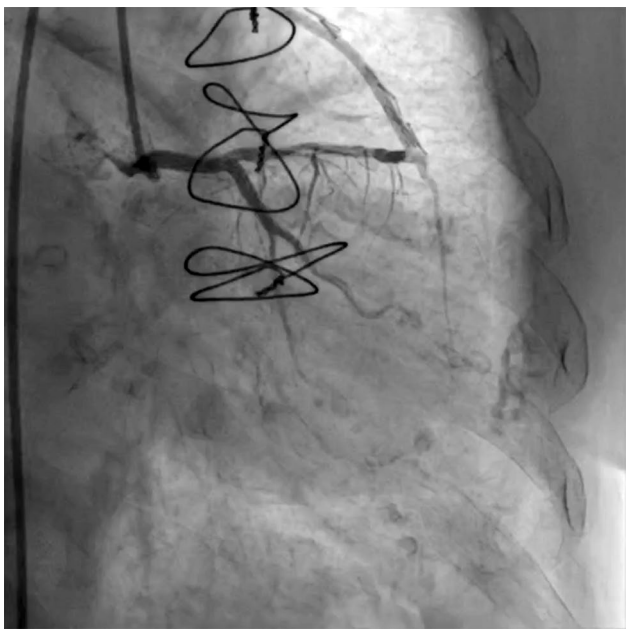
Citation:
Şahin A, Taştekin T, Kocaoğlu AS, Dural M, Dernek S. Coronary subclavian steal syndrome: A case report. Cardiovasc Surg Int 2021;8(1):63-67.

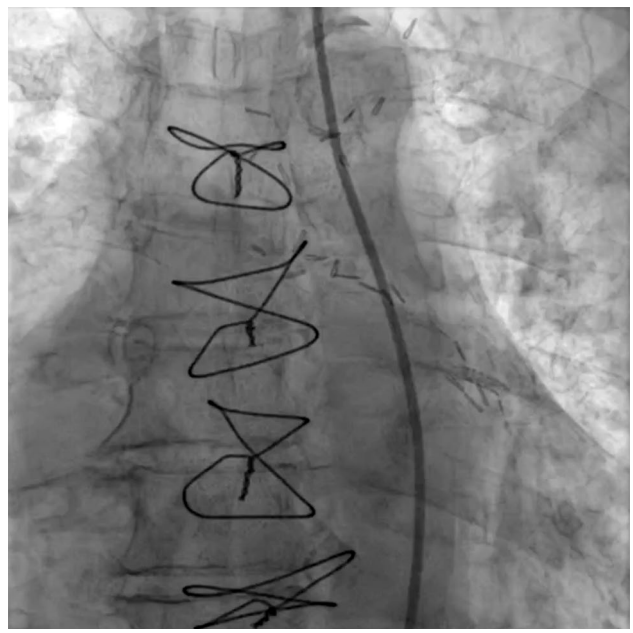
arch and a vertebral catheter was inserted to subclavian artery. Access to the brachial artery level was achieved by crossing the stenotic vascular segment using a hydrophilic guide wire (035"). Contrast infusion through the pigtail catheter revealed a stenotic segment of dissection, which was marked. A peripheral vascular self-expandable stent (8 mm × 40 mm × 120 cm) was appropriately placed in the relevant segment (NAVALIS®, Tsunamed Inc., Hamburg, Germany). The stent and ostium of the left subclavian artery in the aortic arch were expanded under 6 atmosphere pressure using an 8 mm × 60 mm × 135 cm drug-coated percutaneous transluminal angioplasty (PTA) balloon (RD Global Inc., Ankara, Turkey) (Video 3).

Control angiography revealed that the dissected stenotic segment was corrected, and complete patency was achieved (Video 4). The reverse flow in the LIMA graft corrected to the proper direction and the flow was sufficient (Figure 1). No any complication occurred after the intervention. As for medical therapy, acetyl salicylic acid 100 mg and clopidogrel 75 mg was continued. In the post-procedure early follow-up of the patient, the chest pain and the effort-related angina pectoris has relieved. The first-month computed tomography angiography (CTA) revealed full patency of the left subclavian artery and the LIMA. After one year, the patient has been still asymptomatic. A written informed consent was obtained from the patient.

