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Book: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Gleen's thoracic and cardiovascular surgery. 1st ed. London: Appleton&Lange; 1991.

Book Chapter: Weinberg PM. Aortic arch anomalies. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ (eds). Moss and Adams' heart disease in ınfants, children, and adolescents. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 707-735.

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Retrospective Analysis of the Experience in Diagnostics and Surgical Treatment of Rare Cardiac Tumors-Lipomas

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Abstract

The aim of this study is to determine the optimal treatment tactics for cardiac lipomas by performing a retrospective analysis of the features of the clinical course, diagnostics and specifics of surgery for this pathology. At Amosov NICVS, in the period from 1969 to 01.01.2020, 968 patients with various types of cardiac tumors underwent surgical treatment, of which 36 patients were with non-myxomas benign tumors. Cardiac lipoma diagnosed in three cases (0.3%). The described cases demonstrate a significant risk of heart damage by benign neoplasms (lipoma), the operability of neoplasm is largely determined by the localization and volume of myocardial involvement. In the two cases described, a lipoma due to the localization in the left ventricle and right ventricle walls and transmyocardial penetration of the neoplasm led the risk of rupture of the penetrated walls of the ventricles and to almost incurable arrythmias. Surgical tactics for these neoplasms should be based on the size of the tumor, its location and the presence of obvious hemodynamic disturbances due to the obstructive form of the neoplasm.

Keywords: Benign heart tumors, lipoma, surgical treatment

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Introduction

Benign neoplasms account for 75-80% among cardiac tumors, of which myxomas are detected in 75-80% of cases[1-4]. Non-myxomas benign cardiac tumors (NBCTs) account for up to 3.5% of all primary heart tumors[5-7]. Cardiac lipoma is a very occasional variant among primary benign cardiac tumors; we can see rare mentions of this pathology in literary sources[8-10]. Cardiac neoplasms lead to clinical manifestations such as heart failure, embolic complications, arrhythmias and dysfunction of the heart valves, which, in some cases, can be life-threatening. The clinical picture in this pathology is very variable. Despite modern diagnostic methods, it can be challenging to identify a cardiac tumor. Moreover, determining the adequate treatment tactics (especially preoperative management and planning) is of a particularly difficult task for heart team.

Since 1969 to 2020 there were 36 patients with NBCTs, who undergone surgery in Amosov National Institute of Cardiovascular Surgery of the Academy of Medical Sciences of Ukraine (Amosov NICVS). Three of these patients had cardiac lipomas (8.3%). Clinical and pathological aspects, as well as the tactics of surgical intervention are of special interest to cardiac surgeons and cardiologists due to the rare occurrence of this type of tumor.

The aim of this study is to determine the optimal treatment tactics for cardiac lipomas by performing a retrospective analysis of the features of the clinical course, diagnostics and specifics of surgery for this pathology.

Materials and Methods

As of 01.11.2019, 968 patients with primary cardiac tumors were observed in Amosov NICVS. In the vast majority of cases (862) myxomas of the heart were detected, in the rest (36) there were other benign neoplasms. Cardiac lipoma was diagnosed only in three cases, which amounted 0.3% among all primary cardiac tumors.

Among patients with NBCT there were 13 men (36.1%) and 23 women (63.9%). The average age of patients was 37.6±24.6 years (range: 1-56). The duration of the disease averaged 4.5±2.3 months (1-16), (according to the first clinical manifestations).

Clinical manifestations included heart pain - 6 (16.7%), shortness of breath - 8 (22.2%), fatigue - 7 (19.4%), fever 5 (13.9%), weight loss 4 (11.4%), heart rhythm disturbances - 5 (13.8%) and limb plegia as a consequence of cerebral vascular embolism - 2 (5.6%). Localization of different variants of NBCT determined the type of clinical manifestations (Table 1).

Table 1. Localization of non-myxomas benign cardiac tumors

Type of NBCT		Localization				Total	
		LA	LV	RA	RV	n	%
Leiomyofibroma		-	-	2	1	3	8.3
Fibroma		1	2	-	1	4	11.1
Rhabdomyoma		-	1	-	7	8	22.2
Lipoma		-	1	1	1	3	8.3
Hemangioma		21	1	2	3	8	22.2
Papillary fibroelastoma		5	4	-	-	9	25
Immature teratoma		1	-	-	-	1	2,7
Total	n	9	9	5	13	36	100.0
	%	25	25	13.9	36.1	100.0	-

NBCT: Non-myxomas benign cardiac tumors, LA: Left atrium, LV: Left ventricle, RV: Right ventricle, RA: Right atrium, n: Number

In one patient cardiac lipoma was identified in the right atrium (RA), in the second and the third patient lipomas were detected in right ventricle (RV) and left ventricle (LV). In all three cases, there were fatigue at light exertion and shortness of breath. Examinations of these patients revealed an enlargement of the cardiac silhouette on a frontal chest X-ray in two patients (in case of LV and RV lipomas), one patient had sinus tachycardia, two patients had atrial fibrillation. Such imaging techniques as echocardiography and computed tomography (CT) allowed us to identify a mass, differentiate it from vegetations and trombi, determine its attachment point, mobility, structure, the extent of involvement of cardiac structures, as well as the degree of hemodynamic disturbances.

Results

We present the results of three clinical observations of patients with heart lipomas in Table 2.

1. The first case is of the RA lipoma. A thirty years old female patient was hospitalized to Amosov NICVS on 01.30.1985 with a diagnosis of mitral-tricuspid insufficiency. The complexity of the diagnosis was that there was no technical possibility to perform echocardiography at that time at Amosov NICVS. The ECG examination revealed atrial fibrillation, impaired intraventricular conduction, RV hypertrophy and diffuse changes in the myocardium. Cardiac catheterization demonstrated filling defect in a significantly enlarged RA. During surgery, a 20×15 cm lipoma was detected, which was removed with the wall of the RA in the area of the atrial fissure. The defect in the RA wall was sutured using Teflon patches. In early post-operative period normal sinus rhythm was recorded. However, atrial fibrillation resumed 6 months later. Sudden death because of fatal arrhythmia (ventricular fibrillation) happened in this patient 11 years later (according to the report of cardiologist at the place of patients' residence).

2. The second case is of RV lipoma. A 34 years old male patient was hospitalized on 22.09.2003 to Amosov NICVS with complaints on shortness of breath, intermittent chest pain. There were no signs of congestive heart failure and there were no pathological changes in other organs and systems, as well as in laboratory test. There was atrial fibrillation with a frequency of 57 beats per minute detected on the electrocardiogram (ECG).

According to transthoracic echo (TTE) data, the tumor was detected in RV cavity as an echopositive, sedentary mass with indistinct contours. Transesophageal echo was performed due to the low informativeness of TTE to clarify the place of attachment of the tumor, the width of its base and its location relative valve apparatus (Figure 1). In the area of RV apex, an irregularly shaped mass, without clear contours was detected, with the tumor size 4.1x3.2 cm, which did not cause obstruction to the tricuspid valve and to RV outflow tract. Tumors place of attachment was the interventricular septum, RV apex and RV free wall were, which indicated a significant area of tumor invasion to the RV walls. Patency of the tricuspid valve was maintained

Table 2. Clinical manifestations and research data of cardiac lipomas

No	Sex	Localization	Clinical symptoms	Heart failure	Increased cardiac shadow	Arrhythmia	Surgical treatment
1.	F	RA	+	+	++	+ (AF)	Radical resection
2.	M	RV	+	+	+	+ (AF)	Partial resection
3.	F	LV	+	+	-	+	Surgical biopsy; heart transplantation

RV: Right ventricle, RA: Right atrium, AF: Atrial fibrillation, F: Female, M: Male

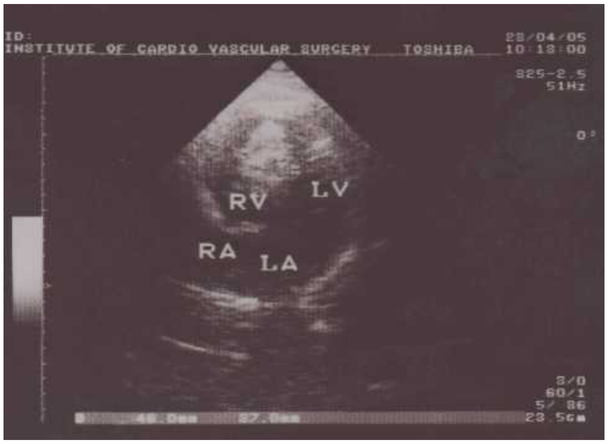

Figure 1. Transthoracic ECHO of patient B. Tumor in the RV apex

RV: Right ventricle, ECHO: Echocardiogram

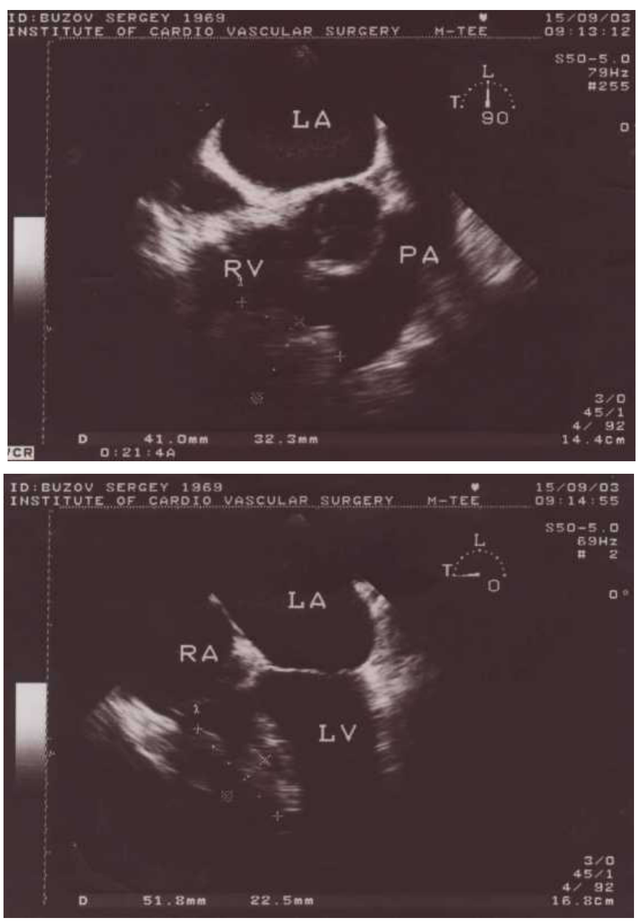

Figure 2. Transesophageal ECHO of patient B. Tumors place of attachment was the interventricular septum, RV apex and RV free wall were, which indicated a significant area of tumor invasion to the RV walls

RV: Right ventricle

(Figure 2).

Endovascular biopsy was unsuccessful. During angiography an additional sedentary, with a large tuberous surface neoplasm was identified in RV cavity. The mass was attached to trabecular section of the RV and occupied most of the ventricular cavity. RV inflow and outflow tracts had no obstruction.

However, the patient, at his request, underwent surgery only in a year and a half, on the background of atrial fibrillation and recurrent ventricular fibrillation. The newly performed cardiac ventriculography revealed an increase of the filling defect in the RV cavity, also the neoplasm's spread in the direction to tricuspid valve was noted, with the threat of its subsequent obstruction.

Partial resection of the tumor from the RV cavity in condition of artificial blood circulation was performed on 05.11.2005. During surgery a yellow mass, with a dense-elastic consistency was found in the apex of the significantly enlarged RV, towering above its surface in the form of a mushroom with a round base with the tumor

Figure 3. RV lipoma, localized in its apex, extending into the RV cavity. Coronary vessels pass on both sides of the neoplasm, tightly adjacent to the tumor

RV: Right ventricle

size 5.5x5.5 cm (Figure 3). Coronary vessels passed on both sides of the neoplasm and were tightly adjacent to the tumor. The tumor spread to the interventricular groove and the LV apex under the epicardium. The RV was revised by access through the RA and tricuspid valve. Similar yellow color dense elastic mass blocked most RV cavity, tightly fused within the RV walls and caused involvement of the papillary muscles and partially the tricuspid valve chordae. RV inflow and outflow tract were patent. Thus, the detected neoplasm replaced the RV wall over a large area, deforming its cavity and rising above the surface of the heart.

The tumor was partially removed from the RV and sent for histological examination. The tricuspid valve remained intact. Partial mobilization of the anterior interventricular artery in the most suspicious place for its possible deformation by the tumor was done. Further surgical manipulations on the heart were considered dangerous and unpromising. An ECG in early postoperative period showed the presence of an acute complete right bundle branch block, subendocardial hypoxia of the myocardium, migration of driver of rhythm with a transition to atrial fibrillation, frequent ventricular ectopy extrasystole. In the further postoperative observation, there was a repeated alternation of atrial fibrillation and sinus rhythm. In the long-term period, the patient had atrial fibrillation. From the questionnaire, it has known that the rhythm disturbance led to the sudden death of the patient 13 years after the surgical treatment.

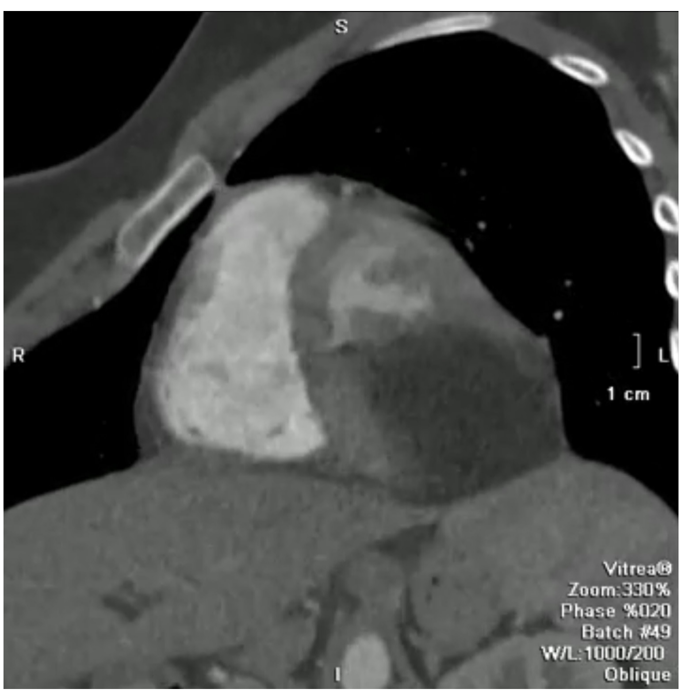

Figure 4. CT scan of the heart of a 19-year-old patient presented in 2011. The short axis of the CT of the heart shows a gigantic, well-defined mass with a fat density (-110 H.U), which replaces and splits the myocardium of the inferior and inferolateral left ventricular segments at the basal and mesoventricular level
CT: Computed tomography

3. The third case is of LV lipoma. Twenty-seven years old female patient, was hospitalized on 22.03.2019 to Amosov NICVS with a diagnosis of a LV tumor. From the anamnesis, it is known that since 2011 the patient had been suffering from cardiac arrhythmia (paroxysmal tachycardia attacks). On CT transmural LV tumor (presumably lipoma) was identified in lateral segments (Figure 4). The clinical condition of the patient was quite satisfactory, and therefore surgical treatment at that time considered inappropriate.

However, rhythm disturbances continued and, during pregnancy in 2018, their frequency increased. The defibrillator was implanted in the patient in 2018 because there were attacks of ventricular tachycardia. With repeated echo, a motionless mass associated with its lateral wall was detect in the LV. Physical examination and laboratory tests did not reveal any pathological abnormalities. There was sinus rhythm on the ECG, the heart rate was 80 beats per minute.

Because of ongoing bouts of arrhythmia, that did not respond well to therapeutic treatment, the patient was sent to the intensive care unit after delivery by Cesarean section in the Amosov NICVS. There were recorded the daily defibrillator responses.

At CT study, which was performed on 2019, a tumor rupture was detected. This was probably due to the reduced resistance of adipose tissue compared to the myocardium to high pressure in the LV cavity (Figure 5). Also, involvement of papillary muscles by cardiac lipoma was noted. These data were regarded as a threat of rupture of the heart wall. Multiplanar reconstructions demonstrated the localization of tumor, the degree of involvement by lipoma of LV walls and papillary muscles, which did not leave any hope for removal of the neoplasm (Figure 6). In this regard, it was decided to perform a biopsy of the tumor tissue to clarify its histological type with a further decision on the issue of heart transplantation.

After performing left thoracotomy on 04.01.2019 (aimed at removing a neoplasm fragment for histological examination), the pericardium was opened. The pale-yellow color neoplasm of dense-elastic consistency, with smooth contours up to 5.5 cm in diameter, was located on the lateral surface of the LV, starting from the circumflex artery (Figure 7).

Visual and palpation examinations made it possible to preliminarily determined the massive lipoma penetrating the LV wall by the infiltration area up to 5 cm, the radical removal of which could lead to irreversible damage of the heart structures and coronary arteries. The diagnosis of lipoma was confirmed by histological examination. In

Figure 5. CT scan of the heart of 27 years old patient, performed a week after the Cesarean section in 2019. The short axis of the CT scan of the heart shows a contrast leak into the giant tumor of the LV. Implantable cardioverter-defibrillator diverted to the RV

CT: Computed tomography, LV: Left ventricle, RV: Right ventricle

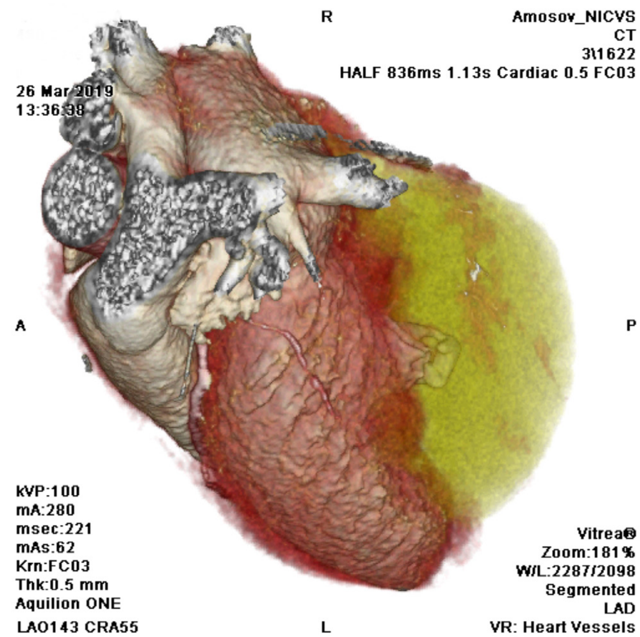

Figure 6. Three-dimensional reconstruction of a cardiac CT study demonstrates the leak of contrast medium into a giant tumor of the LV with a fat density (marked in yellow)

CT: Computed tomography, LV: Left ventricle, LAD: Left anterior descanding artery

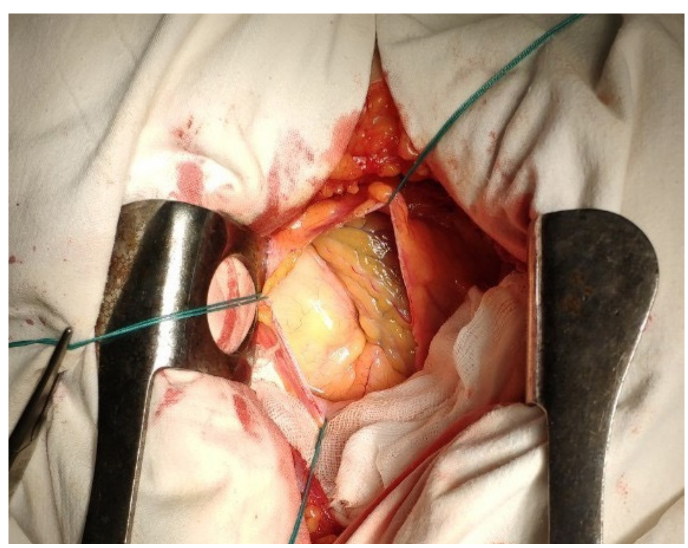

Figure 7. Lipoma of the LV, localized in the region of its lateral wall, extending into the cavity of the heart

LV: Left ventricle

the postoperative period, the patient was in intensive care unit because of ongoing frequent attacks of ventricular tachycardia, which relieved by discharges of the implanted defibrillator.

On the 10th day after the operation the patient was discharged and sent to the specialized heart surgery center, where a heart transplant was subsequently performed. In the long-term postoperative period (1.5 years after heart transplantation), the patient's condition was satisfactory.

Thus, analysis of all three cases of heart lipomas showed, that cardiac arrhythmias were the leading clinical manifestation of the disease, which was refractory to drug treatment. All three patients underwent surgical treatment: in the first and second cases - with the use of cardiopulmonary bypass, in the third case – as a first step a biopsy was performed by surgery, and then heart transplant was performed.

In the long-term postoperative period, arrhythmias were fatal in the first and second patients 11 and 13 years after surgery, respectively. With a high degree of probability, it can be judged that in these cases, the removal of the tumor (lipoma) was not performed radically. Subsequently the neoplasm continued to affect the conducting system, causing persistent arrythmias. This complication was avoided by performing a heart transplant in the latter case.

Discussion

A retrospective analysis of these cases demonstrates the possibility of diagnosing of cardiac tumors. In 1985 there were not standard diagnostic methods as echo or CT in the Amosov NICVS. Diagnosis was based on physical findings, ECG and angiography. Most authors recognize ultrasound as the basis for diagnosing this pathology (2-8). Two subsequent cases, when echo was used, supplemented by CT to clarify the extent of tumor spread and determine the treatment plan, confirmed this, which is also affirmated in the study by Lestuzzi et al.[(7)] Echo is decisive for differential diagnosis of lipomas (0.3%) with the most common cardiac tumors - myxomas. In the differential diagnosis it is important to take into account: 1) tumor localization - in 752 (87.8%) cases myxomas were located in the LA; 2) the mobility of the neoplasm detected on echo in 587 (68.1%) during the cardiac cycle; 3) variability of the auscultatory picture when changing the position of the body, as well as fainting conditions, which occurred in 185 (21.5%) of patients, were typical clinical symptoms of myxoma.

In their study, Pacini et al.[(11)] indicates that the improvement of echo methods contributes to more detailed and accurate information, which allows cardiologists and cardiac surgeons to better assess the condition of patients in the long term. According to Oliveira et al.[(12)] early diagnosis of cardiac tumors, and, accordingly, patient survival, depends on an increase in the frequency of use of imaging research methods - echo and CT, while early, sometimes - accidental detection of these neoplasms can facilitate treatment with better results than in situations where the diagnosis is based primarily on the presence of symptoms.

The optimal tactics for surgical treatment of cardiac tumors is radical removal of the neoplasm[(1-5)]. However, in certain situations, when there is a large volume of penetration of the pathological process into the myocardium, such removal of the tumor can have fatal consequences, and is limited to hemodynamic correction and reconstruction of lesions of the valve structures.

In the analysis of literature data, one can see single mentions of lipomas among cardiac neoplasms. Thus, in a study by Li et al.[(9)] describes 2 cases out of 399 operations for cardiac tumors, Isogai et al. [(10)] - three of 914 cases, Hoffmeier et al.[(8)] mention one out of 181 cases of this pathology. Analysis of the experience of Amosov NICVS demonstrates a significant danger of heart damage by such neoplasms as lipomas. The operability of neoplasm is largely determined by the localization and volume of myocardial involvement. A histologically benign tumor - lipoma due to the localization and transmyocardial penetration of the neoplasm (into LV and RV walls) led to almost incurable arrythmias in all described cases. Moreover, due to the threat of the penetrated by tumor ventricular walls rupture, patients had direct indications for urgent heart transplantation. The case of atrial localization of the lipoma was also distinguished by its aggressive course and, despite the resection of the neoplasm (probably, partial removal), there was fatal arrythmia 11 years after the surgery. Analyzing retrospectively, we can come to the conclusion that the need for heart transplant could have taken place in all three cases.