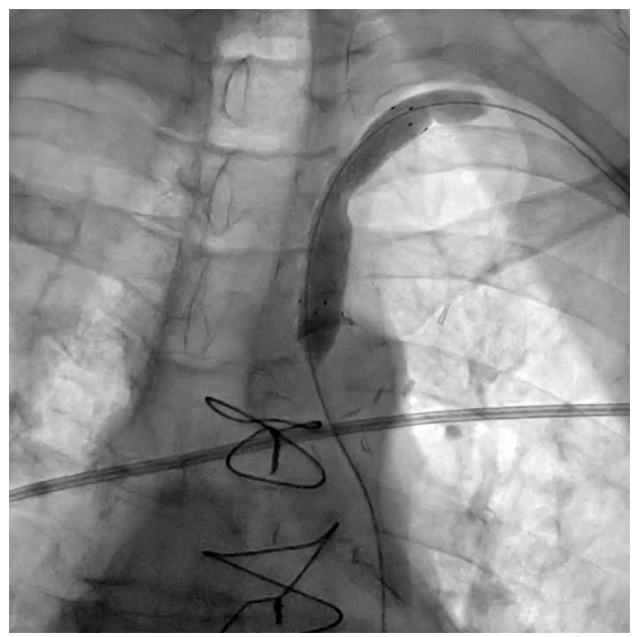


Video 1. Coronary steal syndrome from LAD-to-LIMA-to-subclavian artery.

LAD: Left anterior descending; LIMA: Left internal mammary artery.

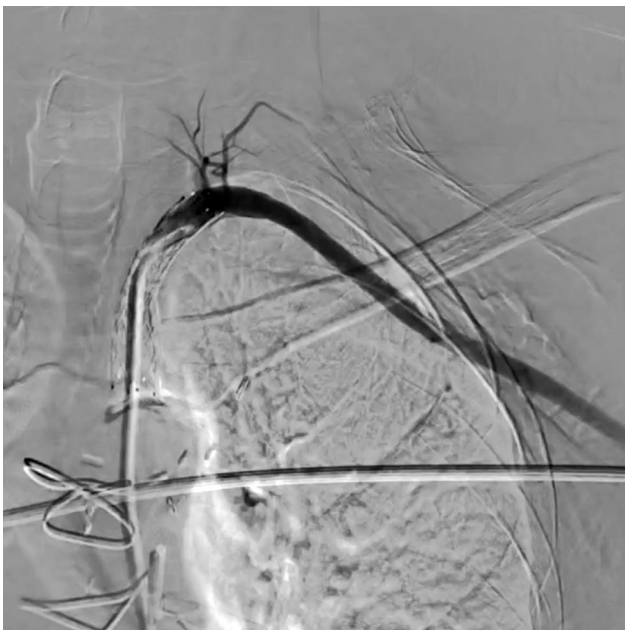


Video 2. The stenosis detected before the procedure in the proximal left subclavian artery.



Video 3. An 8 mm × 60 mm × 135 cm drug-coated PTA balloon application after self-expandable stent on the 8 mm × 40 mm × 120 cm balloon.

PTA: Percutaneous transluminal angioplasty.



Video 4. Removal of the stenosis in the subclavian artery after the procedure and showing the filling in the LIMA.
LIMA: Left internal mammary artery.

DISCUSSION

Atherosclerosis is the major etiological factor of subclavian artery stenosis (SAS), while less common factors are embolic occlusions, infections, radiotherapy, arteritis, and external pressure (i.e., tumors and thoracic outlet syndrome).[4,5] If there is a three-vessel or left main coronary artery disease, the SAS prevalence reaches 5.3%.[6] Subclavian steal syndrome results from stenosis or complete occlusion in the pre-vertebral artery region of the subclavian artery.[7] This phenomenon is stealing coronary flow to subclavian artery via LIMA. In patients undergoing CABG with the LIMA, long-term patency rates are higher than that of saphenous vein or radial artery. Therefore, the use of LIMA is recommended for every suitable patient.[8,9] There should be SSS or occlusion for coronary steal syndrome with LIMA. Although it is not common in the society, it can be seen in CABG patients.[10] Shadman et al.[10] reported that the rate of SSS ranged from 1.9 to 7.1% in four cohorts (n=4,223). English et al.[6] also reported that there was 5.3% SSS in 492 CABG patients undergoing cardiac catheterization. If peripheral arterial disease was present, the prevalence of SSS increased up to 11.8%. However, evaluating the LIMA through the left subclavian artery during coronary angiography in patients who are considered for CABG surgery is still controversial.[7,8]

Screening for SAS has been advocated by some authors,[7,11] as CSSS has a potential to cause stable angina, ST elevation infarction, arrhythmias, or sudden death resembling to other coronary artery syndromes.[7,12,13] Vertigo, dizziness, syncope, extremity hypo-paresthesia, and visual-auditory disturbances may be the symptoms of CSSS.[1,7,9,12] Physical evaluation is critical to make a decision for the evaluation of the LIMA and subclavian artery. Arterial blood pressure difference between the upper extremities can simply reveal a SAS.[14,15] However, some limitations, such as bilateral SAS, arrhythmias, or non-simultaneous measurement, can lead to a misleading SAS decision. More objective evaluation should be performed for a certain diagnosis of SAS.

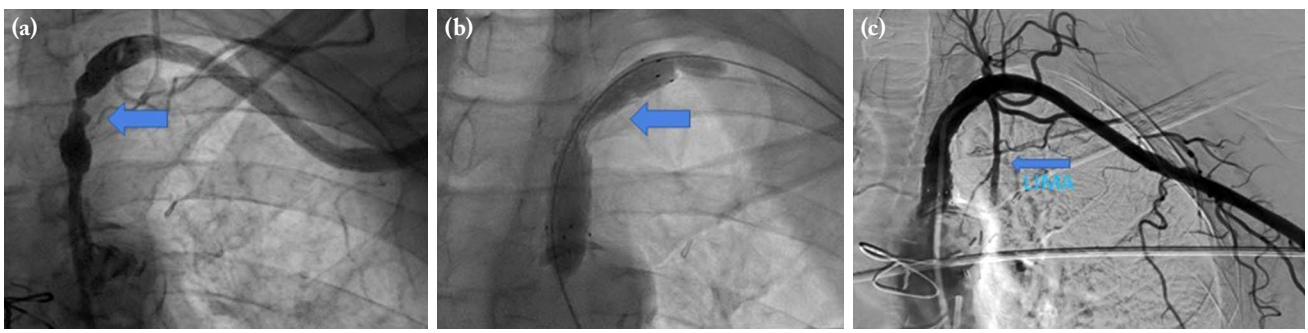


Figure 1. **(a)** The stenosis detected before the procedure in the proximal segment of left subclavian artery. **(b)** An 8 mm × 60 mm × 135 cm drug-coated PTA balloon application after self-expandable stent implantation on the 8 mm × 40 mm × 120 cm balloon. **(c)** Removal of the stenosis in the subclavian artery after the procedure and showing the filling in the LIMA.
LIMA: Left internal mammary artery; PTA: Percutaneous transluminal angioplasty.

In two different studies, Lapropoulos et al.[5] and Tamura et al.[16] showed a very close correlation between SSS and >20-mmHg pressure difference between the arms. In the English et al.'s[6] meta-analysis, a 10-mmHg pressure difference showed a strong association with SAS (<50%). On the other hand, Shadman et al.[10] reported that a 15-mmHg pressure difference was enough for SAS. However, the main limitation of blood pressure measurement is that it is an indirect measurement. In our case, there was a systolic pressure gradient of 25 mmHg and imaging was needed to confirm the diagnosis of SSS. Arterial Doppler ultrasonography is one of the most useful, cost-effective, and sensitive diagnostic tool for the detection of SAS.[17,18] However, conventional angiography is still the gold-standard for the diagnosis in most patients. The CTA is also used quite frequently. Physical evaluation showed SAS in our patient, and the diagnosis was confirmed by further examination. In the event that the reverse flow of LIMA is evaluated, conventional angiography should be performed for LAD.