Conclusion

1. Diagnosis of benign heart tumors, and in particular lipomas, is extremely difficult, due to the absence of pathognomonic signs of the disease and, often, an asymptomatic course. In addition, in some cases, there may be no noise manifestations of the disease (on auscultation), even with a high degree of cardiac involvement. In most of the cases different arrhythmias are the only manifestation of the disease.

2. Surgical tactics for these neoplasms could be bases on the size of the tumor, its location and the presence of obvious hemodynamic disorders due to the obstructive form of neoplasm. Despite the fact that a lipoma is a benign tumor, the nature of its growth with frequent intramural localization does not allow for its complete resection, and the natural course can manifest itself as fatal cardiac arrhythmias. The only method of radical treatment for such patients may be a heart transplantation.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.M.V., V.V.I., D.M.D., Concept: R.M.V., V.V.I., Design: D.M.D., V.F.O., Data Collection or Processing: V.V.I., V.F.O., M.A.T., Analysis or Interpretation: D.M.D., M.A.T., I.V.M., O.A.P., Literature Search: D.M.D., I.V.M., M.A.T., O.A.P., Writing: R.M.V., V.V.I., D.M.D.

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References

1. Boyacıoğlu K, Ak A, Dönmez AA, Çayhan B, Aksüt M, Tunçer MA. Outcomes After Surgical Resection of Primary Non-Myxoma Cardiac Tumors. Braz J Cardiovasc Surg 2018;33:162-8.
2. Burke A, Tavora F. The 2015 WHO Classification of Tumors of the Heart and Pericardium. J Thorac Oncol 2016;11:441-52.
3. Cresti A, Chiavarelli M, Glauber M, et al. Incidence rate of primary cardiac tumors: a 14-year population study. J Cardiovasc Med (Hagerstown) 2016;17:37-43.
4. Lau C, Leonard JR, Schwann AN, et al. A 20-Year Experience With Resection of Primary Cardiac Tumors and Metastatic Tumors of the Heart. Ann Thorac Surg 2019;107:1126-31.
5. Hudzik B, Miszalski-Jamka K, Glowacki J, et al. Malignant tumors of the heart. Cancer Epidemiology 2015;39:665-72.
6. Mkalaluh S, Szczechowicz M, Torabi S, et al. Surgical Treatment of Cardiac Tumors: Insights from an 18-Year Single-Center Analysis. Med Sci Monit 2017;23:6201-9.
7. Lestuzzi C, De Paoli A, Baresic T, Miolo G, Buonadonna A. Malignant cardiac tumors: diagnosis and treatment. Future Cardiol 2015;11:485-500.
8. Hoffmeier A, Sindermann JR, Scheld HH, Martens S. Cardiac tumors--diagnosis and surgical treatment. Dtsch Arztebl Int 2014;111:205-11.
9. Li T, Liu C, Luo Y, et al. Retrospective analysis of 11 cases of primary cardiac valve tumors. Anatol J Cardiol 2019;21:11-7.
10. Li S, Gao Ch. Surgical Experience of Primary Cardiac Tumor: Single-Institution 23-Year Report. Med Sci Monit 2017;23:2111-7.
11. Pacini D, Careddu L, Pantaleo A, et al. Primary malignant tumors of the heart: Outcomes of the surgical treatment. Asian Cardiovasc Thorac Ann 2015;23:645-51.
12. Oliveira GH, Al-Kindi SG, Hoimes C, Park SJ. Characteristics and Survival of Malignant Cardiac Tumors: A 40-Year Analysis of >500 Patients. Circulation 2015;132:2395-402.

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Outcomes of Cardiac Resynchronization Therapy in Heart Failure Patients and Effect of MAGGIC-HF Score on Prognosis

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Abstract

Objectives: Cardiac resynchronization therapy (CRT) has recently become a significant treatment option in patients with heart failure (HF), who do not respond to optimal medical treatment. In this study, we aimed to evaluate the long-term prognosis of CRT and to determine the relationship between the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC-HF) risk score and CRT.

Materials and Methods: One hundred and ten consecutive patients who underwent CRT between 2015 and 2019 were analyzed retrospectively. Baseline characteristics of the patients were recorded and clinical parameters including laboratory, electrocardiographic and echocardiographic were compared before CRT implantation and during patient follow-up. The patients were classified as surviving patients and patients without survival according to the 2-year clinical outcome. The improvement in echocardiographic parameters observed at the 6th month after CRT in surviving patients was defined as a positive response to CRT.

Results: The patients with survival had lower pulmonary artery systolic pressure (PASP) (34.66±18.31 vs 46.50±15.86 p=0.01) and higher left ventricular ejection fraction (LVEF) than patients without survival (27.00±5.86 vs 23.89±5.32 p=0.04). After 6 months from CRT implantation, the improvement of LVEF and PASP and decrease in left ventricular

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Abstract

diameters were found in patients with survival (p=0.015). In addition, there was a weak correlation between MAGGIC risk score levels and hospitalizations in this study population (p=0.031, r=208)

Conclusion: Predictors of long-term survival in CRT treatment are basal LVEF and PASP levels. Basal LVEF is important in the positive response to CRT.

Keywords: Cardiac resynchronization therapy, heart failure, prognosis

Introduction

Heart failure (HF) is still an important health problem today. Despite the positive improvements in treatment, it is associated with poor prognosis and mortality[(1)]. Cardiac resynchronization treatment (CRT) is one of the invasive treatment methods widely used in patients with HF in recent years, and many studies have shown that CRT is an effective treatment method for increasing quality of life and functionality and improving survival. CRT is recommended for patients with unresponsiveness to medical treatment, poor New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) <35% and QRS duration ≥130 ms[(2,3)]. However, the benefit required from CRT may not be seen in 1/3 of the patients. Therefore, it is important to identify patients who will not benefit from CRT due to high cost-effectiveness[(4)]. Before CRT implantation, examining the clinical-demographic characteristics of patients who respond positively to CRT and evaluating echocardiographic, electrocardiographic and laboratory parameters may play an important role in the selection of candidates for this treatment. In addition, various HF risk models may be used to determine the survival after CRT and positive response to CRT in patients with HF. One of these risk models is the MAGGIC-HF (Meta-Analysis Global Group in Chronic Heart Failure) risk score model developed by the Global Group of Meta-Analysis, which can be used in HF patients with both reduced ejection fraction and preserved ejection fraction[(5)]. In this study, we aimed to determine the positive response to CRT and predictors affecting survival and to evaluate the prognostic significance of the MAGGIC risk score calculated before CRT.

Materials and Methods

Study Population

This retrospective observational study was carried out with HF patients who underwent CRT implantation at Pamukkale University Medical Faculty Hospital between January 2015 and January 2019. CRT was applied to patients with LVEF <35% and NYHA class II-III and Iva, who were resistant to optimal medical therapy in the last 3 months, with a QRS duration ≥130 ms in Left bundle branch block (LBBB) morphology or a QRS duration ≥150 ms without LBBB morphology. Before CRT, the MAGGIC-HF risk scores of the patients were calculated and the NYHA functional class was determined by at least 2 experienced cardiologists who were blind to the study. HF was classified in three groups, as ischemic, non-ischemic and other causes according to the underlying etiology. Ischemic HF was defined as HF due to a previous myocardial infarction and severe coronary artery disease with or without intervention. The clinical and demographic characteristics, comorbidities, medications, preoperative and post-operative indicators of the patients and the data collected during the follow-up visits were recorded and stored for later analysis. However, patients who could not be followed up according to the data obtained from the records or who had a lack of data were excluded from the study and finally, the study was carried out with 110 patients.

The subjects were classified as patients with survival within the first 2 years after CRT (group 1, n=91) and patients without survival (group 2, n=19). Patients who survived after CRT were divided into two subgroups as those who responded positively to CRT (group 1a, n=44) and those who did not (group 1b, n=47) and a 10% increase in LVEF after the CRT procedure was defined as a positive response[6]. Preoperative clinical data including laboratory, electrocardiographic and echocardiographic parameters and MAGGIC-HF risk scores of the groups were compared to determine the positive response to CRT and factors affecting survival. Preoperative and postoperative six-month periods of the patients with survival were reanalyzed to determine which parameters were associated with the positive response to CRT.

This study was approved by Pamukkale University Faculty of Medicine Hospital Denizli, Turkey Ethics Review Board in accordance with the Declaration of Helsinki (decision no: 60116787-020/34161, date: 09.06.2020), and informed consent was obtained from all registered patients.

CRT Implantation

The left ventricle pacing was implanted into the lateral or posterolateral vein after the coronary sinus was cannulated with a guide sheath using the left subclavian approach. The right atrial lead was placed in the right atrial appendage and the right ventricular lead was placed in the right ventricular apex or right ventricular outflow tract. Fluoroscopy was used to evaluate the final position of the left ventricular pacing lead, and optimization of device parameters before discharge was provided for each patient.

Clinical Data

Peripheral venous blood samples of the patients were collected for standard blood tests after 8-12 hours of fasting. The resting electrocardiogram data of the patients before and after CRT implantation and during follow-up were analyzed. The QRS duration was defined as the longest measured QRS time in any lead. 2D transthoracic echocardiographic imaging was performed with Vivid 7 GE echocardiography device before and after CRT implantation. Left atrial diameter, left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) were measured using the M-mode method. LVEF was calculated by the bi-plane Simpson method and pulmonary artery systolic pressure (PASP) was calculated by the modified Bernoulli equation by adding the estimated right atrial pressure to the tricuspid regurgitation jet flow velocity.

Clinical Outcomes

The mortality due to HF and all causes within two years after CRT implantation was defined as the primary outcome. The improvements in echocardiographic parameters after CRT implantation were defined as the secondary outcome.

Statistical Analysis

The analysis of all data was performed using SPSS v.21.0 for Windows (SPSS, Inc., Chicago, Ill., USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as frequency and percentage. The Shapiro-wilk test was used to check the normality of continuous data, the student's t-test for variables that were compatible with normal distribution, and the Mann-Whitney U test for variables not compatible with normal distribution. Comparison of categorical variables was performed by the chi-square analysis and the statistical significance level (alpha) was considered as 0.05.

Results

Baseline Demographic and Clinical Characteristics of the Study Population

Baseline demographic and clinical characteristics of the groups are shown in Table 1. There are no significant differences in mean age, distribution of gender and comorbidities such as hypertension, diabetes, coronary artery diseases, cerebrovascular diseases and chronic

Table 1. Baseline characteristics of study population

Variables	Group 1 (n=91)	Group 2 (n=19)	p-value
Demographics			
Mean age, (years)	62.43±12.46	63.89±7.93	0.630
Male gender, n (%)	64 (70)	11 (58)	0.440
Body mass index (kg/m^2)	29.70±3.80	29.60±4.00	0.766
HF characteristics			
HF duration, week	45.50±30.80	49.20±26.90	0.362
Ischemic HF, (n) %	53 (58)	11 (58)	0.821
Non ischemic HF, n (%)	16 (16)	4 (21)	0.558
Other causes of HF, n (%)	21 (25)	4 (21)	0.721
NYHA II, n (%)	11 (12)	1 (5)	0.418
NYHA III, n (%)	76 (84)	16 (84)	0.566
NYHA IVa, n (%)	4 (4)	3 (11)	0.102
ICD/Pacemaker history, n (%)	7 (8)	2 (11)	0.630
Comorbidities			
Hypertension, n (%)	67 (74)	12 (63)	0.546
Diabetes, n (%)	32 (35)	7 (37)	0.763
Dyslipidemia, n (%)	34 (37)	4 (21)	0.218
Current smoking, n (%)	29 (32)	5 (26)	0.732
COPD, n (%)	5 (5)	-	0.309
Previous stroke, n (%)	3 (3)	1 (5)	0.641
CAD, n (%)	70 (77)	13 (68)	0.669
Laboratory			
Creatinine, (mg/dL)	1.14±0.43	1.28±0.46	0.23
BUN, (mg/dL)	24.16±12.30	24.17±13.06	1.00
Sodium, (mEq/L)	138.13±3.40	137.00±3.16	0.19
C-reactive protein, (mg/L)	1.05±1.62	1.61±2.40	0.22
Echocardiographic			
LVEF, (%)	27.00±5.86	23.89±5.32	0.04
LVEDD, (mm)	64.59±8.23	66.67±9.59	0.34
LVESD, (mm)	53.01±8.80	56.78±10.36	0.11
PASP, (mmHg)	34.66±18.31	46.50±15.86	0.01
Medications			
Beta blockers, n (%)	82 (90)	16 (84)	0.866
ACEI/ARB/ARNI, n (%)	75 (82)	14 (73)	0.642
Aldosterone antagonist, n (%)	70 (77)	14 (74)	0.899
Other diuretics, n (%)	58(63)	12 (63)	0.855
Anti-aggregants, n (%)	66 (64)	14 (74)	0.645
Statins, n (%)	41 (45)	6 (32)	0.359
Digitalis, n (%)	23 (25)	5 (26)	0.824
Ivabradine, n (%)	16 (18)	4 (21)	0.642
Electrocardiogram			
Sinus rhythm, n (%)	74 (81)	15 (79)	0.840

Table 1. continued

Atrial fibrillation, n (%)	17 (19)	3 (16)	0.840
QRS duration >150 msn, n (%)	28 (31)	5 (26)	0.801
QRS duration >130 msn, n (%)	63 (67)	13 (68)	0.845
LBBB morphology, n (%)	86 (95)	15 (79)	0.097
RBBB morphology, n (%)	2 (2)	2 (11)	0.066
MAGGIC score	24.41±5.70	25.06±4.70	0.650

HF: Heart failure, NYHA: New York Heart Association, ICD: Implantable cardioverter defibrillator, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PASP: Pulmonary artery systolic pressure, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor neprilysin inhibitor, LBBB: Left bundle branch block, RBBB: Right bundle branch block, MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, n: Number

obstructive pulmonary diseases. (p>0.05) Also, the laboratory findings, electrocardiographic parameter, medications, HF properties such as duration, etiology and NYHA functional class did not show significant differences in HF patients with survival and without survival. (p>0.05) However, LVEF was significantly higher and PASP was significantly lower in patients with survival compared to patients with no survival. (LVEF, 27.00±5.86, 23.89±5.32, p=0.04; PASP, 34.66±18.31, 46.50±15.86, p=0.01, respectively). Also, the MAGGIC risk score did not differ between the groups (p>0.05).

Comparison of the Preoperative and Postoperative 6-month Periods of Patients with Survival After CRT

Comparing the patients with a positive response to CRT (group 1a) and those without (group 1b), the negative response to CRT was shown more frequently in patients with a history of DM and hyperlipidemia and previous pacemaker/implantable cardioverter defibrillator (ICD) history. In addition, the patients who responded positively to CRT had higher LVEF (31.57±9.25, 25.96±5.99; p<0.001) (Table 2).

When the 6-month periods before and after CRT of the surviving patients were compared, it was found that LVEDD, LVESD, and PASP decreased and LVEF increased in the 6th month, and the improvements in these parameters were statistically significant (p=0.015) (Figure 1-4). In the two-year follow-up after CRT implantation, the mean hospitalization time was 1 day and there was a significant but weak correlation between the MAGGIC-HF risk score and re-hospitalizations (p=0.031, r=208) (Table 3).

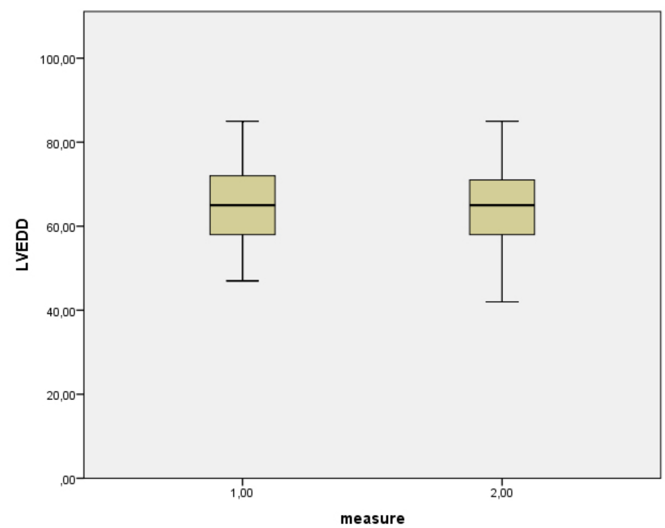

Figure 1. Comparison of preoperative and postoperative 6-month LVEDD measurements of survival patients
LVEDD: Left ventricular end diastolic diameter

Discussion

The regression in LVDD, LVSD, PASP and the increase in LVEF were the parameters showing CRT positive response in this study. The two main determinants of survival in CRT were preoperative PASP level and basal LVEF. The MAGGIC-HF risk score was insufficient to predict prognosis in the post-CRT period. Among the surviving patients, patients who responded positively

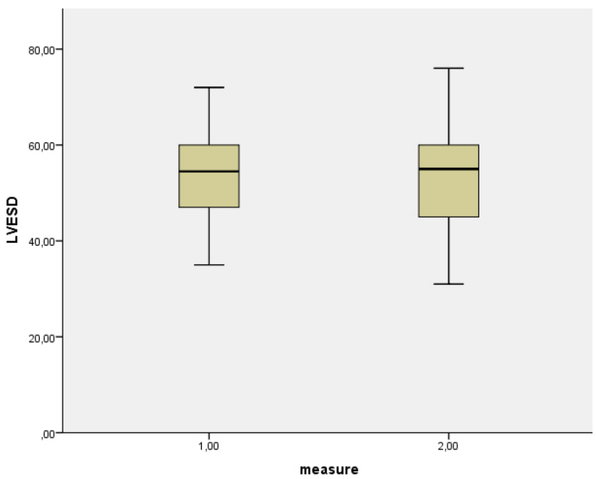

Figure 2. Comparison of preoperative and postoperative 6-month LVESD measurements of survival patients

LVESD: Left ventricular end systolic diameter

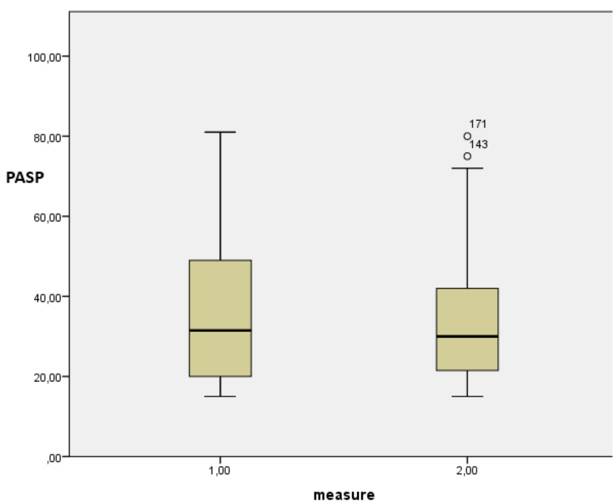

Figure 3. Comparison of preoperative and postoperative 6-month PASP measurements of survival patients

PASP: Pulmonary artery systolic pressure

to CRT had less DM, hyperlipidemia and pacemaker implantation. Besides, basal LVEF was higher in patients who responded positively to CRT.

CRT implantation improves prognosis in patients with HF. However, the randomized controlled studies have shown that the mortality is between 15% and 18% in the 12-24 month period after CRT and this rate increases more in longer periods[7]. Low LVEF is still associated with increased mortality, and basal LVEF should be considered

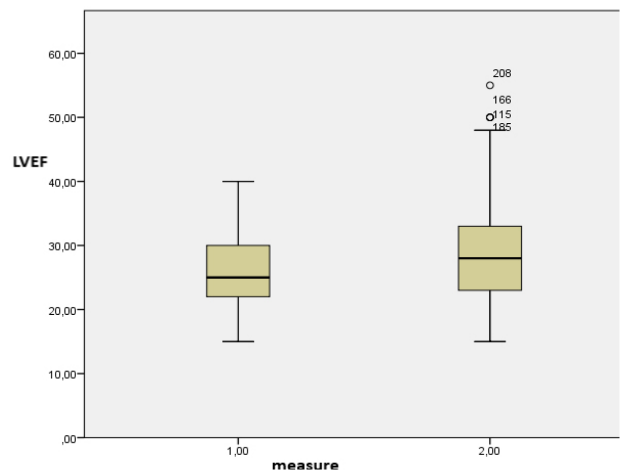

Figure 4. Comparison of preoperative and postoperative 6-month LVEF measurements of survival patients

LVEF: Left ventricular ejection fraction

to determine candidates for CRT implantation[8]. Small previous studies have shown that patients with severe symptoms but higher baseline LVEF exhibit better clinical and echocardiographic improvement[9,10]. In the MADIT-CRT study, patients were classified into three groups as <25%, 26-30% and >30% according to LVEF, and the group with the lowest LVEF had high mortality ratio and recurrent HF. Although the clinical benefit seen from CRT was independent of basal LVEF, the group with LVEF >30% provided more improvements from CRT[11]. In our study, similar to randomized controlled studies, the two-year mortality rate was 17%. In our study, one of the important parameters for survival and positive response to CRT was basal LVEF and the patients with high LVEF showed a more positive response to CRT. However, PROSPECT and REVERSE studies have suggested that the clinical and echocardiographic benefit seen from CRT is independent of LVEF, unlike the MADIT-CRT study and our study[12,13]. The contradictory results obtained from the studies may base on the different definitions of the patients included in the study, like clinical and demographic characteristics or positive response to CRT, the differences of NYHA functional class, and inclusion criteria.

Table 2. Baseline characteristics of the study population with CRT responses

Variables	Group 1a (n=44)	Group 1b (n=47)	p-value
Demographics			
Mean age, (years)	60.24±11.50	63.86±11.95	0.250
Male gender, n (%)	28 (64)	36 (77)	0.140
Body mass index (kg/m^2)	28.20±3.50	29.00±4.40	0.824
HF characteristics			
HF duration, week	44.70±25.10	50.20±27.50	0.362
Ischemic HF, (n) %	23 (52)	31 (66)	0.191
Non ischemic HF, n (%)	9 (20)	7 (15)	0.731
Other causes of HF, n (%)	12 (27)	9 (19)	0.264
NYHA II, n (%)	6 (14)	5 (11)	0.892
NYHA III, n (%)	38(86)	41 (87)	0.922
NYHA IVa, n (%)	0	1 (2)	0.899
ICD/Pacemaker history, n (%)	1 (2)	6 (13)	0.030
Comorbidities			
Hypertension, n (%)	30 (68)	37 (79)	0.446
Diabetes, n (%)	9 (20)	23 (49)	0.006
Dyslipidemia, n (%)	8 (18)	26 (55)	0.004
Current smoking, n (%)	12 (27)	17 (36)	0.710
COPD, n (%)	2 (5)	3 (6)	0.522
Previous stroke, n (%)	2 (5)	1 (2)	0.410
CAD, n (%)	33 (75)	37 (79)	0.864
Laboratory			
Creatinine (mg/dL)	1.17±0.47	1.14±0.40	0.720
BUN (mg/dL)	22.45±9.42	25.20±13.74	0.240
Sodium (mEq/L)	137.96±4.09	137.88±2.64	0.906
C reactive protein (mg/L)	1.15±1.79	1.18±1.79	0.940
Echocardiographic			
LVEF (%)	31.57±9.25	25.96±5.99	<0,001
LVEDD (mm)	65.24±8.56	64.96±8.31	0.87
LVESD (mm)	53.49±9.23	54.15±8.92	0.71
PASP (mmHg)	36.88±18.95	36.89±18.19	0.96
Medications			
Beta blockers, n (%)	39 (89%)	41 (87%)	0.514
ACEI/ARB/ARNI, n (%)	34 (77%)	41 (87%)	0.497
Aldosterone antagonist, n (%)	37 (84%)	33 (70%)	0.899
Other diuretics, n (%)	27 (61%)	31 (66%)	0.894
Anti-aggregants, n (%)	28 (64%)	38 (81%)	0.070
Statins, n (%)	15 (34%)	26 (55%)	0.05
Digitalis, n (%)	14 (32%)	9 (19%)	0.88
Ivabradine, n (%)	10 (23%)	6 (13%)	0.124
Electrocardiogram			

Table 2. continued

Sinus rhythm, n (%)	37 (84)	37 (79)	0.872
Atrial fibrillation, n (%)	7 (16)	10 (21)	0.710
QRS duration >150 msn, n (%)	15 (34)	13 (28)	0.668
QRS duration >130 msn, n (%)	29 (66)	34 (72)	0.375
LBBB morphology, n (%)	43 (98)	46 (98)	0.902
RBBB morphology, n (%)	1 (2)	1 (2)	0.896
MAGGIC score	23.87±5.467	24.95±5.558	0.286

HF: heart failure, NYHA: New York Heart Association, ICD: Implantable cardioverter defibrillator, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PASP: Pulmonary artery systolic pressure, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor neprilysin inhibitor, LBBB: Left bundle branch block, RBBB: Right bundle branch block, MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, n: Number, CRT: Cardiac resynchronization therapy

Table 3. Relationship between MAGGIC risk score and hospitalization in surviving patients

		MAGGIC risk score	Hospitalization day
Hospitalization	**Pearson correlation**	**0.208**	**1**
	Sig. (2-tailed)	0.031	-
	n	108	108

MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure, n: Number

In patients with a positive response from CRT, at the end of the first month, LVDD, LVSD and left ventricle volumes decrease and this improvement continues up to 12 months in approximately 65-75% of the patients. In the MIRACLE and Multicentre InSync™ Randomized Clinical Evaluation-Implantable Cardioverter Defibrillator (MIRACLE-ICD) studies, a significant increase in LVEF was observed with a decrease in left ventricular end systolic-diastolic volume and linear diameters in the patient group with CRT[14]. In our study, similar to the MIRACLE and MIRACLE-ICD studies, there was a significant decrease in LVDD and LVSD and a significant increase in LVEF, and these results were evaluated as a positive response to CRT in patients with survival. The clinical response of HF patients to CRT may differ. Yu et al.[15] could not identify the association of left ventricular end-systolic volume (LVESV) reduction after CRT with NYHA functional class, quality of life, and 6-minute walk test, but in another study, a decrease of <15% in LVESV resulted in better clinical improvement[16]. However, this situation may associate with placebo effects of CRT. Therefore, we did not include clinical improvement indicators after CRT implantation to avoid a subjective evaluation in our study. In the REVERSE study, it was shown that the ratio of re-hospitalization was decreased and the hospitalization's duration was shortened after CRT[17]. Similar to this study, the hospitalization's duration was average of one day in our study.

Several studies have shown that the factors such as impaired renal function, presence of AF, poor NYHA functional class, gender, HF etiology, presence of LBBB and QRS duration >150 ms affect CRT response and prognosis[18,19]. However, Ghanem et al.[20] did not find any relationship between demographic-clinical variables and CRT response. Similar to this study, there was no relationship between demographic-clinical variables with CRT response and clinical outcome in our study.

The increased PASP and right ventricular dysfunction have also been associated with adverse clinical outcomes after CRT[21]. Previous studies have shown that patients with PASP levels higher than 50 mmHg have a worse prognosis. However, little is known about how it affects the long term after CRT. In a study, Bašinskas et al.[22] classified the patients as PASP <50 mmHg and PASP >50 mmHg before CRT implantation and evaluated their CRT response and survival. As a result, the group with higher PASP levels had more deaths and re-hospitalizations. In another study, PASP levels above 39.5 mmHg were associated with increased mortality after CRT, but this result was not confirmed by Cox regression analysis[22,23]. In our study, similar to these studies, one of the important parameters affecting survival and CRT positive response was increased PASP levels and it was closely related to mortality. The decline of PASP was considered as CRT positive response in our study, but this result may be secondary to the improvement of left ventricular functions.

Although various HF risk score models have been developed to evaluate prognosis, to predict survival, and to determine who will benefit from organ transplantation or assist support devices in patients with HF, their reliability is poor on the patient basis and their performance is limited in the estimation of prognosis[24]. We used the MAGGIC risk score, which is one of the HF risk score models, in this study. We showed that MAGGIC score did not provide sufficient long-term prognostic information in HF patients.

Study Limitations

This study had some limitations. This study was designed as a retrospective study and had a relatively small sample. Also, the alterations of HF therapy follow-up may affect the clinical outcome and CRT response in patients. Other limitations included not using modern echocardiographic parameters such as tissue doppler and strain imaging, which are more sensitive and specific, and not evaluating functional mitral regurgitation, which is one of the CRT response indicators.

Conclusion

The strongest predictors of survival in patients implanted with CRT are basal LVEF and PASP. Furthermore, basal LVEF is one of the most important factors in the benefit seen from CRT regardless of underlying HF etiology. However, multi-center, randomized controlled large studies are needed to determine candidate patients for CRT and to see long-term results of CRT.

Ethics

Ethics Committee Approval: This study was approved by Pamukkale University Faculty of Medicine Hospital Denizli, Turkey Ethics Review Board in accordance with the Declaration of Helsinki (decision no: 60116787-020/34161, date: 09.06.2020).

Informed Consent: Informed consent was obtained from all registered patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.N., G.Ş., Concept: G.N., G.Ş., Design: G.N., G.Ş., Data Collection or Processing: G.N., G.Ş., Analysis or Interpretation: S.Ç., G.G., Literature Search: G.N., S.Ç., Writing: G.N., S.Ç., G.Ş., G.G.

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References

1. Alpman A. Heart failure old dominant, new friend: beta blockers. Ankara Üniversitesi Tıp Fakültesi Derg 2000;53:43-7.
2. Bektaşoğlu G, Yılmaz MB, Tandoğan İ. The role of echocardiography in cardiac resynchronization therapy. Cumhuriyet Tıp Derg 2009;31:316-30.
3. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
4. Fuganti C, Melo CS, Moraes Jr AV et al. Diretriz: Terapia de Ressincronização Cardíaca. Relampa 2015;28:1-25.
5. Rich JD, Burns J, Freed BH, Maurer MS, Burkhoff D, Shah SJ. Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: Validation of a Simple Tool for the Prediction of Morbidity and Mortality in Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc 2018;7:009594.
6. Shantha G, Mentias A, Venkata N, et al. Role of obstructive sleep apnea on the response to cardiac resynchronization therapy and all-cause mortality Heart Rhythm. 2018;15:1283-8.

7. Verhaert D, Grimm RA, Puntawangkoon C, et al. Long-term reverse remodeling with cardiac resynchronization therapy: results of extended echocardiographic follow-up. J Am Coll Cardiol 2010;55:1788-95.

8. Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA Jr, Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE study. J Interv Card Electrophysiol 2005;12:107-13.

9. Fung JW, Zhang Q, Yip GW, Chan JY, Chan HC, Yu CM. Effect of cardiac resynchronization therapy in patients with moderate left ventricular systolic dysfunction and wide QRS complex: a prospective study. J Cardiovasc Electrophysiol 2006;17:1288-92.

10. Foley PW, Stegemann B, Smith RE, Sanderson JE, Leyva F. Cardiac resynchronization therapy in patients with mildly impaired left ventricular function. Pacing Clin Electrophysiol 2009;32:186-9.

11. Kutyifa V, Kloppe A, Zareba W, et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). J Am Coll Cardiol 2013;61:936-44.

12. Chung ES, Katra RP, Ghio S, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. Eur J Heart Fail 2010;12:581-7.

13. Linde C, Daubert C, Abraham WT, et al. Impact of ejection fraction on the clinical response to cardiac resynchronization therapy in mild heart failure. Circ Heart Fail 2013;6:1180-9.

14. Melek M, Esen ÖB, Esen AM, Barutçu İ. Resynchronization Therapy in Heart Failure. Türk Kardiyol Dern Arş 2004;32:376-89.

15. Yu CM, Bleeker GB, Fung JW, et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation 2005;112:1580-6.

16. Lafitte S, Reant P, Zaroui A, et al. Validation of an echocardiographic multiparametric strategy to increase responders patients after cardiac resynchronization: a multicentre study. Eur Heart J 2009;30:2880–7.

17. Daubert C, Gold MR, Abraham WT, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol 2009;54:1837-46.

18. van Bommel RJ, Borleffs CJ, Ypenburg C, et al. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome. Eur Heart J 2010;31:2783-90.

19. European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace 2013;15:1070-118.

20. Ghanem MT, Allam LE, Ahmed RS. Cardiac resynchronization therapy in patients with heart failure and moderately reduced ejection fraction: Could it trigger a super-response? Indian Heart Journal 2019;71:229-34.

21. Scuteri L, Rordorf R, Marsan NA, et al. Relevance of echocardiographic evaluation of right ventricular function in patients undergoing cardiac resynchronization therapy. Pacing Clin Electrophysiol 2009;32:1040-9.

22. Bašinskas P, Stoškutė N, Gerulytė A, Abramavičiūtė A, Puodžiukynas A, Kazakevičius T. Prognostication of Poor Survival After Cardiac Resynchronization Therapy. Medicina (Kaunas) 2020;56:19.

23. Wang D, Han Y, Zang H, et al. Prognostic effects of pulmonary hypertension in patients undergoing cardiac resynchronization therapy. J Thorac Dis 2010;2:71-5.

24. Canepa M, Fonseca C, Chioncel O, et al. Performance of Prognostic Risk Scores in Chronic Heart Failure Patients Enrolled in the European Society of Cardiology Heart Failure Long-Term Registry. JACC Heart Fail 2018;6:452-62.

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Effects of Different Heart Positions During Off-pump Coronary Artery Bypass Surgery on Serum Ischemia Modified Albumin Level and Cardiac Output

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Abstract

Objectives: We aimed to evaluate the potential effects of heart positioning during off-pump CABG (OPCAB) without a cardiac stabilizer device on serum levels of ischemia modified albumin (IMA) and cardiac output (CO).

Materials and Methods: This was a prospective study in which consecutive patients who underwent isolated OPCAB were included. Data including electrocardiography and intraarterial hemodynamic monitoring parameters were recorded. Arterial pressure waveform was analyzed. CO was measured for circumflex coronary artery (Cx), diagonal coronary

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Abstract

artery (D1), left anterior descending coronary artery (LAD), and right coronary artery (RCA) positions. Preoperative and postoperative 1st, 2nd, 4th, and 12th-hour blood samples were taken for serum ischemia modified albumin measurements.

Results: Forty patients who underwent OPCAB were included in the study. The mean age was 60.3±10.2 years. Hospital mortality, stroke, postoperative myocardial infarction, acute kidney injury, sternal infection, and re-operation for bleeding/tamponade were not observed postoperatively. Six patients (15%) who developed postoperative atrial fibrillation (AF) had a significantly higher mean serum IMA level compared with patients who did not. There was no statistically significant difference in preoperative and postoperative mean serum IMA levels (p=0.925). Mean CO values measured at four different heart positions were not significantly different from each other except for a difference between LAD and Cx (p=0.002).

Conclusion: Our results showed that when the heart was in the Cx anastomosis position, the CO was significantly lower than the LAD position; however, there was no significant serum IMA raise despite CO decrease. IMA levels did not change significantly from baseline values. Patients who developed postoperative AF had higher IMA levels than patients who did not develop AF.

Keywords: Atrial fibrillation, cardiac ischemia, cardiac output, ischemia modified albumin, off-pump coronary artery bypass

Introduction

Coronary artery bypass grafting is a common surgical procedure for multi-vessel atherosclerotic patients, which can be performed while the heart is still beating off-pump) or with cardioplegia (on-pump)[1-3]. Several studies have shown that off-pump cardiac bypass surgery (OPCAB) is associated with less cardiac injury and systemic inflammation compared to on-pump coronary artery bypass grafting (CABG). Moreover, these molecular changes can lead to clinical outcomes such as lower complication rates, lower mortality rates, and shorter hospital stays in favor of OPCAB[2,4,5]. However, OPCAB is not always innocent of myocardial injury[6], and generally is criticized for its inability for extensive revascularizations. These limitations prompted the use of cardiac stabilizers but that may have negative consequences in terms of systemic hemodynamics.

Postoperative myocardial ischemia is one of the most common factors that cause the development of postoperative myocardial infarction (MI), which is seen between 3% and 20% of CABG patients[7-9]. Detecting and monitoring ischemia before irreversible tissue damage occurs as in postoperative MI should be one of the most important goals. Several myocardial injury markers, including troponin I, Heart-Type Fatty Acid-Binding Protein, choline, and others, are being used for this purpose[10-12].

Ischemia modified albumin (IMA) is generated by the modulation of the tertiary structure of the albumin molecule by reactive oxygen species during ischemia[10]. Several studies up to now have demonstrated the efficacy of serum IMA levels for early detection of ischemia in various settings, including acute coronary syndrome and postoperative MI[13,14]. However, data regarding the utility of serum IMA for the detection of ischemia during OPCAB are insufficient[15,16].

Clinical experiences point to the deleterious effects of cardiac stabilizing devices used during OPCAB. These should be taken with regard to the beneficial effects obtained with OPCAB. Dong et al.[16] evaluated the role of serum IMA levels in patients undergoing OPCAB in which a cardiac stabilizer was used. Thus, we aimed to investigate serum IMA levels and the alterations in cardiac output (CO) when the heart was temporarily suspended at various positions during OPCAB procedures without cardiac stabilizer.

Materials and Methods

Our study was a prospective study that primarily investigated the effects of different surgical positions of the heart provided by simple suspension sutures during isolated off-pump coronary artery bypass surgery on serum ischemia modified albumin levels and CO. The study was performed at Dışkapı Yıldırım Beyazıt Training and Research Hospital between February 2011 and June 2011. The Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital approved the study protocol (approval number: 27, date: 17/08/2011), and all patients provided written informed consent before enrolment in the study. The study was performed in compliance with the Helsinki Declaration.

The consecutive patients who were scheduled to undergo isolated off-pump CABG (OPCAB) were included in the study, irrespective of the number and localization of the atherosclerotic coronary artery. The indications for CABG were determined by a committee involving cardiologists and cardiac surgeons. Patients with the following features were excluded: requirement for emergency surgery, acute MI, on-pump CABG, additional cardiac pathology rather than coronary artery disease requiring intervention such as valve lesions, chronic kidney disease, liver disease, incurable malignancy, cerebrovascular accident, systemic infections and low preoperative serum albumin level.

All patients underwent routine preparation phase for the CABG operation, which was standard at our institution. Intraoperative data including electrocardiography, intraarterial blood pressure, central venous pressure, oxygen saturation obtained with pulse oximetry, urine output, and body temperature were monitored and recorded. Arterial pressure waveform (APW) was analyzed (Flotrac Sensor System, Edwards Lifesciences, Irvine CA, USA). CO was measured noninvasively for 12 hours. CO and the length of stay of the measurement sensor at the respective position were measured for circumflex coronary artery (Cx), diagonal coronary artery (D1), left anterior descending coronary artery (LAD) and right coronary artery (RCA).

Several venous blood samples were obtained for the measurement of serum IMA levels. The first sample was taken before the induction of anesthesia (first measurement). Subsequent blood samples were obtained in a serum separator at postoperative 1^{st}, 2^{nd}, 4^{th} and 12^{th}-hour time points (second, third, fourth and fifth IMA measurements, respectively). After 30 minutes, the clotted samples were centrifuged for 15 minutes at 1,000 g. All serum samples were kept at −20 °C until analysis and being centrifuged again after thawing before its use in the assay. The serum IMA levels were analyzed using the Cusabio Biotech human IMA ELISA kits (catalog number: CSB-E09594h, USCN, Houston, TX, USA).

The logistic version of the European System for Cardiac Operative Risk Evaluation (Log-EuroSCORE) was calculated to predict operative mortality[17]. EuroSCORE incorporates patient, cardiac and operation related risk factors to produce an overall risk score. In the logistic version, the same risk factors are used.

Surgical Procedure

Anesthesia induction was performed using propofol (3-4 mg/kg/hour), thiopental (3-5 mg/kg), or fentanyl citrate (5-10 μg/kg). Maintenance of anesthesia was achieved with propofol, fentanyl or sevoflurane at low concentrations. Unfractionated heparin of 5,000 U was administered to all patients during internal thoracic artery harvesting and the same dose was re-administered when apparent coagulation was observed at the operation site. Median sternotomy was performed. Left internal mammary artery (LIMA), radial artery, and saphenous vein grafts depending on the coronary anatomy were prepared simultaneously. The targeted intraoperative heart rate was 50-70 beats per minute. The heart rate was controlled by the application of beta-blockers, namely, esmolol or metoprolol. Systolic blood pressure was maintained at 50-70 mmHg during the distal anastomosis.

Patients were placed into Trendelenburg position and the dose of the inhaled anesthetic was adjusted to keep the systolic blood pressure within the target range. Neither intracoronary shunts nor commercial stabilizer devices were used in any of the operations. During the surgery, stabilization of target coronary arteries was achieved via simple radial traction sutures as described elsewhere[18]. During the creation of distal anastomoses, bleeding arising from the target coronary artery was controlled with atraumatic bulldog clamps. The proximal anastomosis of the radial artery graft was performed on LIMA in eligible patients, and in the rest of the patients, the ascending aorta with a side-clamp was used for this purpose.

After the construction of the anastomosis, a bleeding check was made, epicardial pacing wires and thorax drains were placed. Thereafter, sternum was closed and the patient was transported to the surgical ICU.

All patients were administered metoprolol 50 mg/day, acetylsalicylic acid 300 mg/day, and clopidogrel 75 mg/day postoperatively unless a contraindication was present. Patients whose conditions were stable were transported to the surgical ward and discharged when appropriate.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to compare the CO values measured in LAD, D1, Cx, and RCA positions of the patients, and the Tukey test was used for binary comparisons for statistically significant parameters. In the analysis of the changes in the IMA values in post-operative measurements, repeated measures ANOVA was used if the test assumptions were met, and the Friedman test was used if the assumptions were not met. Multivariable regression analysis and the Pearson correlation analysis were used to investigate the effect of CO values measured at four positions of the heart and the IMA levels. The Kruskal-Wallis H statistical analysis was used in the comparison of CO at four different positions and IMA level according to the number of grafts. Statistical analysis was performed using SPSS 16 Statistical Package for Social Sciences (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago). A p-value lower than 0.05 was considered statistically significant.

Results

Forty patients who underwent elective, isolated, primary CABG with the off-pump technique were included in the study. There were 10 (25%) women and 30 (75%) men. The mean age of the patients was 60.3±10.2 years. The mean Log-EuroSCORE and left ventricle ejection fraction (LVEF) of the patients were (4.62±6.73) and (44.6±5.3%), respectively. Hospital mortality, stroke, postoperative MI, acute kidney injury, sternal infection, and re-operation for bleeding/tamponade were not observed postoperatively in any of the patients. None of the patients required intra-aortic balloon pump and conversion from OPCAB to CABG with cardiopulmonary bypass due to hemodynamic instability. Atrial fibrillation (AF) was seen in 6 (15%) patients postoperatively. The mean length of stay in the intensive care unit (ICU) and the hospital were 2.02±1.4 and 6.5±2.0 days, respectively. The clinicodemographic characteristics and perioperative features of the entire study population are presented in Table 1.

There was no statistically significant difference in preoperative and postoperative mean serum IMA levels (p=0.925) (Table 2 and Figure 1). Postoperative IMA values measured at 1st, 2nd, 4th, and 12th hours were not significantly different from each other and mean preoperative IMA value. There was no significant correlation between the mean serum IMA level and LogEuroscore, LVEF, number of grafts, length of operation, postoperative hemoglobin level, and length of ventilation.

The mean CO values measured in four different positions of the heart were not significantly different from each other except the difference between LAD and Cx (Table 3 and Figure 2). The mean CO was 3.44±0.76 L/minute at LAD position, and 2.80±0.48 L/minute at Cx position (p=0.002). None of the CO values measured at different positions was correlated with age, LVEF, LogEuroscore, length of operation, and serum IMA levels.

Table 1. Clinicodemographic characteristics and perioperative features of the entire study population

Parameters	Variable value [n (%) or mean ± SD]
Preoperative data	
Age (years)	60.3±10.2
Sex (male)	30 (75%)
Body mass index (kg/m²)	26.12±4.33
Peripheral vascular disease	2 (5%)
Diabetes mellitus	15 (37%)
Hypertension	32 (80%)
Hyperlipidemia	13 (32%)
COPD	11 (27%)
Smoking history	24 (60%)
Cerebrovascular disease	0
LogEuroScore	4.62±6.73
LVEF	44.6±5.3%
Operative data	
Conversion to CPB	0
Number of bypassed vessel	3 (7%)
CABGx1	12 (30%)
CABGx2	13 (33%)
CABGx3	12 (30%)
CABGx4	0
IABP	287.30±72.06
Mean skin-to-skin OR time (minutes)	
Postoperative data	
Hospital mortality	0
Postoperative MI	0
Atrial fibrillation	6 (15%)
Stroke	0
Chronic kidney disease	0
Re-operation for bleeding/tamponade	0
Sternal infection	0
Length of ICU stay (days)	2±0.45
Length of hospital stay (days)	6.49±0.93

CABG: Coronary artery bypass grafting, COPD: Chronic obstructive pulmonary disease, CPB: Cardiopulmonary bypass, IABP: Intraaortic balloon pump support commenced at perioperative period only, ICU: Intensive care unit, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, OR: Operating room, SD: Standard deviation

The mean CO values at four different positions and mean IMA levels were not significantly different in patients who underwent 1st, 2nd, 3rd, and 4th vessel CABG.

The only observed complication during the postoperative follow-up was AF in six patients (15%). The patients who developed postoperative AF had significantly higher mean serum IMA level compared to patients who did not (Table 4).

Discussion

The feature results of our study were as follows:

CO measured at the position of LAD anastomosis was significantly higher than in the Cx position. Patients who developed postoperative AF had higher IMA levels than those who did not develop AF.

Table 2. Median serum IMA values at preoperative and several postoperative time points (n=40)

	IMA	p-value
Pre-operative	92.4 (91.7-94.3)	0.907
Post- operative (1st hour)	92.4 (92-94.9)	
Post- operative (2nd hour)	93.6 (91.8-95.4)	
Post- operative (4th hour)	93.1 (91.8-95.3)	
Post- operative (12th hour)	93.4 (91.8-95.1)	

IMA: Ischemia modified albumin, n: Number

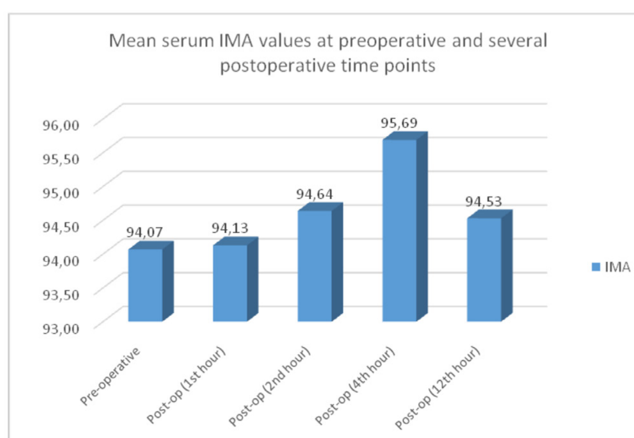

Figure 1. Mean serum IMA values at preoperative and several postoperative time points

IMA: Ischemia modified albumin, Post-op: Post-operative

One of the most important disadvantages of OPCAB surgery is its lack of capacity for performing extensive revascularization procedures mainly due to the hemodynamic instability caused by changing the positions of the heart[19,20]. On the other hand, using stabilizer devices may extend the duration of the operation and cumbersome to use. Therefore, we did not use stabilizer devices in OPCAB operations in this study. We sought to answer the question of whether different positionings of the heart during OPCAB without a stabilizer device had any bearings on the CO. In addition, we attempted to evaluate whether any potential decrease in CO led to ischemia that we measured via IMA levels in this study.