In patients whose anginal complaints begin or continue after CABG, coronary angiography is recommended to evaluate the subclavian artery together with the LIMA-LAD anastomosis. In patients with stenosis of the proximal subclavian artery, the LIMA-LAD flow is impaired and ischemia is detected in the region of LAD artery on myocardial perfusion scintigraphy.[2,11] The absence of LIMA flow is seen in subclavian artery occlusion.[4,7,19]

An axillary-to-axillary or carotico-subclavian bypass are major surgery techniques for the treatment of SAS.[7,14] Percutaneous transluminal angioplasty and subclavian artery bypass surgery associated with stenting are the most commonly used methods in the treatment of SSS. The PTA is preferred owing to its low morbidity and shorter hospital stay.[4,20,21] Also, in the 2017 European Society of Cardiology (ESC) guidelines, both revascularization options (stenting or surgery) should be considered and discussed case by case according to the lesion characteristics and patient's risk.[22] In a study, the stroke rate was 2.6% and 2.4% who were treated by PTA and open surgery, respectively.[23] In such cases, endovascular treatment is mostly the preferred strategy.[21-23] In a retrospective study conducted by De Vries et al.,[24] the success of PTA and stenting was 93%, and the patency rate was 93% after three years. Although the carotico-subclavian artery bypass surgery method is relatively less frequently performed, the success rate was reported as 98%, with a 10-year patency rate of around 95%.[19] In the study by Jahic et al.,[25] PTA treatment was performed in 22 of 26 patients, and a 100% patency rate was achieved within one-year follow-up. As a result of this study, PTA treatment was suggested for those with subclavian stenosis, while surgical treatment was recommended for those with obstruction.[25]

In recent years, new laser cutting balloon therapies and drug-coated balloon therapies have been developed.[9,26] Self-expendable stents have more stronger radial force and easier to deploy in more calcific lesions.[9,25] Medical therapy after PTA or surgery is similar. Antiaggregant-based therapy (acetylsalicylic acid and clopidogrel) is the mainstay, although patient-based individualized therapy is always the primary preference. Anticoagulant therapy can be prescribed in cases who has a concomitant atrial fibrillation or a hypercoagulation state.[9,19,27] In this case, we preferred PTA treatment, due to the advanced age of the patient and the presence of a stenosis rather than a complete occlusion of the subclavian artery. Additionally, the lesion was deemed suitable for a percutaneous intervention.

The literature consists controversial issues. First and more controversial of them is the performance of a subclavian artery and LIMA imaging during preoperative angiography. The second issue is using the LIMA in patients receiving a surgical or endovascular intervention for SAS.[4,24] However, in a study, CABG with LIMA was performed at the same day of successfully treated SAS patients and the authors used acetylsalicylic acid after CABG.[28] The third is the treatment selection: surgery versus PTA. The literature review reveals that patient-based selection is more important and both surgery and PTA treatment are safe.[4,7,22]

In conclusion, although coronary SSS is rare, it is a critical syndrome due to its possible role in the disruption of myocardial perfusion and development of angina pectoris and symptoms of dyspnea. Percutaneous treatment is safe and effective in eligible cases. We recommend physical examination of SAS for CABG candidates preoperatively and angiographic evaluation of the subclavian artery in patients who has a concomitant peripheral arterial disease.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2021;8(1):68-69
http://dx.doi.org/DOI: 10.5606/e-cvsi.2021.969
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Cardiovascular Surgery and Interventions

How to do it? Open Access

Aortic sponge sling to improve mitral exposure

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Received: September 17, 2020 ***Accepted:*** February 17, 2021 ***Published online:*** March 29, 2021

ABSTRACT

Superior septal approach provides the best exposure of the mitral valve and is the preferred approach for mitral valve procedures. In the presence of the larger aorta, surgical exposure may be impeded during mitral valve surgery, even for forcefully suction of the aortic vent. Herein, we describe a simple maneuver to avoid this problem. Previously prepared a long sponge sling passed from transverse sinus after a cannulation procedure is completed and the slinged sponge is retracted leftward and superiorly immediately after aortic cross-clamping and cardioplegia infusion.