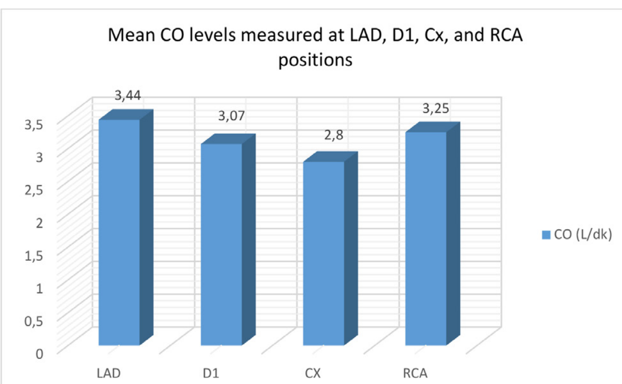

Figure 2. Mean CO levels measured at LAD, D1, Cx, and RCA positions

CO: Cardiac output, LAD: left anterior descending coronary artery, D1: Diagonal coronary artery, Cx: Circumflex coronary artery, RCA: Right coronary artery

Dong et al.[16] assessed the level of IMA in patients who underwent OPCAB. The authors found that serum IMA level reached peak values immediately after surgery, then gradually regressed, finally was significantly higher than the baseline levels during the first 24 h after OPCAB in all 63 patients. Ten patients (16%) had postoperative MI. The patients who developed postoperative MI had significantly higher IMA levels than those without postoperative MI at 3 hours after CABG. Moreover, in both groups, serum IMA levels were significantly higher compared to baseline values. In another study conducted with patients who underwent OPCAB, the authors evaluated the relationship between IMA and MI. They observed perioperative MI in eight patients (16%) out of 50 study participants. The IMA levels of the postoperative MI group at 30 minutes and at three, six, and 12 hours after declamping were found significantly higher than the patients who did not develop postoperative MI. Additionally, the IMA levels at 30 minutes after aortic cross-clamping were higher than the baseline IMA levels in both groups[13].Our study was not in agreement with the findings of these two studies. First, we did not observe any postoperative MI in our study cohort. Second, the serum IMA levels were comparable throughout the study at different time points.

Interpositional CO comparisons detected significant difference only between Cx and LAD cardiac positions (lower in Cx) (p=0.002) In our study, compared to the previous studies, postoperative serum IMA levels did not

Table 3. Comparison of mean CO values measured in four different positions of the heart

	LAD (n=40)	D1 (n=20)	CX (n=29)	RCA (n=25)	p-value
CO (L/dk)	3.44±0.7553	3.07±0.6255	2.80±0.4801	3.25±0.6811	0.003*

CO: Cardiac output, Cx: Circumflex, D1: Diagonal 1, LAD: Left anterior descending, RCA: Right coronary artery, n: Number
**There was only one significant intergroup difference between LAD and Cx (Tukey post-hoc test, p=0.002)*

Table 4. IMA levels in patients with and without postoperative atrial fibrillation

	Atrial fibrillation (AF)		p-value
	AF (-) (n=34)	AF (+) (n=6)	
IMA (Mean ± SD)	93.7±2.4	99.4±5.5	0.011

IMA: Ischemia modified albumin, SD: Standard deviation, n: Number, AF: Atrial fibrillation show any change from baseline. However, most studies reported increased IMA levels after cardiac surgery even in patients without postoperative MI[21,22]. This was also detected even in patients who underwent off-pump bypass surgery.

Kanko et al.[22] studied the prognostic value of serum IMA levels in patients undergoing CABG. Sixteen out of thirty patients (53%) developed paroxysmal AF after surgery. The mean serum IMA levels in these patients was found to be significantly higher than in those who did not develop AF. Up to current clinic data, our study is the second study confirming this preliminary result. In our study, six patients (16%) developed AF postoperatively and the mean IMA levels of these patients were significantly higher than those of patients without postoperative AF. Regarding the potential predictive role of serum IMA levels for the development of postoperative AF, further studies are required.

Study Limitations

There are some limitations in this study, which deserve to be mentioned: First, our sample size was relatively small. Second, apart from six patients with postoperative AF, the postoperative course was uneventful for the majority of the patients; in other words, the study population did not have any ischemic event such as postoperative MI. We did not have any patients with postoperative MI in contrast to the most reported studies. This fact might have led to unchanged postoperative serum IMA levels compared to baseline serum IMA levels. In addition, it would have been better if we had studied other markers of myocardial injury and ischemia. Measuring serum IMA levels is more effective in early detection of ischemia than other established markers. Despite these limitations, to our knowledge, this is the first study in the literature reporting the effect of OPCAB without stabilizing device on CO and serum IMA levels.

Conclusion

This is the first study evaluating OPCAB without a stabilizing device on CO along with serum IMA levels as a marker of ischemia. Our results showed that when the heart was in Cx anastomosis position, the CO was significantly lower than LAD position; however, there was no significant serum IMA increase despite CO decrease. Interestingly, patients who developed postoperative AF had higher IMA levels than patients who did not develop AF. Our results revealed favorable effects of OPCAB on hemodynamics and ischemia, which is quite common during bypass surgery.

Ethics

Ethics Committee Approval: The Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital approved the study protocol (approval number: 27, date: 17/08/2011).

Informed Consent: All patients provided written informed consent before enrolment in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B., Ö.E., İ.İ., Z.T., K.Ö., U.K., Concept: M.B., Ö.E., K.Ö., U.K., Design: M.B., U.K., Data Collection or Processing: M.B., Ö.E., Z.T., K.Ö., Analysis or Interpretation: M.B., R.Ö., U.K., Literature Search: M.B., Ö.E., İ.İ., R.Ö., Z.T., K.Ö., U.K., Writing: M.B., İ.İ., R.Ö.

Conflict of Interest: The authors are declaring to have no conflict of interest.

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References

1. Schulze C, Conrad N, Schütz A, et al. Reduced expression of systemic proinflammatory cytokines after off-pump versus conventional coronary artery bypass grafting. Thorac Cardiovasc Surg 2000;48:364-9.
2. Aklog L. Future technology for off-pump coronary artery bypass (OPCAB). Semin Thorac Cardiovasc Surg 2003;15:92-102.
3. Shroyer AL, Hattler B, Wagner TH, et al. Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass. N Engl J Med 2017;377:623-32.

4. Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ, Angelini GD. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. Circulation 2000;102:1530-5.

5. Hannan EL, Wu C, Smith CR, et al. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. Circulation 2007;116:1145-52.

6. Paparella D, Cappabianca G, Malvindi P, et al. Myocardial injury after off-pump coronary artery bypass grafting operation. Eur J Cardiothorac Surg 2007;32:481-7.

7. McFalls EO, Ward HB, Moritz TE, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. Eur Heart J 2008;29:394-401.

8. Järvinen O, Julkunen J, Saarinen T, Laurikka J, Huhtala H, Tarkka MR. Perioperative myocardial infarction has negative impact on health-related quality of life following coronary artery bypass graft surgery. Eur J Cardiothorac Surg 2004;26:621-7.

9. Dahlin LG, Olin C, Svedjeholm R. Perioperative myocardial infarction in cardiac surgery--risk factors and consequences. A case control study. Scand Cardiovasc J 2000;34:522-7.

10. Mair J, Hammerer-Lercher A. Markers for perioperative myocardial ischemia: what both interventional cardiologists and cardiac surgeons need to know. Heart Surg Forum 2005;8:319-25.

11. Lin S, Yokoyama H, Rac VE, Brooks SC. Novel biomarkers in diagnosing cardiac ischemia in the emergency department: a systematic review. Resuscitation 2012;83:684-91.

12. Singh V, Martinezclark P, Pascual M, Shaw ES, O'Neill WW. Cardiac biomarkers - the old and the new: a review. Coron Artery Dis 2010;21:244-56.

13. Mentese U, Dogan OV, Dogan S, et al. The relationship between ischemia-modified albumin and myocardial infarction in on-pump coronary artery bypass grafting. Türk Göğüs Kalp Damar Cer Derg 2015;23:245-50.

14. Oran I, Oran B. Ischemia-Modified Albumin as a Marker of Acute Coronary Syndrome: The Case for Revising the Concept of "N-Terminal Modification" to "Fatty Acid Occupation" of Albumin. Dis Markers 2017;2017:5692583.

15. Wang H, Lyu Y, Liao Q, et al. Effects of Remote Ischemic Preconditioning in Patients Undergoing Off-Pump Coronary Artery Bypass Graft Surgery. Front Physiol 2019;10:495.

16. Dong SY, Wang XJ, Xiao F, Wang J, Li YF, Li Y. Detection of perioperative myocardial infarction with ischemia-modified albumin. Asian Cardiovasc Thorac Ann 2012;20:252-6.

17. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816-22.

18. Kurtoglu M, Ates S, Demirozü T, Duvan I, Karagoz HY, Aybek T. Facile stabilization and exposure techniques in off-pump coronary bypass surgery. Ann Thorac Surg 2008;85:30-1.

19. Gründeman PF, Borst C, van Herwaarden JA, Mansvelt Beck HJ, Jansen EW. Hemodynamic changes during displacement of the beating heart by the Utrecht Octopus method. Ann Thorac Surg 1997;63:88-92.

20. Mathison M, Edgerton JR, Horswell JL, Akin JJ, Mack MJ. Analysis of hemodynamic changes during beating heart surgical procedures. Ann Thorac Surg 2000;70:1355-60.

21. Thielmann M, Pasa S, Holst T, et al. Heart-Type Fatty Acid Binding Protein and Ischemia-Modified Albumin for Detection of Myocardial Infarction After Coronary Artery Bypass Graft Surgery. Ann Thorac Surg 2017;104:130-7.

22. Kanko M, Yavuz S, Duman C, Hosten T, Oner E, Berki T. Ischemia-modified albumin use as a prognostic factor in coronary bypass surgery. J Cardiothorac Surg 2012;7:3.

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The Relationship Between Coronary Collateral Circulation and Visceral Fat

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Abstract

Objectives: Collateral circulation is assumed to prevent myocardial ischemia in healthy subjects and in patients with coronary artery disease. Visceral adipose tissue is an active component of total body fat, which holds some biochemical characteristics that have impact on several normal and pathological processes in the human body. In this study, we investigated the relationship between visceral fat ratio and coronary collateral circulation (CCC).

Materials and Methods: Totally 148 patients with stable angina pectoris were recruited to the study and all patients' heights and weights were recorded after the coronary angiography. The study subjects were divided into two groups as those between 1 and 9, and those >10 by classifying their visceral fat ratio with bioelectrical impedance analysis method. Patients were classified as poor CCC group (grade 0 and 1) and good CCC group (grade 2 and 3) based on the Rentrop's classification of CCC.

Results: In the analysis in accordance with collateral classification, visceral fat percentage (13.7±4.7 versus 10.1±4.0, p=0.01) and body mass index (28.2±2.4 versus 27.3±2.3, p=0.040) were found significantly higher in the poor collateral group. Diabetes mellitus was significantly higher in patient with high visceral fat ratio. In multivariate logistic regression analysis for collateral growth, visceral fat percentage [odds ratio (OR): 0.740, %95 confidence interval (CI): 0.602-

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Abstract

0.909, p=0.040] and coronary stenosis percentage (OR: 1.220, %95 CI: 1.070-1.390, p=0.003) were found meaningful, independent from the other factors. In ROC analysis, increase in visceral fat level decreased collateral growth with 72.7% sensitivity and 58.5% specificity.

Conclusion: The increase in visceral fat seems an independent factor for poor collateral development.

Keywords: Coronary artery disease, collateral vessel, visceral fat, coronary artery disease risk factor

Introduction

Coronary artery disease (CAD) is a progressive, systemic and inflammatory disease with atherosclerosis in its etiology[1]. Coronary collateral circulation (CCC) is defined as vascular structures those present non-functional in the normal heart, becomes activated upon a serious stenosis or complete obstruction, disrupts blood circulation as an adapting response between the sections of the same coronary artery or different coronary arteries in order to provide blood flow into the ischemic myocardial area[2]. Collateral circulation is quite crucial since it is a potential alternative source upon any insufficiency in coronary arteries for providing blood circulation. Anti-ischemic effects, reducing myocardial infarction frequency, limiting infarct area, preventing the formation of aneurysms, maintaining ventricular functions, antiarrhythmic effects, and decreasing coronary mortality are the benefits of CCC[3-6]. It is a fact that the status of the collaterals is different even between individuals even with the same level of artery disease[7]. Visceral fat is a unique part of the total body fat and possesses several biochemical functions. Visceral fat is associated with a constellation of various metabolic abnormalities, including insulin resistance, hyperinsulinemia, type 2 diabetes, dyslipidemia, inflammation, and altered cytokine profile. Such metabolic abnormalities may have an effect on the endothelial tissue which is in the cornerstone point of development of new vessels in injured or ischemic tissues.

In our study, we have tried to show the relationship between visceral fat percentage, which is one of the factors considered to be efficient in coronary collateral vessel development, and CCC development.

Materials and Methods

Study Population

Our patients were selected from the cases who applied to our center due to chest pain and were hospitalized in our clinic after receiving coronary angiography indication with stable angina pectoris diagnosis after routine examinations. All patients were informed preceding the study.

Coronary angiography images, which were performed in our cardiology angiography laboratory, were scanned, and post-procedure hospital records were examined for patients with at least 90% and above critical stenosis in at least one of their coronary arteries. Baseline demographic data and laboratory results were obtained from the cases and hospital database system. Echocardiographic examination and electrocardiography were performed in all patients during the hospital stay. Left ventricular ejection fraction was measured using the Modified Simpson Method.

Among 200 patients who were eligible for the study criteria, patients with acute coronary syndrome requiring intervention in the first 72 hours, cancer, hematological disease, hypothyroidism, serious valvular heart disease, decompensated heart failure, severe liver disease, autoimmune disease, chronic kidney disease, inflammatory and infectious disease, corticosteroids or cytotoxic drug use, bedbound patients with a history of bleeding diathesis, patients weighing above 150 kg or below 40 kg, patients whose height was above 180 cm or below 140 cm, and patients under 18 or over 80 years old were excluded from the study. Our study included 148 patients who were eligible according to inclusion criteria.

Coronary Angiography

By using right and left femoral approach, selective coronary angiography was performed to patients with the Judkins method by using 6F or 7F catheters. Coronary angiography images were evaluated by two experienced cardiologists who had no knowledge on the clinical characteristics and laboratory data of patients. The levels of stenosis in coronary arteries were determined depending on the projection with the highest stenosis. Collateral development was evaluated according to the Rentrop classification. The grades of the evaluation according to the Rentrop classification were as follows: Rentrop grade 0: No collateral fill, Rentrop grade 1: very weak collateral flow, but no filling in epicardial arteries, Rentrop grade 2: Partial filling, presence of contrast material on epicardial arteries but no complete filling, Rentrop grade 3: Complete perfusion, contrast material determined to fill epicardial vessels completely. Rentrop Grades 0 and 1 were evaluated as poorly developed collateral circulation, while Rentrop grades 2 and 3 were evaluated as well-developed collateral circulation(8).

Visceral Fat Percentage, Body Mass Index and Waist Circumference Measurement

Body weight in kilograms and height in centimeters were measured and recorded before the discharge of patients. Body mass index (BMI) was obtained by dividing body weight in kg to the square of the height in meters. Body fat tissue percentage (%) and visceral fat percentage (%) were measured with the Omron HBF-500 Digital Body Analysis Scale that worked with Bioelectrical Impedance Analysis method(9).

Statistical Analysis

All analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the distribution of continuous variables fit in normal. Descriptive statistics were expressed as mean ± standard deviation for continuous variables, and case number and (%) for nominal variables. The continuous variables showing normal distribution were compared with the Student's t-test, while continuous variables with no normal distribution were compared by using the Mann-Whitney U test. The chi-square test or Fischer's Exact test were used in the comparison of categorical variables. Statistical significance was assumed for p-value <0.05. The Pearson correlation test was used in the evaluation of the relationship between parameters with normal distribution, while the Spearman's rho correlation test was used to examine the relationship between parameters that did not show normal distribution. Multivariate logistic regression analysis was used for evaluating independent markers on collateral use during analysis. Receiver operating characteristic (ROC) analysis was performed in order to determine the sensitivity and specificity of estimating the negative effect of visceral fat tissue, BMI and increase in waist circumference on coronary collateral development.

Results

A total of 148 patients were included in our study, consisting of 64 females (43.2%) and 84 males (56.8%) aged between 41 and 80 years with the mean age of 62±8.8 years.

From an angiographic aspect, 66 patients were classified in the good collateral group, and 82 patients were in the poor collateral group. Patients with good collaterals and poor collaterals were compared according to their demographic and clinical characteristics (Table 1).

Patients who were included in the study were separated in two groups according to visceral fat percentage. Those with values between 1% and 9% were placed in group 1 while those with values above 10% were placed in group 2. Ninety-three of those had high visceral fat percentage and remaining 55 patients were determined to have low visceral fat percentage.

Visceral fat percentage level of patients in the poor collateral group varied between 5% and 24%, and the mean visceral fat percentage was determined as 13.7%±4.7%. Meanwhile, visceral fat percentage level of patients in the good collateral group varied between 6% and 20%, and the mean visceral fat percentage was determined as 10.1±4.0%. This difference was determined to be statistically significant (p=0.011).

Laboratory results of the patients are shown in Table 2. The comparison of coronary angiographic and echocardiographic characteristics of the groups is presented in Table 3. Upon analyzing the relationship between the CCC and visceral fat percentage, linkage analyses are shown in Figure 1 according to the distinction of good and poor collateral and Rentrop classification.

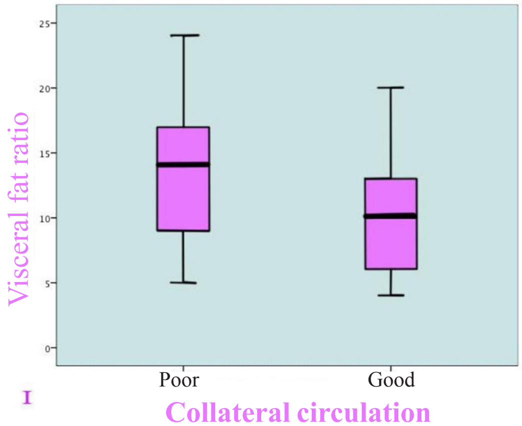
A weak negative correlation was determined upon performing correlation analysis between collateral level and visceral fat percentage, and despite being modest, it was found to be statistically significant (r=-0.415, p<0.001). A very weak correlation was found upon performing correlation analysis between collateral development and BMI (r=-0.211, p=0.010) and waist circumference (r=-0.203, p=0.013), and it was also determined to be statistically significant. There was a very weak correlation between collateral development and diabetes mellitus (DM) and it was found to be statistically significant (r=0.184, p=0.025). There was also a moderately positive but statistically significant correlation between stenosis percentage and collateral development (r=0.548, p<0.001).

The patients included in the study were divided into two groups: those with visceral fat ratio between 1 and 9 and those above 10. In 93 of these, visceral fat ratio was above 10 (high), and in the remaining 55 patients, it was observed between 1 and 9 (low). 52.7% of patients with low visceral fat ratio were male, and 59.1% of those with high ratio were male. However, no statistically significant difference was found (p=0.447). The mean age of the patients with low visceral fat ratio was 63.5±9.6 years,

Table 1. Demographic and clinical characteristics of patients

Demographic and clinical characteristics		Poor collateral (n=82)	Good collateral (n=66)	p
Age, years		61.2±9.3	63.0±8.2	0.233
Gender, (%)	**Male**	43 (52.4%)	41 (62.1%)	0.237
	Female	39 (47.6%)	25 (37.9%)	
BMI, (kg/m²)		28.2±2.4	27.3±2.3	**0.040**
Waist circumference, (cm)		98.9±8.4	96.4±8.8	0.081
Visceral fat	**Between 1-9**	23 (28.0%)	32 (48.5%)	**0.011**
	10 and above	59 (72.0%)	34 (51.5%)	
HT, s (%)		53 (64.6%)	39 (59.1%)	0.489
DM, s (%)		33 (40.2%)	18 (27.3%)	0.099
Dyslipidemia, s (%)		62 (75.6%)	47 (71.2%)	0.546
Smoking, s (%)		33 (40.2%)	21 (31.8%)	0,290
Family history, s (%)		26 (31.7%)	19 (28.8%)	0.701
Antiplatelet agents, s (%)		50 (36.1%)	36 (54.5%)	0.431
Beta blockers, s (%)		49 (59.8%)	37 (56.1%)	0.651
ACE inh/ARB, s (%)		43 (52.4%)	28 (42.4%)	0.225
Statin, s (%)		30 (36.6%)	27 (40.9%)	0.591

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, ACE inh: Angiotensin converting enzyme inhibitors, ARB: Angiotensin receptor blockers, n: Number
Important p-values shown as bold



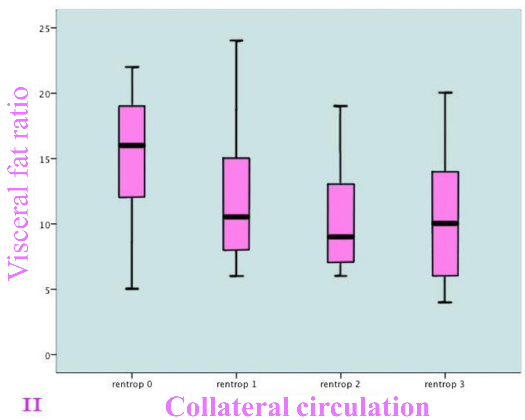


Figure 1. Linkage analyses between coronary collateral circulation and visceral fat percentage: (I) According to the distinction of good and poor collateral, (II) According to Rentrop classification

and the ratio was 61.1±8.2 in those with high ratio. There was no statistically significant relationship (p=0.108). We compared visceral fat ratio with each of the cardiovascular risk factors. Those with high visceral fat were found to be higher than those with low visceral fat; DM (40 vs 11 patients, p=0.004), hypertension (HT) (61 vs 33 patients, p=0.495), dyslipidemia (71 vs 38 patients, p=0.333), smoking (35 vs 19 patient, p=0.706), family history of CAD (31 vs 14 patients, p=0.314). However, except DM, there was no statistically significant difference (Table 4).

Visceral fat ratio was found to be significantly higher in those with higher BMI and waist circumference (p<0.001). The mean BMI was found to be 26.0±1.7 in those with low visceral fat, while it was found to be 28.8±2.2 in those with high visceral fat. Waist circumference was 92.6±7.6 in those with low visceral fat, while it was 100±7.7 in those with high visceral fat. In addition, In laboratory parameters compared with low and high visceral fats, respectively, triglyceride (170±82.9 vs 201±92.3, p=0.042) and cholesterol (179±42.6 vs 195±47.9, p=0.037, respectively) were higher. This was statistically significant (Table 4).

Very weak negative and positive correlations were determined in the correlation analysis of other parameters that might affect collateral development, and no statistically significant difference was determined between the groups

Table 2. Laboratory results of study groups

Laboratory results	Poor collateral (n=82)	Good collateral (n=66)	p
WBC, (x10³ µL)	8.6±1.4	8.2±1.9	0.139
Neutrophil	5.3±1.5	4.7±1.6	**0.016**
Lymphocyte	2.2±0.69	2.0±0.71	0.044
Hemoglobin, g/dL	13.6±1.7	13.8±1.7	0.465
MCV	84.2±4.4	85.4±4.7	0.110
Platelet (x10³ µL)	280±85.0	262±61.5	0.147
Glucose, mg/dL	153±55.5	142±51.6	0.215
Creatinine, mg/dL	0.89±0.2	0.90±0.19	0.798
LDL, mg/dL	112.3±40.7	109.8±35.0	0.693
HDL, mg/dL	40.5±7.2	40.4±8.8	0.989
Triglycerides, mg/dL	200±95.7	175±80.6	0.091

WBC: White blood cells, MCV: Mean corpuscular volume, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, n: Number
Important p-values shown as bold

(Table 5). In the correlation between and cardiovascular risk factors, a statistically significant positive correlation was determined between visceral fat percentage and DM (r=0.314, p<0.001).

A high positive correlation with BMI (r=0.704, p<0.001) and a moderate positive correlation with waist circumference (r=0.592, p<0.001) were determined upon performing correlation between BMI and waist circumference and visceral fat percentage, and they were determined to be statistically significant.

In the correlation between triglyceride and cholesterol levels and visceral fat percentage, a statistically significant

Table 3. Coronary angiographic and echocardiographic characteristics of groups

		Poor collateral (n=82)	Good collateral (n=66)	p
Critical coronary vessel	LAD	38 (46.3%)	29 (43.9%)	0.360
	Cx	21 (25.6%)	12 (18.5%)	
	RCA	23 (28.0%)	25 (37.9%)	
Rentrop collateral grade	Rentrop 0	46 (56.1%)	0	-
	Rentrop 1	36 (43.9%)	0	
	Rentrop 2	0	25 (37.9%)	
	Rentrop 3	0	41 (62.1%)	
Stenosis percentage, (%)		93.5±4.4	97.1±4.3	0.033
Lesion location	Proximal	33 (40.2%)	35 (53%)	0.121
	Distal	49 (59.8%)	31 (47%)	
LVEF, (%)		54.1±9.6	54.7±7.6	0.675

LAD: Left anterior descending artery, Cx: Circumflex, RCA: Right coronary artery, LVEF: Left ventricular ejection fraction, n: Number

Table 4. The comparison of visceral fat percentage and clinical and demographic characteristics

Visceral fat		Between 1 and 9 (n=55)	10 and above (n=93)	p
Age, years		63.5 ± 9.6	61.1 ± 8.2	0.108
Gender, (%)	Male	29 (52.7%)	55 (59.1%)	0.447
	Female	26 (47.3%)	38 (40.9%)	
BMI, (kg/m²)		26.0 ± 1,7	28.8 ± 2,2	**<0.001**
Waist circumference, (cm)		92.6 ± 7.6	100 ± 7.7	**<0.001**
HT, (%)		33 (60%)	61 (65.6%)	0.495
DM, (%)		11 (20%)	40 (43%)	**0.040**
Dyslipidemia, (%)		38 (69.1%)	71 (76.3%	0,333
Smoking, (%)		19 (34.5%)	35 (37.6%)	0,706
History of CAD, (%)		31 (56.4%)	61 (65.6%)	0.263
Family history, (%)		14 (25.5%)	31 (33.3%)	0.314
Triglycerides, mg/dL		170 ± 82.9	201 ± 92.3	**0.042**
Cholesterol, mg/dL		179 ± 42.6	195 ± 47.9	**0.037**
HDL, mg/dL		41.7± 9.5	39.7 ± 6,8	0.131
LDL, mg/dL		103.8 ± 34.4	115 ± 36.9	**0,038**

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery diseases, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, n: Number
Important p-values shown as bold

Table 5. Correlation analysis for collateral development

	r	p
Age, years	0.097	0.242
Gender	0.146	0.077
Visceral fat	**-0.415**	**<0.001**
BMI	-0.211	**0,010**
Waist circumference (cm)	-0.203	**0.013**
Stenosis percentage	0.548	**<0.001**
Lesion location	-0.096	0.244
Number of critical vessels	-0.136	0.100
HT, (%)	-0.098	0.234
DM, (%)	-0.184	**0.025**
CAD	-0.094	0.255
Family history, (%)	-0.029	0.726
Smoking	-0.127	0.124
Dyslipidemia, (%)	-0.053	0.522
Neutrophil	-0.150	0.070
Lymphocyte	-0.157	0.056
Platelet, ($x10^3$ µL)	-0.106	0.200
Glucose, mg/dL	-0.159	0.053
CRP	-0.154	0.122
Triglycerides, mg/dL	-0.144	0.080
Cholesterol, mg/dL	-0.113	0.172
LDL, mg/dL	-0.028	0.735

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery diseases, CRP: C-reactive protein, LDL: Low-density lipoprotein, n: Number
Important p-values shown as bold

Table 6. Correlation analysis about visceral fat level

	r	p
Age, years	0.143	0.082
Gender	0.019	0.821
Collateral circulation	-0.415	**<0.001**
BMI	0.704	**<0.001**
Waist circumference, (cm)	0.592	**<0.001**
HT, (%)	0.106	0.199
CAD	0.106	0.198
DM, (%)	0.314	**<0.001**
Smoking	0.131	0.111
Family history, (%)	0.060	0.470
Triglycerides, mg/dL	0.168	**0.041**
Cholesterol, mg/dL	0.216	**0.008**
LDL, mg/dL	0.184	**0.025**

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery diseases, CRP: C-reactive protein, LDL: Low-density lipoprotein
Important p-values shown as bold

weak positive correlation was determined with triglyceride (r=0.168, p=0.041), cholesterol (r=0.216, p=0.008) and low-density lipoprotein (r=0.184, p=0.025) levels. Although a very weak positive correlation was determined in the correlation analysis between other cardiac risk factors and visceral fat percentage level, these correlations were not statistically significant (Table 6).

In the multivariate logistic regression analysis performed to determine the factors affecting collateral development, visceral fat tissue and coronary stenosis percentage were determined to be statistically significant independent factors among the variables. Accordingly, it was determined that the increase in coronary stenosis percentage and the decrease in visceral fat percentage were independent predictors of good collateral artery development (Table 7).

Collateral development and visceral fat percentage, BMI, and waist circumference were compared in the ROC analysis of data. There was a statistically significant negative correlation between visceral fat level, BMI and collateral development. With 72.7% sensitivity and 58.5% specificity, a decrease was predicted in collateral

Table 7. Evaluation of the predictors of collateral development with multivariate logistic regression analysis

Parameter	OR	95% CI	p
Age, years	0.948	0.874-1.028	0.948
Gender	0.851	0.203-3.560	0.851
Visceral fat	0.740	0.602-0.909	**0.040**
BMI, (kg/m²)	0.989	0.631-1.549	0.960
Waist circumference, (cm)	1.040	0.941-1.153	0.430
HT, (%)	0.380	0.099-1.454	0.158
DM, (%)	0.344	0.048-2.460	0.289
Dyslipidemia, (%)	0.308	0.048-1.976	0.214
Smoking, (%)	0.440	0.127-1.530	0.197
Family history, (%)	3.716	0.798-1730	0.094
Stenosis percentage	1.220	1.070-1.390	**0.003**
Lesion location	0.409	0.116-1.437	0.163
Statin, (%)	0.450	0.116-1.749	0,249
Glucose, mg/dL	0.994	0.976-1.012	0.494
Creatinine, mg/dL	2.540	0.107-6020	0.564
CRP	0.620	0.336-1.114	0.126
Triglycerides, mg/dL	0.993	0.975-1.011	0.450
Cholesterol, mg/dL	1.016	0.937-1.101	0.699

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CRP: C-reactive protein
Important p-values shown as bold

Table 8. ROC analysis

	AUC	95% CI	Cut-off	Sensitivity	Specificity	p
Visceral fat	720	638-801	125	72.7%	58.5%	<0.001
BMI, (kg/m²)	600	508-692	28.3	72.7%	51.2%	0.370
Waist circumference, (cm)	587	495-679	101.5	66.7%	47.6%	0.690

ROC: Receiver operating characteristic curve, BMI: Body mass index, AUC: Area under the curve, CI: Confidence interval
Important p-values shown as bold

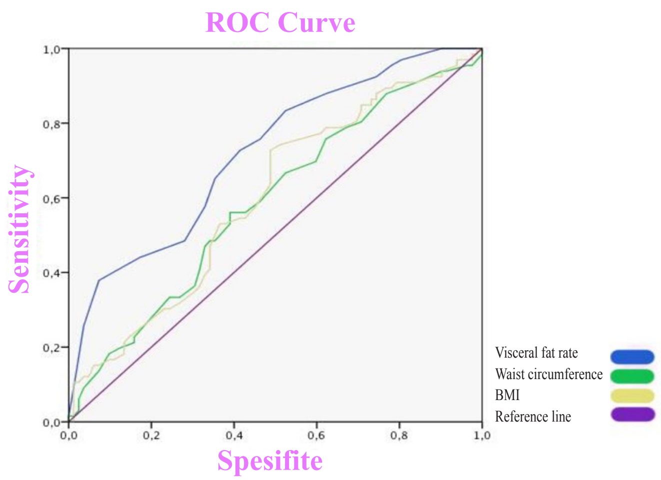


Figure 2. ROC analysis, comparison of the relation between collateral development and visceral fat percentage, BMI (body mass index), waist circumference with ROC analysis
ROC: Receiver operating characteristic

development at 12.5 cut-off level for visceral fat percentage (Table 8, Figure 2).

Discussion

It is considered that the development of coronary collateral vessels in human heart is processed through the combined development of two different types of adaptation mechanisms, angiogenesis and arteriogenesis[10]. Endothelial functions are known to have a crucial role in the maturation process of collateral vessels[11,12]. The interpersonal difference in collateral development level is suggested to be caused by endothelial dysfunction. Fat tissues do not only store fatty acids, they also play a central role in glucose and lipid metabolism. Numerous hormones such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), adiponectin and leptin are produced in adipose tissue and increase in adipose tissue mass directly increases systemic inflammation[13]. In the current study population, visceral fat percentage was significantly higher in the poor collateral group compared to the good collateral group (p=0.011). A significant negative relation was determined between visceral fat percentage and Rentrop flow upon separating the patients into sub-groups according to the Rentrop classification (p=0.003). High visceral fat percentage was determined to be a negative predictor for coronary collateral development in logistic regression analysis. In our study, we showed that the increase in visceral fat percentage was an independent factor in terms of poor collateral development. Regarding other cardiovascular risk factors, apart from visceral fat tissue, there is no significant difference between the subjects with good and poor collateral development.

Among cardiovascular risk factors, diabetes, HT, hyperlipidemia, smoking and family history of CAD were observed to be more common in the group with high visceral fat percentage; however, no statistically significant difference was determined in the risk factors other than diabetes. The frequency of other factors was more prominent in the group with high visceral fat percentage, albeit not statistically significant.

The measurement of waist circumference reveals abdominal obesity[14]. However, it does not distinguish visceral fat from subcutaneous fat tissue. The reason for that is visceral fat tissue is not affected from skin and muscle layers as in waist circumference measurement. We determined higher waist circumference and BMI in people with high visceral fat percentage (p<0.001). Although a positive correlation was determined between visceral fat percentage with waist circumference and BMI, visceral fat percentage was determined to be a determinant on collateral development with higher sensitivity and specificity compared to other factors. Although a statistically significant negative correlation was determined between collateral development and visceral fat percentage and BMI, no statistically significant difference was determined between those and waist circumference despite a negative correlation. Accordingly, it was determined that the effect of visceral fat tissue on coronary collateral development was stronger compared to BMI and waist circumference.

There is a positive correlation between body mass and peripheral leukocyte count. It was shown in a high number of studies that inflammatory proteins in circulation (CRP, IL-6, PAI-1, P-selectin, vascular cell adhesion molecule-1, fibrinogen, angiotensinogen, SAA3) are increased with an increase in body mass[15].

Coronary collaterals are potential vascular structures presenting in normal heart and emerge in the presence of serious CAD and work for the protection of myocardial vitality. It is well-known that the presence of collateral vessels and increased collateral circulation level are associated with left ventricular function status[16,17]. Studies have demonstrated that collateral circulation reduces myocardial ischemia, decreases infarct area, positively increases left ventricular function, decreases ventricular aneurysm formation, and most importantly, increases survival[18,19]. However, left ventricular systolic functions were statistically similar between the groups of good and poor collateral development in our analysis. This difference may be determined more accurately in studies of patient follow-up after discharge.

While collateral vessel development is formed as a response to severe coronary stenosis, the factors that affect collateral development level in the presence of severe CAD may not be clearly determined[20]. Stenosis in the artery providing the collateral flow (donor artery) is another important factor in collateral vessel development. It has been indicated that stenosis rate should be ≥90% and collateral vessel diameter should be above 100 µm for angiographic imaging[21]. Arteriogenesis is induced in the result of increased "shear stress" after serious artery obstructions[22]. It is suggested that MCP-1 (monocyte chemotactic protein-1) is effective on this mechanism[10]. While there is maximum shear at the beginning, this is gradually reduced with the increasing diameter of collateral vessels[23]. Assuming that hypertension will play a facilitating role in this mechanism, it can be considered to affect collateral development positively. In the result of some studies investigating the relationship between the presence of coronary collateral in hypertension and left ventricular hypertrophy in CAD, it has been determined that hypertensive patients have better developed collateral, and a positive relationship has been demonstrated between coronary collaterals and left ventricular wall thickness[24,25]. Although studies on humans and animals have shown that epicardial coronary arteries are dilated in hypertrophic ventricle, it is now clear why left ventricular hypertrophy increases CCC; it may be associated with myocardial ischemia. While the hypertension incidence was higher in the poor collateral group compared to the good collateral group in our study, no significant difference was determined between the two groups. We have attributed this result to the fact that HT was under control due to drug therapy in our patients.

In type II DM, in which insulin resistance plays a significant role, deaths are largely associated with cardiovascular diseases[26]. There are various opinions on the effect of DM on collateral development. Abaci et al.[27] have shown that collateral development is weaker in DM due to the fact that endothelial function, which plays a large role in collateral development, is impaired in diabetics. Melidonis et al.[28] have determined higher coronary collateral vessel development rate in diabetics compared to the non-diabetics. Zbinden et al.[29] did not determine a significant difference between the two groups with regard to collateral flow in their study in which they compared patients with or without DM. As in diabetic retinopathy, DM is known to induce angiogenesis but inhibits arteriogenesis[30]. In our study, 51 of 148 patients had diabetes, and DM prevalence was not determined to be statistically significant even though it was higher in the poor collateral group, which might be due to low diabetic case number.

Study Limitations

Although no collateral was observed with angiographic method, the recovery in left ventricular function with revascularization is attributed to the fact that capillary collateral flow that could not be imaged in angiography protects myocardial function in a hibernated manner[10]. Considering that we can detect collaterals above 100 µm, the presence of collateral flow at an angiographically invisible level may have prevented the development of infarction in some cases with poor collaterals. The use of angiography in the evaluation of collateral flow and this limitation in the collateral evaluation of angiography may have affected the results.

Conclusion

Despite the advancements in treatment modalities, cardiovascular diseases are still the first underlying reason of morbidity and mortality around the world. This study reveals that one of the components of obesity, increased visceral fat percentage, may negatively affect coronary collateral development in metabolic syndrome. In addition, cardiovascular diseases are increased in parallel with the increase in visceral fat tissue. The cardiovascular risk factors and the development of cardiovascular diseases may be prevented with visceral fat percentage follow-up and treatment. For this reason, ensuring weight loss, regular exercise and healthy diet poses utmost importance in these patients.

Ethics

Ethics Committee Approval: Ethics committee approval of our study was obtained from Dicle University Faculty of Medicine Clinical Research Ethics Committee on 25.12.2015 with the decision number 139.

Informed Consent: The study was designed retrospectively. All patients have been informed preceding the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., Bu.A, Concept: M.Ö., M.D., Design: R.K., B.A., Data Collection or Processing: A.A., Analysis or Interpretation: A.A., T.G., Literature Search: A.A., Bu.A., Writing: A.A., T.G.

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References

1. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340:115-26.
2. Cohen MV. The functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance collateral flow. Am Heart J 1978;95:396-404.
3. Charney R, Cohen M. The role of the coronary collateral circulation in limiting myocardial ischemia and infarct size. Am Heart J 1993;126:937-45.
4. Newman PE. The coronary collateral circulation: determinants and functional significance in ischemic heart disease. Am Heart J 1981;102:431-45.
5. Schwarz F, Flameng W, Ensslen R, Sesto M, Thormann J. Effect of coronary collaterals on left ventricular function at rest and during stress. Am Heart J 1978;95:570-7.
6. Vanoverschelde JL, Wijns W, Depré C, et al. Mechanisms of chronic regional postischemic dysfunction in humans. New insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993;87:1513-23.
7. Murphy JG, Lloyd MA. Mayo Clinic Cardiology Concise Textbook.3rd Ed. Rochester, Minnesota: Mayo Clinic Scientific press, 2005;p.687-781.
8. de Vries J, Anthonio RL, van den Heuvel AF, et al. Incidence and angiographic predictors of collateral function in patients with stable coronary artery disease scheduled for percutaneous coronary intervention. Catheter Cardiovasc Interv 2007;70:197-202.
9. Rahmouni K, Mark AL, Haynes WG, Sigmund CD. Adipose depot-specific modulation of angiotensinogen gene expression in diet-induced obesity. Am J Physiol Endocrinol Metab 2004;286:891-5.
10. van Royen N, Piek JJ, Buschmann I, Hoefer I, Voskuil M, Schaper W. Stimulation of arteriogenesis; a new concept for the treatment of arterial occlusive disease. Cardiovasc Res 2001;49:543-53.
11. Glasser SP, Selwyn AP, Ganz P. Atherosclerosis: risk factors and the vascular endothelium. Am Heart J 1996;131:379-84.
12. Schaper W, Sharma HS, Quinkler W, Markert T, Wünsch M, Schaper J. Molecular biologic concepts of coronary anastomoses. J Am Coll Cardiol 1990;15:513-8.
13. Engeli S, Gorzelniak K, Kreutz R, Runkel N, Distler A, Sharma AM. Co-expression of renin-angiotensin system genes in human adipose tissue. J Hypertens 1999;17:555-60.
14. Pouliot MC, Despre´s JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460–8.
15. Ling Y, Lee H, Berg AH, Lisanti MP, Shapiro L, Scherer PE. The Lipopolysaccharide-activated Toll-like Receptor (TLR)-4 Induces Synthesis of the Closely Related Receptor TLR-2 in Adipocytes JBC 2000;275:24255-63.
16. Blanke H, Cohen M, Karsch KR, Fagerstrom R, Rentrop KP. Prevalence and significance of residual flow to the infarct zone during the acute phase of myocardial infarction. J Am Coll Cardiol 1985;5:827-31.

17. Nicolau JC, Pinto MA, Nogueira PR, Lorga AM, Jacob JL, Garzon SA. The role of antegrade and collateral flow in relation to left ventricular function post-thrombolysis. Int J Cardiol 1997;61:47-54.

18. Habib GB, Heibig J, Forman SA, et al. Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. Circulation 1991;83:739-46.

19. Hirai T, Fujita M, Nakajima H, et al. Importance of collateral circulation for prevention of left ventricular aneurysm formation in acute myocardial infarction. Circulation 1989;79:791-6.

20. Lazarous DF, Scheinowitz M, Shou M, et al. Effects of chronic systemic administration of basic fibroblast growth factor on collateral development in the canine heart. Circulation 1995;91:145-53.

21. Newman PE. The coronary collateral circulation: determinants and functional significance in ischemic heart disease. Am Heart J 1981;102:431-45.

22. Scholz D, Schaper W. Preconditioning of arteriogenesis. Cardiovasc Res 2005;65:513-23.

23. Heil M, Schaper W. Pathophysiology of collateral development. Coron Artery Dis 2004;15:373-8.

24. Braunwald E. Heart Disease: A Textbook of Cardiovasculer Medicine. Philadelphia: W.B. Saunders Company 1997.

25. Zenon SK, Dimitrios TK, Nicholas AM, Evangelos PM, Thomas D, Pavlos KT. Coronary collateral circulation in coronary artery disease and systemic hypertension. Am J Cardiol 1991;67:687-90.

26. Gray RP & Yudkin JS Int Textbook of Diabetes mellitus, 1997.

27. Abaci A, Oğuzhan A, Kahraman S, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. Circulation 1999;99:2239-42.

28. Melidonis A, Tournis S, Kouvaras G, et al. Comparison of coronary collateral circulation in diabetic and nondiabetic patients suffering from coronary artery disease. Clin Cardiol 1999;22:465-71.

29. Zbinden R, Zbinden S, Billinger M, Windecker S, Meier B, Seiler C. Influence of diabetes mellitus on coronary collateral flow: an answer to an old controversy. Heart 2005;91:1289-93.

30. Schaper W, Buschmann I. Collateral circulation and diabetes. Circulation 1999;99:2224-6.

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Association Between Microalbuminuria and Pulse Pressure Among Patients with Isolated Systolic and Diastolic Hypertension

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Abstract

Objectives: The aim of this study is to examine the prevalence and predictors of microalbuminuria and to investigate the association between microalbuminuria and pulse pressure among patients with isolated systolic and diastolic hypertension (DH).

Materials and Methods: In this cross-sectional study, patients with DH and isolated systolic hypertension (ISH) were included. Data including patient age, sex, duration of hypertension (HT), comorbidities, and drugs were recorded. Blood analysis of serum total cholesterol, high D-density lipoprotein (HDL) cholesterol, triglyceride, urea, creatinine, and fasting blood glucose, urinalysis, electrocardiography (ECG), transthoracic echocardiography, exercise stress test (EST), and coronary angiography (if the patient had a positive EST result) were performed.

Results: Overall, we included 183 patients (58.5% female) with HT. The patients with ISH had significantly higher pulse pressure, left ventricular (LV) mass, and LV mass index, but had a shorter duration of HT and lower diastolic blood pressure than those with DH. All patients were in sinus rhythm, and there were no ischemic ECG changes. Fifty-

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Abstract

nine (32.2%) patients had microalbuminuria (MA) (≥20 µg/min). LV mass, left atrial diameter, E/A ratio, systolic blood pressure (SBP), pulse pressure, and frequency of LVH were significantly higher in patients with MA than in patients without MA. The prevalence of angiographically proven atherosclerotic heart disease was similar in patients with and without microalbuminuria. Multivariate binary logistic regression analysis revealed that only systolic pressure and left atrial diameter were independent associates of microalbuminuria. Each 1 mmHg increase in SBP was associated with a 3% increase in the risk of having microalbuminuria (p=0.04). In addition, each 1 mm increase in the diameter of the left atrium increased the risk of having microalbuminuria by 20% (p=0.02).

Conclusion: This study demonstrated that microalbuminuria in hypertensive patients was independently associated with left atrial size and systolic blood pressure, but not with pulse pressure.