Keywords: Larger aorta, sponge sling, superior septal approach.

Superior septal approach provides the best exposure of the mitral valve. It is a preferred approach for all mitral operations.[1-3] The incision on the left atrial dome is sometimes advanced to the beneath of the ascending aorta. Ascending aorta (particularly a large aorta of >4 cm in size) may impede surgical exposure during mitral valve surgery. Despite forcefully aortic suction, mitral exposure cannot be sufficient in some cases. Herein, we describe a simple technique to avoid this unfavorable condition.

SURGICAL TECHNIQUE

Long sponge sling is passed from the transverse sinus after cannulation is completed (Figure 1a). The sling sponge is retracted leftward and superiorly immediately after aortic cross-clamping and cardioplegia infusion (Figure 1b). The sling is released during the subsequent cardioplegia administration. This simple maneuver easily improves the surgical exposure of the left atrial dome and, then, extended left atriotomy can be done more comfortably.

DISCUSSION

Although superior septal approach provides a better exposure, it carries certain limitations such as arrhythmias and bleeding. In particular, the dome of the left atrium has a friable tissue. Direct primary closure may cause suture disruption and intimidating bleeding. Using our technique, we sutured the dome of the left atrium by pericardial buttressed sutures to avoid suture disruption and bleeding. Most surgeons do not use any retractors for extended left atrial mitral exposure. Four/six pledgeted sling sutures are placed

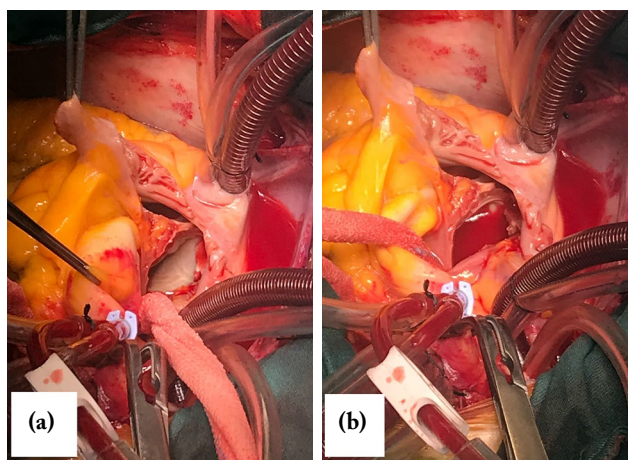

Figure 1. **(a)** Sponge sling passing from transverse sinus immediately after cannulation. **(b)** Sponge sling retracting leftward and superiorly immediately after aortic cross-clamping and cardioplegia infusion.

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Citation:
Şahin MA, Kuralay E. Aortic sponge sling to improve mitral exposure. Cardiovasc Surg Int 2021;8(1):68-69.

into the interatrial septum and left atrial dome in both sides. However, the ascending aorta may impede surgical exposure, despite these pledgeted sling sutures. Automatic retractor system or Cosgrove mitral valve retractor or vein retractors (Kapp Surgical Instrument, Inc. Cleveland, OH, USA) can also be used to improve mitral valve exposure. However, additional retractors may not only increase the cost of surgery, but also disrupt the surgical field with instrument clutter and needs extra-hand. Retraction of the ascending aorta leftward and superiorly by sponge sling improves the surgical field until the root of the left atrial auricula. Based on our experience, our simple maneuver ensures a better surgical mitral exposure.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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