Keywords: Hypertension, pulse pressure, microalbuminuria, cardiac disease, isolated systolic hypertension, diastolic hypertension

Introduction

Microalbuminuria (MA) is defined as the presence of 30-300 mg of albumin in a 24-hour collected urine sample (or 20-200 mcg/min)[1]. MA occurs as a result of disruption in the glomerular filtration barrier. Major causes of MA include, but not limited to, diabetes mellitus (DM), hypertension, and renal disease. In addition, diurnal variation and a number of functional causes of MA have been reported[2].

MA is common even in the general population. Several epidemiologic studies reported the prevalence of MA in the healthy general population ranging between 2.2% and 11.8%[3].

Mogensen, who was the pioneer reporting the significance of albuminuria in cardiorenal disease, reported first that the presence of MA was predictive of overt proteinuria as well as cardiovascular mortality in type 2 diabetic patients[4]. After this first report, it was elucidated that there was a linear relationship between MA level and cardiovascular risk. Even albuminuria levels below the MA lower threshold were associated with increased cardiovascular risk in the Framingham Offspring Study[5].

Hypertension is one of the major causes of MA, which is considered as a target organ damage of high blood pressure[6]. It has been reported that MA is found in up to 15% of patients with primary hypertension[7]. On the other hand, some other studies reported an exceptionally high prevalence of MA in hypertensive patients reaching up to 50%[8,9].

Several factors may account for the great variability of MA prevalence among hypertensive patients. First, higher blood pressure levels are associated with higher degrees of MA. Second, factors such as exercise, fever, heart failure, and urinary tract infection may lead to temporary albumin excretion with urine. Third, some factors related to high blood pressure might be at work. For instance, different types of blood pressure patterns such as nocturnal blood pressure elevation, masked hypertension and white-coat hypertension are independently associated with MA development[10,11]. In addition, subsequent studies also showed an association between systolic (but not diastolic) blood pressure and pulse pressure with the development of MA[12-15]. Considering the magnitude of the problem, available studies investigating the relationship between blood pressure patterns and MA seem inadequate. In another population-based study, pulse pressure was reported to affect MA development in an ethnicity-dependent manner[16]. Thus, further studies in different ethnic groups seem necessary to better understand the relationship between pulse pressure and MA.

Due to the high prevalence of MA in the general population and hypertensive patients and its unequivocal causal association with cardiovascular and renal disease, we aimed to study the prevalence and predictors of MA in hypertensive patients. We exerted special attention on the relationship between pulse pressure, systolic and diastolic hypertension (DH) as well as cardiovascular disease in a Turkish hypertensive patient cohort.

Materials and Methods

Design, Setting and Population

In this cross-sectional study, patients with DH and isolated systolic hypertension (ISH) were included. The study was approved by the ethics committee of Uludağ University Medical Faculty (2003-18/36). Written informed consent forms were signed by each study participant.

Data including patient age, sex, duration of HT, comorbidities, and drugs were recorded for each participant. Inclusion criteria were as follows: having DH or ISH, having serum urea and creatinine levels in normal limits for age and sex, and normal urine microscopy.

Exclusion criteria were the presence of severe valvular heart disease, angina pectoris, findings of previous myocardial infarction in electrocardiography, coronary artery disease (CAD), urinary tract infection, fasting blood glucose >110 mg/dL, having with pacing rhythm and atrial fibrillation, segmentary wall motion abnormalities, thyroid disease, anemia, liver disease, chronic obstructive pulmonary disease and secondary hypertension.

Laboratory Evaluations

Blood analysis of serum total cholesterol (TC), high density lipoprotein (HDL) cholesterol, triglyceride (TG), urea, creatinine, and fasting blood glucose and urinalysis were performed after 12 hours of fasting. Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula as follows: LDL (mg/dL) = TC (mg/dL) - HDL (mg/dL) - TG (mg/dL)/5[17].

MA level was measured in 24-hour urine by an immunometric assay with fluorescence detection on the DPC IMMULITE 2000 analyzer (Euro/DPC Ltd, Llanberis, UK). Urinary albumin concentration of ≥20 µg/minute (approximates to 30 mg/day) was considered as MA.

Anthropometric and Blood Pressure Measurements

Patient height and weight were measured. Body mass index was calculated by dividing weight in kilograms by the square of height in meters[18].

Blood pressure (BP) was measured three times with two-minute intervals, from the right arm with a mercury manometer based on Korotkoff sounds, sitting upright position, after a rest of at least 10 minutes. The arithmetic mean of the three BP values was calculated for each patient as the final BP measurement.

ISH was defined when systolic BP was ≥140 mmHg and diastolic BP was <90 mmHg[19]. DH was diagnosed according to the Joint National Committee (JNC7) guideline (systolic BP less than 140 mmHg and a diastolic BP of at least 90 mmHg)[19]. Pulse pressure was calculated by subtracting the diastolic BP value from systolic BP value. All anthropometric and BP measurements were performed by the same investigator.

Cardiac Evaluation

Standard 12-lead electrocardiography (ECG), transthoracic echocardiography, and exercise stress tests (EST) were performed in all patients. If the patient had a positive EST result, coronary angiography was performed additionally.

Two-dimensional, M-mode, and Doppler echocardiography was performed using the SONOS 2000 device (Hewlett-Packard Medical Systems, Andover, MA, USA) in accordance with the recommendations of the American Society of Echocardiography[20]. Echocardiography was performed while the participant was lying on the left side. Doppler measurements were carried out during expiration. All measurements were taken by the same experienced echocardiography operator who was blinded to the status of the patient. E wave, A wave, and E/A ratio were measured by taking pulsed Doppler records of the mitral valve along with ECG recording. Left ventricular (LV) systolic and diastolic diameter, interventricular septal (IVS), and LV posterior wall thickness (PWT) were measured. Interventricular septal (IVS) and LV PWT, and end-diastolic diameter (EDD) were calculated with the Devereux formula[21]. LV mass index (LVMI) was computed using the following equation: LVMI= LV mass/body surface area. A patient was considered to have LV hypertrophy (LVH) if the LV mass index was greater than 134 g/m^2 in men and greater than 110 g/m^2 in women[22,23].

The EST was performed with the standard Bruce protocol[24]. Drugs that could interfere with the test results, such as beta-blockers, calcium channel blockers, digoxin, etc., were discontinued twice the drug half-life before the test. The test was terminated in case of obtaining the predetermined heart rate (220-age), development of severe shortness of breath, chest pain, weakness, ST depression (>3 mm), ST-elevation (>2 mm), ventricular or supraventricular tachyarrhythmias, left bundle branch block, second or third-degree block, decrease (more than 20 mmHg) or increase (more than 250 mmHg) in systolic blood pressure (SBP). The result was interpreted as positive in terms of ischemia in the presence of ST elevation (>1 mm, in derivation that without Q wave) or downsloping ST depression in at least two successive leads after 80 milliseconds from the J point, 20 mmHg decrease in SBP, occurrence of angina pectoris, and angina equivalent shortness of breath.

Coronary angiography was performed in patients whose EST result was positive for ischemia by using the femoral artery with the Judkin's technique (Philips DCI device)[25]. The coronary angiograms were interpreted by experienced invasive cardiologists. Atherosclerotic plaques in the epicardial coronary arteries (greater than 30% in lumen narrowing) were accepted as CAD[26].

Statistical Analysis

The Kolmogorov-Smirnov test was used to check the normality assumptions of the data. Normally distributed variables were presented as a mean ± standard deviation, whereas non-normally distributed variables were given as median and min-max. The Independent samples t-test or the Mann-Whitney-U test were used for numerical variables, and chi-square was employed for categorical variables. Binary logistic regression analysis was performed to determine independent associates of MA.

SPSS 10.0 software package (IBM, Armonk, NY, USA) was used to analyze data of the study. A p-value <0.05 was accepted as statistically significant.

Results

Overall, we included 183 patients (58.5% female) with hypertension. The mean age of the entire study cohort was 55.1±9.2 years (range: 31-80 years). The median length of duration of hypertension was 4 years (ranging from 1 to 20 years). Clinicodemographic characteristics and laboratory values of the entire study cohort are shown in Table 1.

When the patients who had DH and ISL were compared, it was observed that patients with ISL had significantly higher pulse pressure, LV mass, and LV mass index, but had a shorter duration of HT and lower diastolic BP. Moreover, patients with ISL were significantly older than the patients with DH (Table 2). The prevalence of angiographically proven atherosclerotic heart disease was similar in patients with and without MA.

We divided the study population into two groups according to their MA levels. While patients with MA ≥20 μg/min were considered MA positive group, those with MA <20 μg/min were defined as MA negative group. Fifty-nine (32.2%) patients were MA positive. The resting ECG parameters were compared in patients with and without MA. All patients were in sinus rhythm, and there were no ischemic ECG changes. Patients with MA were significantly older than patients without MA. Besides, LV mass, LVMI, left atrial diameter, E/A ratio, SBP, pulse

Table 1. Clinicodemographic characteristics and laboratory values of the entire study cohort

Parameters	Values (mean ± SD or median and min-max)
Age, (years)	55±9.2
Gender	
Female/male	107 (58.5%)/76 (41.5%)
BMI, (kg/m^2)	27.9±4.1
Comorbidities, n (%)	
Coronary artery disease (family history)	26.2%
Duration of hypertension, (years)	4 (max: 20, min: 1)
Dyslipidemia	39.3%
Microalbuminuria	59 (32.2%)
Smoking	20.2%
Antihypertensive medications, n (%)	
No medication	27 (14.9%)
ACE inhibitors	15%
Beta-blockers	29%
Calcium channel blockers	15%
Multi-drug	26.1%
Laboratory parameters	
Fasting blood glucose, (mg/dL)	81±11
Total cholesterol, (mg/dL)	206±40
LDL-cholesterol, (mg/dL)	128±37
HDL-cholesterol, (mg/dL)	46±7
Triglycerides, (mg/dL)	133 (max: 386, min: 35)
Microalbuminuria, (µg/min)	13 (max: 179, min: 1.2)
Blood pressure measurements	
Systolic blood pressure, (mmHg)	152.2±19.2
Diastolic blood pressure, (mmHg)	91.1±9.3
Pulse pressure, (mmHg)	61.1±17

BMI: Body mass index, ACE: Angiotensin-converting enzyme, LDL: Low density lipoprotein, HDL: High density lipoprotein, max: Maximum, min: Minimum, SD: Standard deviation, n: Number

pressure, and frequency of LVH were significantly higher in patients with MA than those without MA (Table 3).

Multivariate binary logistic regression analysis revealed that only systolic pressure and left atrial diameter were independent associates of MA. Each 1 mmHg increase in SBP was associated with a 3% increase in the risk of having MA (p=0.04). In addition, each 1 mm increase in the diameter of the left atrium increased the risk of having MA by 20% (p=0.02) (Table 4).

Discussion

The notable findings of the present study were as follows: (i) there was not a difference between the patients with diastolic and ISH in terms of rate of MA. (ii) SBP and pulse pressure were statistically significantly higher among patients who had MA compared to patients without MA. (iii) Although there was no difference regarding the rate of CAD, patients with MA had a significantly higher LV mass and LV mass index relative to patients without MA. (iv) Multivariate logistic regression analysis

Table 2. Comparison of demographic characteristics, clinical and laboratory data of patients with diastolic hypertension and isolated systolic hypertension

	Diastolic hypertension (n=124)	Isolated systolic hypertension (n=59)	p-value
Age, (years)	51.5±7.9	62.6±6.9	0.001
Gender			
Female/male	76/48	31/28	NS
BMI, (kg/m^2)	28.1±4.2	27.5±3.7	NS
Comorbidities, n (%)			
Duration of hypertension	5 (max: 10 min: 3)	3.5 (max: 20 min: 1)	0.007
Microalbuminuria positivity	28%	40.7%	NS
Echocardiographic left ventricular measurements			
Left ventricular mass, (gram)	197±55.3	246.9±75	<0.001
Left ventricular mass index, (gram/m^2)	106 ± 27.5	134.7±40	<0.001
Laboratory parameters			
Fasting blood glucose, (mg/dL)	87±11	91±10	NS
Total cholesterol, (mg/dL)	205±39	207±43	NS
LDL-cholesterol, (mg/dL)	127±38	131±35	NS
HDL-cholesterol, (mg/dL)	46.8±9.6	46.6±9.7	NS
Triglycerides, (mg/dL)	132	137	NS
Microalbuminuria, (µg/min)	13.1	12.8	NS
Blood pressure measurements			
Systolic blood pressure, (mmHg)	149.1±18.1	159.1±18.1	0.001
Diastolic blood pressure, (mmHg)	93±10.3	83.6±5.5	<0.001
Pulse pressure, (mmHg)	56.1±14	71.8±18	<0.001

BMI: Body mass index, ACE: Angiotensin-converting enzyme, LDL: Low density lipoprotein, HDL: High density lipoprotein, max: Maximum, min: Minimum, SD: Standard deviation, NS: Not significant, n: Number

revealed that independent predictors of MA were SBP and left atrial diameter.

The causal association between elevated BP and the development of MA has been firmly established(27,28). Moreover, it has been demonstrated that not only the level of BP but also several characteristics of BP elevation such as systolic and diastolic components, pulse pressure, non-dipping pattern (nocturnal hypertension) had an impact in this respect(10,11,29). However, studies exploring the relationship between BP components such as pulse pressure and SBP are limited(12,14,15,30,31). Several hypotheses have been put forward to explain the effect of systolic and pulse pressures on MA development. Actually, SBP is reflected in the glomerulus and associated with intraglomerular HT and consequent glomerular injury(32,33). A study recruited 1,858 treatment-naïve hypertensive patients and they found SBP [odds ratio (OR): 1.010, confidence interval (CI): 1.005-1.016, p<0.001] and pulse pressure (OR: 1.009, 95% CI: 1.003-1.015, p=0.003) as independent predictors of MA(27).

In our study, the only independent associates of MA were left atrial diameter and SBP. In contrast to previous studies, pulse pressure was not found as an independent predictor of MA in hypertensive patients. Since our patients were not treatment-naïve, this might have led to the negative finding of pulse pressure and MA interaction. On the other hand, each 1 mmHg increase in SBP was associated with a 3% increased risk of MA.

MA is long established as an independent cardiovascular risk factor(33). This effect is independent of accompanying

Table 3. Comparison of demographic characteristics, clinical and laboratory data of patients with and without microalbuminuria

	Patients with MA (MA ≥20 μg/min) (n=59)	**Patients without MA (MA <20 μg/min) (n=124)**	**p-value**
Age, (years)	57.2±9.9	54.3±8.8	0.045
Gender			
Female/male	32/27	75/49	NS
BMI, (kg/m²)	27.4±4.8	28.2±3.7	NS
Comorbidities, n (%)			
Coronary artery disease (family history)	32%	23.4%	NS
Duration of hypertension, (years)	5.7 (max: 19, min: 1)	5.3 (max: 20, min: 1)	NS
Dyslipidemia	30.5%	43.5%	NS
Smoking	13.6%	23.6%	NS
Cardiac measurements			
Frequency of LVH (in ECG), (%)	27.1%	20.2%	NS
Frequency of LVH (in ECHO), (%)	50.8%	29%	0.004
Left ventricular mass (in ECHO), (gram)	231.6±67	205.2±64	0.001
LVMI (in ECHO), (g/m²)	125.6±34.6	111±34.1	<0.001
Left atrial diameter, (mm)	39.1±3.26	37.3±3.2	<0.001
E wave	0.69±0.19	0.68±0.17	NS
A wave	0.73±0.18	0.75±0.16	NS
E/A ratio	1.03±0.46	0.94±0.33	0.014
E wave DT, (milliseconds)	178.3±50.8	182.5±47.5	NS
IVRT, (milliseconds)	91.2±28.7	94.1±21.4	NS
Positive stress test result, (%)	9 (15.3%)	13 (10.5%)	NS
Coronary artery disease, (%)	9 (15.3%)	8 (6.5%)	NS
Laboratory parameters			
Fasting blood glucose, (mg/dL)	89±9.2	88±12	NS
Total cholesterol, (mg/dL)	203±45	207±38	NS
LDL-cholesterol, (mg/dL)	128±39	128±35	NS
HDL-cholesterol, (mg/dL)	46±10	47±9	NS
Triglycerides, (mg/dL)	151 (max: 380, min: 40)	145 (max: 386, min: 35)	NS
Microalbuminuria, (μg/min)	25.8	10.6	<0.001
Blood pressure measurements			
Systolic blood pressure, (mmHg)	159.5±19.1	148.9±18.5	<0.001
Diastolic blood pressure, (mmHg)	91.2±11.6	89±9.2	NS
Pulse pressure, (mmHg)	66.1±17.1	58.8±17.2	0.008

DT: Deceleration time, IVRT: Isovolumic relaxation time, LVH: Left ventricle hypertrophy, LVMI: Left ventricular mass index, MA: Microalbuminuria, NS: Non significant, ECHO: Echocardiogram, BMI: Body mass index, LDL: Low density lipoprotein, HDL: High density lipoprotein, max: Maximum, min: Minimum, E: Early ventricular filling velocity, A: Late ventricular filling velocity, SD: Standard deviation

hypertension or DM, too. Some hypotheses regarding this independent and strong relationship point to the fact that MA is a marker of generalized endothelial dysfunction, which also underpins the development of atherosclerotic heart disease[34-36]. Wider pulse pressure operates as a marker of the pulsatile hemodynamic load and conduit vessel stiffness. Hence pulse pressure seems as a significant cardiovascular risk factor[15]. Thus, wider pulse pressure

Table 4. Multivariate logistic regression analysis to determine the independent associates of microalbuminuria

	Multivariate LR		
Variables	**OR**	**95% CI**	**p-value**
Systolic blood pressure	1.03	1.009-1.046	0.04
Left atrial diameter	1.202	1.073-1.347	0.02

OR: Odds ratio, CI: Confidence interval, LR: Logistic regression

seems like a plausible common risk factor impacting both MA and atherosclerotic heart disease. Recently, pulse pressure has been linked to diabetes inflammation and obesity, all of which are associated with MA. Thus, pulse pressure might be related to the development of MA not only through high BP but also with diabetes, inflammation and obesity[37].

Our results revealed that the prevalence of atherosclerotic disease that was demonstrated with coronary angiography among hypertensive patients with MA was no different from those who did not have MA. On the other hand, microalbuminuric patients had significantly higher rates of LV mass, LV mass index, and left atrial diameter relative to non-microalbuminuric patients. The lack of difference regarding atherosclerotic disease between the groups might be due to the relatively small sample size of our study and drug use, such as statins and angiotensin-converting enzyme (ACE) inhibitors that might affect the development of manifest atherosclerotic disease.

Some limitations of the present work are as follows: First, we did not recruit treatment-naïve patients. We are not sure that patients on statin and ACE inhibitor treatments were matched between the microalbuminuric and nonmicroalbuminuric patients. Second, we did not employ ambulatory BP measurement, which was shown to be a better predictor of cardiovascular morbidity and mortality. Instead, we relied on the office measurement, which may be suffered from the white coat effect. Third, our sample size might not be sufficient to elucidate subtle differences between the MA groups.

Despite its limitations, we think that current work makes important contributions to the literature. We evaluated the association between MA and BP components in the context of cardiovascular disease. We evaluated the cardiac function of the study participants in detail with echocardiography, ESTs, and angiography, when needed. Thus, we think that our results portrayed a more real-world situation in which the association of MA and BP was investigated.

Conclusion

This present study demonstrated that MA in prevalent hypertensive patients was independently associated with left atrial size and systolic BP, but not with pulse pressure. Moreover, the frequency of proven atherosclerotic heart disease was not different between the microalbuminuric and non-microalbuminuric hypertensive patients. It seems there is an exact need to conduct more studies in this field.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Uludağ University Medical Faculty (2003-18/36).

Informed Consent: Written informed consent forms were signed by each study participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception and design: Ş.C., J.C., D.Y., Acquisition of data: E.M., S.S., Drafting of the manuscript: Ş.C., S.S., Critical revision of the manuscript for important intellectual content: J.C., D.Y., O.A.S., Statistical analysis: Ş.C., Administrative, technical or material support: D.Y., Supervision: J.C., D.Y., O.A.S., S.G., A.A.

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References

1. Basi S, Fesler P, Mimran A, Lewis JB. Microalbuminuria in type 2 diabetes and hypertension: a marker, treatment target, or innocent bystander? Diabetes Care 2008;31:194-201.
2. Segura J, Ruilope LM, Rodicio JL. Microalbuminuria. Clin Exp Hypertens 2004;26:701-7.
3. Yuyun MF, Khaw KT, Luben R, et al. Microalbuminuria, cardiovascular risk factors and cardiovascular morbidity in a British population: the EPIC-Norfolk population-based study. Eur J Cardiovasc Prev Rehabil 2004;11:207-13.
4. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310:356-60.
5. Arnlöv J, Evans JC, Meigs JB, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005;112:969-75.
6. Reboldi G, Gentile G, Angeli F, Verdecchia P. Microalbuminuria and hypertension. Minerva Med 2005;96:261-75.
7. Jones CA, Francis ME, Eberhardt MS, et al. Microalbuminuria in the US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis 2002;39:445-59.
8. Böhm M, Thoenes M, Danchin N, Bramlage P, La Puerta P, Volpe M. Association of cardiovascular risk factors with microalbuminuria in hypertensive individuals: the i-SEARCH global study. J Hypertens 2007;25:2317-24.
9. Aggarwal HK, Jain D, Mor S, Yadav RK, Jain P. Prevalence and Clinical Correlates of Microalbuminuria in Patients with Essential Hypertension - A Tertiary Care Center Cross Sectional Study. J Assoc Physicians India 2018;66:30-4.
10. Mateo-Gavira I, Vílchez-López FJ, García-Palacios MV, Carral-San Laureano F, Jiménez-Carmona S, Aguilar-Diosdado M. Nocturnal blood pressure is associated with the progression of microvascular complications and hypertension in patients with type 1 diabetes mellitus. J Diabetes Complications 2016;30:1326-32.
11. Hata J, Fukuhara M, Sakata S, et al. White-coat and masked hypertension are associated with albuminuria in a general population: the Hisayama Study. Hypertens Res 2017;40:937-43.
12. Cirillo M, Stellato D, Laurenzi M, Panarelli W, Zanchetti A, De Santo NG (2000) Pulse pressure and isolated systolic hypertension: association with microalbuminuria. Kidney İnternational 2000;58:1211-8.
13. Xie N, Li X, Zhong Q, et al. Association of systolic blood pressure and pulse pressure with microalbuminuria in treatment-naïve hypertensive patients. Arch Med Sci 2019;15:832-6.
14. Tsakiris A, Doumas M, Lagatouras D, et al. Microalbuminuria is determined by systolic and pulse pressure over a 12-year period and related to peripheral artery disease in normotensive and hypertensive subjects: the Three Areas Study in Greece (TAS-GR). Angiology 2006;57:313-20.
15. Pedrinelli R, Dell'Omo G, Penno G, et al. Microalbuminuria and pulse pressure in hypertensive and atherosclerotic men. Hypertension 2000;35:48-54.
16. Agyemang C, van Valkengoed I, van den Born BJ, Stronks K. Prevalence of microalbuminuria and its association with pulse pressure in a multi-ethnic population in Amsterdam, the Netherlands. The SUNSET Study. Kidney Blood Press Res 2008;31:38-46.
17. Tremblay AJ, Morrissette H, Gagné JM, Bergeron J, Gagné C, Couture P. Validation of the Friedewald formula for the determination of low-density lipoprotein cholesterol compared with beta-quantification in a large population. Clin Biochem 2004;37:785-90.
18. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998;6:51-209.
19. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-219.
21. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072-83.
22. Jafary FH. Devereux formula for left ventricular mass--be careful to use the right units of measurement. J Am Soc Echocardiogr 2007;20:783.
23. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.
24. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
25. Page HL Jr. The Judkin's technique. Cathet Cardiovasc Diagn 1979;5:187-9.
26. Arbab-Zadeh A, Fuster V. The Risk Continuum of Atherosclerosis and its Implications for Defining CHD by Coronary Angiography. J Am Coll Cardiol 2016;68:2467-78.
27. Xia F, Liu G, Shi Y, Zhang Y. Impact of microalbuminuria on incident coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis of prospective studies. Int J Clin Exp Med 2015;8:1-9.
28. Palatini P. Microalbuminuria in hypertension. Curr Hypertens Rep 2003;5:208-14.
29. Karadag B, Ozyigit T, Serindag Z, Ilhan A, Ozben B. Blood pressure profile is associated with microalbuminuria and retinopathy in hypertensive nondiabetic patients. Wien Klin Wochenschr 2018;130:204-10.
30. Tanaka M, Babazono T, Takeda M, Iwamoto Y. Pulse pressure and chronic kidney disease in patients with type 2 diabetes. Hypertens Res 2006;29:345-52.
31. Thieme K, Oliveira-Souza M. Renal hemodynamic and morphological changes after 7 and 28 days of leptin treatment: the participation of angiotensin II via the AT1 receptor. PLoS One 2015;10:122265.
32. Kusunoki H, Taniyama Y, Rakugi H, Morishita R. Cardiac and renal protective effects of irbesartan via peroxisome proliferator-activated receptorγ-hepatocyte growth factor pathway independent of angiotensin II

Type 1a receptor blockade in mouse model of salt-sensitive hypertension. J Am Heart Assoc 2013;2:000103.

33. Diercks GF, van Boven AJ, Hillege JL, de Jong PE, Rouleau JL, van Gilst WH. The importance of microalbuminuria as a cardiovascular risk indicator: A review. Can J Cardiol 2002;18:525-35.

34. Khosla N, Sarafidis PA, Bakris GL. Microalbuminuria. Clin Lab Med 2006;26:635-53.

35. Stehouwer CD, Henry RM, Dekker JM, Nijpels G, Heine RJ, Bouter LM. Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction--the Hoorn Study. Kidney Int Suppl 2004;(92):42-4.

36. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. J Am Soc Nephrol 2006;17:2106-11.

37. Strandberg TE, Pitkala K. What is the most important component of blood pressure: systolic, diastolic or pulse pressure? Curr Opin Nephrol Hypertens 2003;12:293-7.

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Are Atrial High-rate Episodes a Kind of Sympathetic Overactivity in Patient with Permanent Pacemaker?

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Abstract

Objectives: Atrial high-rate episodes (AHREs) are important cardiac conditions. The purpose of the trial was to assess sympatho-vagal interaction as evaluated by the heart rate variability (HRV) of holter recordings in patients with AHRE.

Materials and Methods: All subjects with cardiac devices including dual chamber permanent pacemakers, attending the outpatient pacemaker control units were included. Transthoracic echocardiography and a rest electrocardiogram, and 24-hour Holter monitoring were performed to all patients.

Results: One-hundred and fifty subjects were included in this trial. There were 44 patients (29.3%) with AHRE and 106 subjects (70.7%) without AHRE in all population. Standard deviation of all N-N intervals for a selected time period (102.1±30.5 vs 124.0±50.2; p=0.008) and normalized power in high-frequency band (9.4±6.6, 12.7±7.1; p=0.006) were significantly decreased; however, normalized power in low-frequency band (28.5±12.5, 23.8±11.6; p=0.006) and LF/HF ratio (4.71±3.60, 2.63±1.65; p<0.001) were significantly increased in AHRE patients.

Conclusion: There was a sympathetic overactivity in patients with AHRE. Further studies are needed to demonstrate the role of HRV parameters in AHRE patients.

Keywords: Atrial high-rate episodes (AHRE), HRV, autonomic nervous system

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Introduction

Atrial high-rate episodes (AHREs), known as subclinical arrhythmias, are notable cardiac conditions. Atrial high-rate episode can be described as an episode of faster heart rate, generally higher than 180 beats/minute lasting at least 5 minutes according to the current guidelines[1]. AHRE can be recognized by documentation type from atrial fibrillation (AF). AF is detected on an electrocardiogram or Holter monitoring; however, AHREs are merely recorded on a cardiac implantable electronic devices (CIED) read-out[1]. The rate of AHRE can reach 50%[2].

Heart rate variability (HRV) has some parameters which represent sympato-vagal interaction of the sinoatrial node (SAN). It is also related to autonomic modulation of SAN. It has been studied to identify the role of autonomic nervous system (ANS) activity in different cardiovascular conditions[3].

The purpose of the trial was to assess sympatho-vagal interaction as evaluated by the HRV of Holter recordings in subjects with AHRE.

Materials and Methods

Patients with CIEDs including dual chamber permanent pacemakers and attending the outpatient pacemaker control unit of three Cardiovascular Centers from March 2010 to February 2019 were enrolled to the study. Patients with heart failure, chronic obstructive pulmonary disease, acute coronary syndrome, previous myocardial infarction, AF, those with decreased ejection fraction (<40%), and those with implantable defibrillator or cardiac resynchronization therapy device were excluded due to heart failure that could impair HRV parameters. We also excluded fulltime pacemaker dependent patients and single-chamber VVI devices. Atrial sensitivity was programmed to 0.5 mV with bipolar sensing.

Clinical assessment, laboratory test, echocardiography and 12 lead electrocardiogram before the Holter recording were done to all subjects.

Ethics committee approval was obtained from University of Health Sciences Turkey, Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (decision no: KAEK2013-18, date: 12.04. 2013).

Holter Monitoring

CONTEC Holter system was utilized to handle the Holter analysis.

All 24-hour recordings were utilized to assess HRV indexes. Time-domain and spectral results of HRV were calculated using the guideline of ESC[4].

The standard parameters [standard deviation of all NN intervals for a selected time period (SDNN), square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) and the proportion of differences in successive NN intervals greater than 50 ms (pNN50)] and spectral analysis [high-frequency (HF) component (0.15-0.40 Hz), low-frequency (LF) component (0.04-0.15 Hz)] were used for HRV analysis.

The normalized high-frequency power (HFnu)=100xhigh-frequency power/total power, normalized low-frequency power (LFnu)=100xlow-frequency power/total power, and low/high-frequency power ratio low-frequency power/high-frequency power (LF/HF ratio) were calculated. LF/HF ratio reflects sympatovagal balance (higher 2.5 reflects sympatetic, lower 2.5 reflects parasympaptetic overactivity)[4].

Transthoracic Echocardiography

All subjects underwent transthoracic echocardiography by using a Philips affinity 50 echocardiography machine.

Statistical Analysis

The Pearson chi-square test, ANOVA and Mann-Whitney U-test were used to compare variables. For post-hoc analysis, the Tukey test was utilized. SPSS 15.0 software was used.

Results

One-hundred and fifty subjects were included in this trial. Patient characteristics and echocardiography results are demonstrated in Table 1. There were 44 patients (29.3%) with AHRE and 106 subjects (70.7%) without AHRE in all population. No significant difference was present between two groups in terms of age and gender ratio. Patients with AHRE had increased left atrial diameter and left atrial area, whereas cardiac diastolic functional parameters assessed by mitral valve Continuous Wave Doppler indexes were similar. It was demonstrated in Table 1.

HRV parameters of all subjects were shown in Table 2. SDNN (102.1±30.5 vs 124.0±50.2; p=0.008) and HFnu (9.4±6.6, 12.7±7.1; p=0.006) were significantly lower. LFnu (28.5±12.5, 23.8±11.6; p=0.006) and LF/HF ratio (4.71±3.60, 2.63±1.65; p<0.001) were significantly higher in AHRE patients (Figure 1). The alterations in LF nu and LF/HF ratio showed a higher sympathetic tone and disparity in autonomic activity in AHRE subjects.

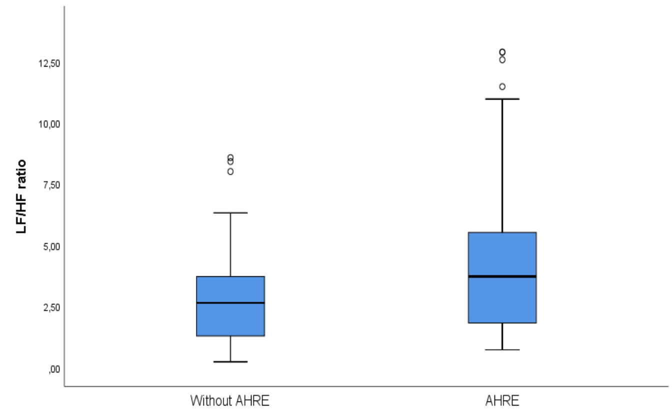

Figure 1. LF/HF ratio of Subjects with AHRE and without AHRE
LF: Low frequency, HF: High frequency, AHRE: Atrial high rate episodes

Table 1. Baseline characteristics of the patients with AHRE and without AHRE

	AHRE Patients (n=44)	Patients without AHRE (n=106)	p
Age, year	60.4±9.3	58.5±8.4	NS
Gender, M/F (%)	24/20 (54.5/45.5%)	57/49 (53.7/46.3%)	NS
LVEF, %	65.4±4.5	66.3±4.7	NS
Left atrial diameter (cm)	3.7±0.7	3.2±0.4	**0.001**
Left atrial area (cm²)	20.4±3.2	13.1±1.9	**<0.001**
E peak (m/sec)	0.7±0.1	0.7±0.2	NS
A peak (m/sec)	0.7±0.1	0.8±0.2	NS
E deceleration time (msec)	215±28	217±34	NS
Isovolumic relaxation time (IVRT) (msec)	104±14	103±12	NS

M/F: Male/female, LVEF: Left ventricle ejection fraction, AHRE: Atrial high-rate episodes, NS: Not significant

Table 2. HRV parameters in subjects with AHRE and without AHRE

	AHRE subjects	Subjects without AHRE	p
Heart rate	81.2±17.5	73.8±14.2	**<0.001**
SDNN (ms)	102.1±30.5	124.0±50.2,	**<0.001**
RMSSD (ms)	40.2±21.2	38.1±19.0	NS
PNN50 (%)	11,7±1,5	10±1,4	NS
24-hour LFnu	28.5±12.5	23.8±11.6	**0.02**
24-hour HFnu	9.4±6.6	12.7±7.1	**0.029**
LF/HF ratio	4.71±3.60	2.63±1.65	**<0.001**

SDNN: Standard deviation of all NN intervals for a selected time period, AHRE: Atrial high-rate episodes, RMSSD: Square root of the mean of the sum of the squares of differences between adjacent RR intervals, PNN50: The proportion of differences in successive NN intervals greater than 50 ms, LFnu: Normalized power in low frequency band, HFnu: Normalized power in high-frequency band

Any correlation could not be found between any HRV parameters and demographic features of the subjects.

Discussion

In the study, we showed that patients with AHRE had more impaired HRV parameters reflecting sympathetic overactivity compared to those without AHRE. To the best of our knowledge, this is the first study examining HRV parameters in patients with AHRE in preserved LV systolic function.

AHREs are not a rare condition in subjects having intra-cardiac devices without AF after development in cardiovascular follow up. Atrial high-rate episodes can be observed highly in next times. Atrial high-rate episodes are usually thought of similar to clinical paroxysmal AF. It could be given support by former trials showing that AHREs have an increased relation to clinical AF[5].

HRV parameters reflect the autonomic activity on the heart. It is related to alterations in autonomic balance. In the study, the deterioration of both various parameters of HRV in AHRE patients was shown. It has been mentioned that disrupted sympatho-vagal interaction for the good of sympathetic system can be caused by heart repolarization abnormalities and tachyarrythmias[6].

Several risk factors such as inflammation, autonomic changes, high pressure or volume burden can play roles as potential agents to cause a favorite substrate for AHRE creation[7]. Various trials have investigated that different promoting agents to atrial arrhythmias look like autonomic layout. Parasympathetic activation is demonstrated to decrease the atrial effective refractory period and tendency to atrial arrhythmias[8]. In some cardiac disorders, sympathetic activity plays a crucial role in atrial arrhythmia initiation[9]. In this study, higher sympathetic tone in patients with AHRE was also found.

Conclusion

There was a sympathetic overactivity in patients with AHRE in the current study. Further larger trials are needed to demonstrate the role of HRV parameters in AHRE patients.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (decision no: KAEK2013-18, date: 12.04. 2013).

Informed Consent: Informed consent was obtained from all participants.

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References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
2. Chen-Scarabelli C, Scarabelli TM, Ellenbogen KA, Halperin JL. Device-detected atrial fibrillation: what to do with asymptomatic patients? J Am Coll Cardiol 2015;65:281-94.
3. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. Int J Cardiol 2002;84:1-14.
4. Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology on Heart Rate Variability. Standards of measurement, physiological interpretation, and clinical use. European Heart Journal 1996;17:354-81.
5. Pollak WM, Simmons JD, Interian A Jr, et al. Clinical utility of intraatrial pacemaker stored electrograms to diagnose atrial fibrillation and flutter. Pacing Clin Electrophysiol 2001;24:424-9.
6. Valensi PE, Johnson NB, Maison-Blanche P, Extramania F, Motte G, Coumel P. Influence of cardiac autonomic neuropathy on heart rate dependence of ventricular repolarization in diabetic patients. Diabetes Care 2002;25:918-23.
7. Goldberger JJ, Arora R, Green D, et al. Evaluating the Atrial Myopathy Underlying Atrial Fibrillation: Identifying the Arrhythmogenic and Thrombogenic Substrate. Circulation 2015;132:278-91.
8. Hirose M, Leatmanoratn Z, Laurita KR, Carlson MD. Partial vagal denervation increases vulnerability to vagally induced atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:1272-9.
9. Lu Z, Scherlag BJ, Lin J, et al. Atrial fibrillation begets atrial fibrillation: autonomic mechanism for atrial electrical remodeling induced by short-term rapid atrial pacing. Circ Arrhythm Electrophysiol 2008;1:184-92.

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Association of SYNTAX Score with PATIMA Index, Carotid Intima- and Extra- Media Thicknesses

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Abstract

Objectives: Several risk scoring systems have been validated for cardiovascular risk prediction and prognosis. Periarterial adipose tissue intima media adventitia (PATIMA) index combining carotid intima media thickness (CIMT), carotid extra media thickness (CEMT), cardiac epicardial fat thickness (EFT), and body mass index (BMI) are related to coronary artery disease (CAD).

Materials and Methods: One-hundred-twenty-four patients were categorized as low synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) (<22) (n=84) or high SYNTAX (≥22) (n=40) score groups. Association of PATIMA index and its components with SYNTAX score were analyzed.

Results: CIMT, CEMT, BMI, EFT, and PATIMA index were not significantly different between groups. SYNTAX score was not significantly correlated with traditional CVS risk factors (diabetes, hypertension, hyperlipidemia, smoking, age). There was a significant correlation between the PATIMA index and age (r=0.308, p=0.001) but not with other risk factors. Age was significantly correlated with CIMT (r=0.289, p=0.001) and EFT (r=0.208, p=0.02) but not with CEMT (r=0.091, p=0.313). There was a significant correlation between CIMT and CEMT (r=0.414, p<0.001) and between CIMT and EFT (r=0.267, p=0.004).

Conclusion: We have found that the recently described PATIMA index and its components, CIMT, CEMT, and EFT are not associated with the severity of CAD assessed by the SYNTAX score. Furthermore, they have not correlated with classical risk factors apart from age.

Keywords: Carotid extra-media thickness, carotid intima-media thickness, coronary artery disease, PATIMA index, SYNTAX score

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Introduction

Strong correlation has been reported between the extent of carotid and coronary atherosclerosis(1,2). Cardiovascular (CVS) risk prediction is an important goal in daily medical practice. Several risk scoring systems have been validated for CVS prognosis(3-5). These systems usually use common risk factors and lack individual characteristics. Therefore, the results are inconclusive.

To improve predictive power of the risk score systems, several ultrasound-based indices have been suggested for the assessment of prognosis of atherosclerosis in addition to major clinical CVS risk factors. Carotid artery intima-media thickness (CIMT) is used for the early risk prediction of atherosclerosis, ischemic stroke, and myocardial infarction(6). Few studies used common carotid artery extra-media thickness (CEMT) and reported its associations with CVS risk factors some of which were independent of CIMT(7).

Recently, a new index called periarterial adipose tissue intima media adventitia (PATIMA) is a combination of several arterial wall and adipose tissue indices [CIMT and CEMT, cardiac epicardial fat thickness (EFT) and body mass index (BMI)] predicting the atheroscleoris and coronary artery disease (CAD) in different aspects. It has been reported that PATIMA index and CEMT are associated with the severity and also the presence of coronary artery disease(8). However, the data are limited.

The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score (SS) is an angiography-based scoring system that evaluates the characteristics of the obstructive coronary lesions(9). In the literature, it has been reported that there is a strong association between SS and cardiac complications after angiographic revascularization treatment in CAD patients. It has also been reported that there is a strong association between CIMT and SS(9-11).

The aim of the study was to investigate the association between PATIMA index and the presence and the severity of CAD determined based on the SYNTAX scoring system in patients with high and very-high risk.

Materials and Methods

This study was prospectively designed, approved by the Local Ethics Committee of Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (reference no: 2019/26, date: 30.01.2019), and conducted according to the Helsinki Declaration between January and December 2019. A written and verbal informed consent was obtained from each subject. One hundred twenty-four consecutive patients undergoing coronary angiography for typical anginal symptoms or other noninvasive tests suggesting stable CAD in the university hospital's cardiology department, who had had at least single vessel CAD with ≥50% stenosis, were enrolled in the study.

Having a previous history of coronary, carotid or peripheral artery atherosclerosis, myocardial infarction, and moderate to severe heart valve disease, heart failure, significant renal failure, severe liver dysfunction and poor ultrasound image quality were determined as exclusion criteria.

Two experienced cardiologists analyzed the angiographic data of the patients blindly. Each coronary lesion causing a ≥50% diameter stenosis was scored based on the angiogram and using the SS algorithm, and these scores were combined to determine the total SS and the patients were grouped as low SS (<22) or high SS (≥22) groups(12).

Hypertension (HT) was determined in case of prior diagnosis or systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure >90 mmHg in follow up. Following plasma lipid levels were determined as dyslipidemia [total cholesterol higher than 190 mg/dL, low-density lipoprotein cholesterol higher than 115 mg/dL, triglycerides higher than 150 mg/dL, high-density lipoprotein (HDL) cholesterol higher than 40 mg/dL in men and <50 mg/dL in women](13). Patients with plasma fasting glucose level >126 mg/dL and HbA1c level >6.5% were diagnosed as diabetes mellitus (DM). In case of having doubt for the diagnosis of DM, having second hour post-load plasma glucose level >200 mg/dL was defined as DM[14,15]. The presence of CAD in a first-degree relative of a male younger than 55 years or a first-degree relative of a female younger than 65 years was defined as a family history of CAD[16,17].

Ultrasonographic Measurements

The electrocardiography-based ultrasonographic examination of bilateral carotid arteries was performed using high-resolution ultrasound (GE Healthcare, M4S-RS, Tokyo, Hino-Shi, Japan) with a 7.5 MHz linear transducer. The measurement of each carotid arteries was repeated three times and the mean values were used for analysis. All ultrasonographic measurements were performed by the same experienced physician who was blinded to the study. All the ultrasonographic images were recorded and measured by an experienced cardiologist blinded to the study, using constant settings. For each parameter, intra-observer variability was determined by comparing data of the same physician at two different measurement sessions. Intra-observer variabilities of measurements were assessed by the method which was defined by Bland and Altman[18].

Carotid Intima-media Thickness

Both common carotid arteries of the participants were longitudinally scanned. Images obtained from the distal part of the common carotid artery, 1-2 cm proximal to the carotid bulb, were used for evaluation. The two hyper-echogenic lines on the arterial wall were determined as the intima and media lines. The distance from these two hyper-echogenic lines was used for the measurements of carotid intima-media thickness (CIMT). Intra-observer variability for CIMT measurement was 3.6%.

Carotid Extra-media Thickness

Carotid extra-media thickness (CEMT) incapsulates outer layer of the arterial wall, the adventitia layer, interstitial tissue, and perivascular adipose tissue[7]. The distance between the border of carotid media-adventitia, at approximately 1 to 1.5 cm proximal to the carotid bulb, and the wall of the jugular vein. The measurements were taken at end-diastole. Among ten patients, CEMT was measurable only in one carotid artery and these unilateral measurements were included in the study. CEMT could not be measured in four patients due to inadequate image quality to define CEMT border in either carotid arteries. Intra-observer variability for CEMT measurement was 2.7%.

Epicardial Fat Thickness

The 4-Mhz transducer of Vivid S5 N (GE Vingmed, N-3191 Horten-Norway) was used to perform echocardiographic procedures. A single blind cardiologist took all echocardiographic images. The mean value of the three cardiac cycles was used. EFT was noted as an echo-free or hyperechoic area between the epicardium and the visceral layer of the pericardium and it reflected visceral adipose tissue[19]. The assessment of EFT thickness was performed from the parasternal long- and short axis views of the free wall of the right ventricle. The measurement was made at the level of the aortic annulus perpendicular to the free wall of the right ventricle. The measurements of maximum values were made at the end of diastole. The intra-observer variation for EFT was 4.3%.

PATIMA Index

PATIMA index was calculated as (CEMT / BMI x 35) + CIMT + (EFT x 60), which was described by Haberka et al.[8]

Statistical Analysis

SPSS (version 16; SPSS Inc. Chicago, Illinois) software was used to perform statistical analysis. Data were presented as mean ± standard deviation and nonparametric data were expressed as number and percentages of the total. The Kolmogorov-Smirnov test was used to test whether the data were distributed normally. Data between the groups were compared with the chi-square test for qualitative variables and the Student's t-test or Mann-Whitney U test for quantitative variables. The correlation between atherosclerosis markers was evaluated using the Spearman correlation test. A p-value below 0.05 was considered as significant.

Results

A total of 124 CAD patients were included in the study. There were 84 low- and 40 high-SS patients. There was no significant difference between low- and high-SS patients in terms of baseline clinical characteristics. CIMT, CEMT, BMI, EFT, and PATIMA index were also not significantly different (Table 1).

SYNTAX score was not significantly correlated with classical CVS risk factors. A significant correlation was found between PATIMA index and age but not with other CVS risk factors (Table 2). Age was significantly correlated with CIMT (r=0.289, p=0.001) and EFT (r=0.208, p=0.02) but not with CEMT (r=0.091, p=0.313). There was a significant correlation between CIMT and CEMT (r=0.414, p<0.001) and between CIMT and EFT (r=0.267, p=0.004).

Discussion

We have found that recently described PATIMA index and its components, CIMT, CEMT, and EFT are not associated with CAD severity calculated by SS. Furthermore, they are not correlated with classical CAD risk factors [DM, HT, smoking, Hyperlipidemia (HL)] apart from age.

The SS consists of a combine validated angiographic evaluation to classify the coronary lesions in terms of the number, functional impact, and complexity of them[20]. The SS is essentially recommended for decision making for coronary angiography rather than prediction for functional outcome of the patients. However, its prognostic utility has been validated in different settings, including patients with three-vessel or left-main CAD undergoing either percutaneous coronary intervention or coronary bypass surgery[21-24]. The SS has also been used to assess the relationship between carotid ultrasonographic findings and CAD severity[9-11]. Association of CIMT with CAD severity is controversial. Although several studies have reported that there is an association between CIMT and

Table 1. Comparison of baseline clinical characteristics and ultrasound indices between the groups

	SYNTAX score <22 (group 1) (n=84)	SYNTAX score ≥22 (group 2) (n=40)	p-value
Age (years), mean ± SD	63.8±10.9	64.6±9.3	0.670
Sex (male)	75% (63)	82.5% (33)	0.491
HT	60.7% (51)	52.5% (21)	0.439
DM	36.9% (31)	45% (18)	0.435
HL	13.1% (11)	10% (4)	0.772
FH	15.5% (13)	25% (10)	0.223
Smoking	22.6% (19)	27.5% (11)	0.625
EF, (%)	57.5±8.3	54.9±8.6	0.018
CEMT, (µm)	700 (600-800)	700 (600-800)	0.750
BMI, (kg/m²)	28.69±4.43	28.85±4.73	0.775
CIMT, (µm)	700 (600-800)	700 (600-900)	0.987
EFT, (mm)	6.71±2.42	7.10±2.13	0.383
PATIMA index	1,999.86±351.60	2,022.99±405.05	0.746

HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, FH: Family history, SD: Standard deviation, EF: Ejection fraction, CEMT: Carotid artery extra media thickness, BMI: Body mass index, CIMT: Carotid artery intima-media thickness, EFT: Epicardial fat tissue, PATIMA: Periarterial Adipose Tissue Intima Media Adventitia, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery n: Number
Data are expressed as mean ± (SD) or median (minimum-maximum)

the presence and severity of CAD[9,25], Saedi et al.[26] found no significant correlation between CIMT and SS. Ikeda et al.[10] studied CIMT and SS in 501 patients and reported a significant correlation between the CIMT and the SS and similar to our population, majority of patients (84.8%) had a low SS value (<22). However, the mean CIMT value in their study was higher than that in our study (0.9 mm vs. 0.7 mm). Lack of association between CIMT and SS in our study may be partially explained with relatively low mean CIMT value (0.7 mm) compared to previous studies. However, Costanzo et al.[27] reported high prevalence of carotid lesion in patients with complex CAD with relatively high average CIMT (1.15 mm) but similar to our findings, SS was not correlated with the presence of carotid disease in their multivessel CAD patients.

Different from a well-known CIMT, CEMT is an ultrasound index of outermost layer of distal segments of the common carotid artery and jugular vein[19,28,29]. It has been shown that arterial adventitia has undergone thickening and remodeling in response to experimental HT and HL[30]. However, assessment of this outer part of arterial wall has not gained popularity. Lefferts et al.[31] found that CEMT, but not CIMT, was significantly associated with carotid stiffness in young, apparently healthy men. They suggested that visceral adiposity and carotid hemodynamics detrimentally affect CEMT and in turn, impact carotid wall stiffness. CEMT was also found to be related to metabolic syndrome and adiposity[28]. CIMT and CEMT were shown to be increased in HT[32]. Skilton et al.[7] found that CEMT was increased in DM and HL. They reported that there was a negative association between HDL and CIMT, a J-shaped association between SBP and CIMT, and a positive association between DM and CIMT. Saedi et al.[26] reported that the presence of HT and DM may be related to increased CIMT. However, in the present study, we could not find such an association of CIMT and CEMT with CVS risk factors including DM and HL in patients with documented CAD. Supporting our findings, in a retrospective study, Cai at al.[33] reported that there was an association between CIMT and CVS events

Table 2. Correlation Between SYNTAX Score and PATIMA Index and The Clinical and Ultrasound Indices in Study Subjects

Variables	SYNTAX score	PATIMA index
Age	r=0.059 p=0.512	r=0.308 p=0.001
HT	r=0.048 p=0.597	r=0.010 p=0.910
DM	r=0.039 p=0.667	r=0.015 p=0.873
HL	r=0.158 p=0.08	r=0.118 p=0.193
Smoke	r=0.053 p=0.560	r=0.118 p=0.193
EFT	r=0.155 p=0.088	r=0.479 p<0.001
CEMT	r=0.040 p=0.662	r=0.716 p<0.001
CIMT	r=0.020 p=0.827	r=0.774 p<0.001
BMI	r=0.001 p=0.992	r=0.255 p=0.004
PATIMA index	r=0.039 p=0.665	-

HT: Hypertension, DM: Diabetes mellitus, HL: hyperlipidemia, EFT: Epicardial fat tissue, CEMT: Carotid artery extra media thickness, CIMT: Carotid artery intima-media thickness, BMI: Body mass index, PATIMA index: Periarterial Adipose Tissue Intima Media Adventitia, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery n: Number in adults having the risk of CAD and reported that unlike CIMT, there was no significant association between CEMT and CVS events in high-risk adults. Different results about the association of other CVS risk factors with ultrasound indexes may depend on the population studied but age is constant. Aging itself has an important role in the pathogenesis of atherosclerosis through physiological degenerative CVS changes. Of the CVS risk factors, age has the strongest independent association with atherosclerosis possibly combining the role of other established risk factors and aging itself.

Haberka et al.[8] have combined CEMT and CIMT with periarterial fat indices and proposed PATIMA index as a combined reflection of these well-known and relatively new CVS risk predictors. They reported that PATIMA was related to the presence and as well as the severity of CAD. Furthermore, higher PATIMA indices were suggested to predict more complex CAD comparing with single-ultrasound variables and clinically assessed risk factors[34]. Recently, Haberka et al.[35] have reported that carotid vascular indices (CIMT, CEMT, and PATIMA index), may provide to predict the indication of coronary revascularization in high or very high-risk CAD patients, although clinical evaluation and the presence of CVS risk factors did not have provided a predictive value. In contrast to the reports of Haberka et al.[36], in our study, however, no significant association was found between PATIMA index and the severity of CAD assessed by SS. The design of our study is cross-sectional, and the number of patients is relatively small. Therefore, the relationship between ultrasound indexes and their combined outcome-PATIMA index with the severity of CAD can be limited due to individual variations of the studied indexes. Such that some parameters that influence the SS may not be related to atherosclerosis burden like vessel tortuosity and bifurcation lesion angle.

Study Limitations

Measurements of CEMT, EFT and to a lesser extent CIMT require training and experience to obtain optimal image[28,29,36]. However, the measurements were performed by an experienced observer and patients with inadequate image quality were excluded. Relatively small number of study patients may be a reason for our unavailability to find an association between PATIMA and CEMT with severity of CAD. Due to lack of a control group having normal coronary arteries, we were not able to speculate about predictive value of studied indices for the presence of CAD.

Conclusion

In this single-center study, on the contrary to previous few studies, we found that PATIMA index and its components, CIMT, CEMT and EFT were not associated with CAD severity calculated by SS. Larger studies are required to determine the association between these parameters and severity of CAD.

Ethics

Ethics Committee Approval: This study was approved by Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (ref. no: 2019/26, date: 30.01.2019).

Informed Consent: Informed consents were obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: M.C., Z.C., Design: M.C., Z.C., Y.G., Data Collection/Processing: M.C., E.E., A.K.M., M.İ., Analysis and/or Interpretation: M.C., Z.C., İ.S., Literature Review: M.C., Y.G., Drafting/Writing: M.C., E.E., Y.G., Critical Review: M.C., Y.G.

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References

1. Mitchell Jr, Schwartz Cj. Relationship between arterial disease in different sites. A study of the aorta and coronary, carotid, and iliac arteries. Br Med J 1962;1:1293-301.

2. Demirel ME, Donmez I, Ucaroglu ER, Yuksel A. Acute coronary syndromes and diagnostic methods. Med Res Innov 2019;3:1-8.

3. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med 1975;4:518-25.

4. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987-1003.

5. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. Circulation 2002;105:310-5.

6. Alipour M, Masri D, Mofazzali A, Chitsazan M. Carotid artery intima-media thickness in patients undergoing coronary artery bypass graft surgery. Arch Cardiovasc Imaging 2013;1:27-31.

7. Skilton MR, Sérusclat A, Sethu AH, et al. Noninvasive measurement of carotid extra-media thickness: associations with cardiovascular risk factors and intima-media thickness. JACC Cardiovasc Imaging 2009;2:176-82.

8. Haberka M, Gąsior Z. A carotid extra-media thickness, PATIMA combined index and coronary artery disease: Comparison with well-established indexes of carotid artery and fat depots. Atherosclerosis 2015;243:307-13.

9. Korkmaz L, Bektas H, Korkmaz AA, et al. Increased carotid intima-media thickness is associated with higher SYNTAX score. Angiology 2012;63:386-9.

10. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. Eur Heart J 2012;33:113-9.

11. Ikeda N, Saba L, Molinari F, et al. Automated carotid intima-media thickness and its link for prediction of SYNTAX score in Japanese coronary artery disease patients. Int Angiol 2013;32:339-48.

12. SYNTAX score calculator. Available at: http://www.SYNTAXscore.com. SYNTAX working-group. Accessed May 2013.

13. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635-701.

14. World Health Organization (WHO) Consultation, Definition and Diagnosis of Diabetes and Intermediate Hyperglycaemia, 2006; p. 1-50.

15. World Health Organization (WHO), Abbreviated Report of a WHO Consultation. Use of Glycated Hemoglobin (HbA1c) in the Diagnosis if Diabetes Mellitus, 2011. p.1-25.

16. British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005;91:v1-52.

17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.

18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.

19. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.

20. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.

21. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072-81.

22. Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. Catheter Cardiovasc Interv 2009;73:612-7.

23. Capodanno D, Di Salvo ME, Cincotta G, Miano M, Tamburino C, Tamburino C. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;2:302-8.

24. Birim O, van Gameren M, Bogers AJ, Serruys PW, Mohr FW, Kappetein AP. Complexity of coronary vasculature predicts outcome of surgery for left main disease. Ann Thorac Surg 2009;87:1097-104.

25. Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M. Association of increased carotid intima-media thickness with the extent of coronary artery disease. Heart 2004;90:1286-90.

26. Saedi S, Ghadrdoost B, Pouraliakbar H, Zahedmehr A, Jebelli A. The association between increased carotid intima-media thickness and SYNTAX Score in coronary artery disease: A single center study. Indian Heart J 2018;70:627-9.

27. Costanzo L, Campisano MB, Capodanno D, et al. The SYNTAX score does not predict presence of carotid disease in a multivessel coronary disease population. Catheter Cardiovasc Interv 2014;83:1169-75.

28. Haberka M, Gąsior Z. Carotid extra-media thickness in obesity and metabolic syndrome: a novel index of perivascular adipose tissue: extra-media thickness in obesity and metabolic syndrome. Atherosclerosis 2015;239:169-77.

29. Falk E, Thim T, Kristensen IB. Atherosclerotic plaque, adventitia, perivascular fat, and carotid imaging. JACC Cardiovasc Imaging 2009;2:183-6.

30. Herrmann J, Samee S, Chade A, Rodriguez Porcel M, Lerman LO, Lerman A. Differential effect of experimental hypertension and hypercholesterolemia on adventitial remodeling. Arterioscler Thromb Vasc Biol 2005;25:447-53.

31. Lefferts WK, Sperry SD, Jorgensen RS, et al. Carotid stiffness, extra-media thickness and visceral adiposity in young adults. Atherosclerosis 2017;265:140-6.

32. D'Amico F, Grasso R. Carotid intima-media and extra-media thickness in hypertensive elderly subjects. Journal of Hypertension 2015;33:497.

33. Cai TY, Magnussen C, Haluska B, et al. Carotid extra-medial thickness does not predict adverse cardiovascular outcomes in high-risk adults. Diabetes Metab 2016;42:200-3.

34. Haberka M, Lelek M, Bochenek T, et al. Novel combined index of cardiometabolic risk related to periarterial fat improves the clinical prediction for coronary artery disease complexity. Atherosclerosis 2018;268:76-83.

35. Haberka M, Bałys M, Matla M, Kubicius A, Maciejewski Ł, Gąsior Z. Carotid artery stenosis and ultrasound vascular indexes predict the coronary revascularization in patients with high cardiovascular risk scheduled for coronary angiography. Kardiol Pol 2019;77:1028-33.

36. Haberka M, Sosnowski M, Zuziak-Pruska J, Gąsior Z. Extra-media thickness and epicardial fat: Comparison of a novel carotid artery ultrasound index and a well-established cardiac magnetic resonance fat quantification method. Nutr Metab Cardiovasc Dis 2015;25:763-70.

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Evaluation of Reintervention Frequency in Patients Undergoing Interventional and/or Surgical Treatment for Aortic Coarctation

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Abstract

Objectives: The aim of the study was to evaluate the frequency of reintervention in patients who underwent interventional and/or surgical treatment for aortic coarctation, and to determine the causative factors.

Materials and Methods: Our study included 85 patients who were treated with the diagnosis of aortic coarctation between 2011 and 2018. Data processing, echocardiography, cardiac catheterization-angiocardiography, and operative records of the patients were retrospectively evaluated.

Results: As the initial treatment choice, 38 (44%) patients underwent percutaneous interventional procedure [31 (36%) patients balloon angioplasty and 7 (8%) patients stent implantation, respectively], while 47 (55%) patients were treated surgically. Of the treated patients, 17 (28%) developed recoarctation. Among the patients who were treated and followed up, 20% of those who underwent balloon angioplasty developed recoarctation, while 8% of those who underwent surgery developed recoarctation (p=0.02). Seven patients who underwent stent implantation had no recoarctation throughout the follow-up period. The presence of discrete coarctation (p=0.00), high pre-procedural peak-to-peak pressure gradient

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Abstract

(p=0.00) and high post-procedural peak-to-peak pressure gradient (p=0.00), and performing balloon angioplasty (p=0.02) as the initial treatment were evaluated as the factors leading to recoarctation development.

Conclusion: It was concluded that the best treatment modality would be preferred based on the characteristics of the patient because of the lower incidence of recoarctation in surgical treatment but fewer procedure-related complications in interventional treatments.

Keywords: Coarctation of the aorta, balloon angioplasty, surgery, pediatrics, stent

Introduction

Aortic coarctation (CoA) accounts for 4-6% of all congenital heart diseases, with an incidence of 3 per 10,000 births[1,2]. CoA is a congenital obstructive anomaly of the aortic lumen. It may coexist with other cardiac anomalies such as bicuspid aortic valve (BAV), aortic arch hypoplasia, patent ductus arteriosus (PDA), ventricular septal defect (VSD), and atrial septal defect (ASD)[3].

Various symptoms can occur depending on the severity of coarctation and concomitant cardiac anomalies. The clinical presentation varies greatly depending on age[4]. Neonates may develop heart failure with the closure of the ductus arteriosus, and children may exhibit signs of getting exhausted quickly, leg pain with exercise, chest pain, and hypertension. Since the clinical manifestation may be insignificant in patients without severe coarctation, the diagnosis may be delayed until adolescence or even adulthood.

CoA is diagnosed with physical examination findings (systemic hypertension, difference between upper and lower limb blood pressure, absence of femoral artery pulse) and using one or more of the techniques of echocardiographic examination, cardiac computarized tomography, cardiac magnetic resonance imaging (cMRI), cardiac catheterization, and angiography.

In the literature, there are different options regarding the treatment of CoA Mostly preferred treatment options are surgical repair, transcatheter balloon angioplasty, and transcatheter stent implantation depending on the anatomy of coarctation, age of the patient, size of the patient, and other comorbidities. For neonates and young infants, surgery is accepted as the initial intervention of choice for significant CoA. Transcatheter balloon angioplasty for native discrete CoA is for children over one year old and is also preferred in younger patients with recoarctation, and in neonates and young infants, this option is mainly reserved in patients with associated ventricular dysfunction to get them stabilized for definitive surgical repair. The transcatheter stent implantation is a preferred treatment method for native and recurrent CoA in older children, adolescents, and adults[5,6].

Surgical resection and end-to-end anastomosis, extended resection and end-to-end anastomosis, subclavian flap aortoplasty, prosthetic "patch plasty", and Dacron patch/tube graft are used.

In the literature, there are different results regarding the treatment of CoA in terms of treatment success and incidence of recoarctation by the patient's age, characteristics of the coarctation, the treatment method chosen, and patients' follow-up period[7-10].

Materials and Methods

The study included patients (n=85) who were followed-up by the Pediatric Cardiology Clinic of University of Health Sciences Turkey, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital and who underwent interventional procedures and/or were operated for CoA by cardiovascular surgery between 2011 and 2018.

Patients' echocardiography, cardiac catheterization-angiocardiography, and surgical records were evaluated retrospectively.

Design of the Study

The study included patients between the ages of 0 and 18 years with a cardiac index of ≥3 L/min/m², who were diagnosed with CoA and who underwent cardiac catheterization. Having congenital cyanotic and complex heart disease and the presence of intracardiac tumors were considered as exclusion criteria.

In our study, patients' demographics such as age, gender, body weight and age at diagnosis, as well as conventional measurements obtained by 2-dimensional, M-Mode and Doppler echocardiography (left ventricular wall thickness and diameters, aortic valve, ascending aorta, aortic arch, and isthmus diameters, left ventricular fractional shortening and ejection fraction values, Doppler echocardiographic peak instantaneous pressure gradient of the coarctation area) were retrospectively obtained from hospital records. The diameters of the isthmus, descending aorta, coarctation area (mm, Z-score) of patients measured during the catheter-angiography were recorded. During the hemodynamic study, peak-to-peak pressure gradients at the coarctation level were recorded in pull-back pressure recordings. The data on the surgical technique used were obtained from the operative records of the pediatric cardiovascular surgery clinic.

In our study, patients were grouped as those who underwent an interventional procedure (balloon angioplasty, stent) and those who underwent coarctation surgery. And, patients who were retreated were evaluated by their treatment modalities (Figure 1).

Statistical Analysis

SPSS 20.0 (Statistical Package for Social Sciences for Windows Software) was used for the statistical analysis of the data. The Kolmogorov-Smirnov test was employed to evaluate the normality of the distribution of quantitative variables. The Student's t-test was used for normally distributed samples, while the Mann-Whitney U test was performed to compare the data of non-normally distributed variables. The chi-square analysis was used for the comparison of categorical variables, while the Wilcoxon signed-rank test was utilized for the comparison of pre- and post-treatment variables. A p-value of <0.05 was considered as statistically significant.

Results

Of the patients included in our study, 55 (65%) were male and 30 (35%) were female, with a male to female

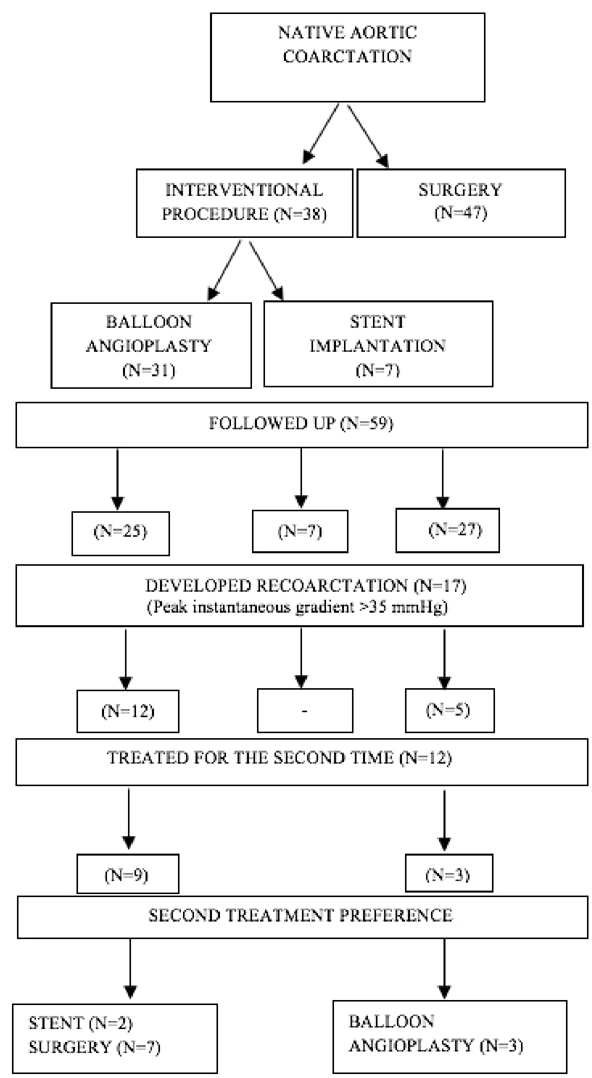

Figure 1. Patients who were retreated were evaluated by their treatment modalities

ratio of 1.8. The ages of the patients at the time of diagnosis ranged from 7 days to 14 years (median age: 3 months). The median bodyweight of the patients at the time of diagnosis was 5 kg (range: 3-17 kg). One patient had the diagnosis of Turner syndrome.

Of a total of 85 patients, 21 (24.7%) had preductal, 58 (68%) had juxtaductal, and 6 (7%) had postductal coarctation. Of the patients, 45 (52%) were diagnosed with isolated AC, and 40 (47%) had additional cardiac defects; 20 (23%) had PDA, 17 (20%) had BAV, 11 had (12%) VSD, 9 (10%) had ASD, and two had aberrant right subclavian artery. None of the patients had cardiac dysfunction.

In the coarctation area, the pre-procedural peak instantaneous pressure gradient measured by echocardiography was 45.0±16.4 mmHg, while the peak-to-peak pressure gradient determined by cardiac catheterization was 31.0±14.7 mmHg.

It was found that the initial treatment choice was surgical repair for neonates, while it was balloon angioplasty for patients older than one year (Table 1). All of the patients who underwent stent implantation were older than 10 years.

Balloon angioplasty resulted in a decrease of 22.6±11.7 mmHg ($p<0.05$) in the peak-to-peak pressure gradient at the coarctation level, while a decrease of 23 mmHg (14-40 mmHg) ($p=0.02$) was achieved in those who underwent stent implantation; there was no significant difference between the two treatment modalities in terms of efficacy in the early period (Table 2).

In patients treated surgically, the peak instantaneous pressure gradient achieved in the left subclavian artery distal decreased from the median value of 40 mmHg (30-50 mmHg) to 12 mmHg (10-19 mmHg) ($p<0.05$).

The type and location of coarctation were significantly different in terms of the initial treatment choice. Juxtaductal coarctation was more frequent in patients who underwent interventional procedures compared to those treated surgically ($p<0.05$). All patients with preductal coarctation underwent surgical procedures, and of the six patients with postductal coarctation, five patients were treated interventionally and one surgically. Tubular

Table 1. Distribution of treatment modalities by age groups of patients

Age groups	Total		Balloon angioplasty		Surgical treatment	
	n	%*	n	%**	n	%**
1-29 days	23	27.1	2	8.7	21	91.3
1-12 months	37	43.5	17	45.9	20	54.1
1-5 years	8	9.4	7	28	1	4
5-10 years	8	9.4	4	16	4	16
>10 years	9	10.6	1	4	1	4

n: Number
**Percentages among all patients in the study, **Percentages within the same age group*

Table 2. Cardiac catheterization measurements and treatment distributions

	Balloon angioplasty (n=31) Mean ± SD	Aortic stent (n=7) Mean ± SD	p-value
Isthmus diameter Z-score	-0.30±0.93	0.23±0.58	0.128
Coarctation area, (mm)	5.1±2.5	8.5±4.5	0.022
Pre-procedural peak-to-peak gradient, (mmHg)	30.8±13.3	32.3±22.2	0.794
Post-procedural peak-to-peak gradient, (mmHg)	8.2±7.2	2.7±6.5	0.022

SD: Standard deviation, n: Number

coarctation was more frequent in the surgical group than in the interventional group ($p<0.05$). Of the patients with discrete coarctation, 66% underwent balloon angioplasty. Those with a Z-score below -2 for aortic (ascending, arcus, isthmus, descending Ao) diameter measurements were considered to have hypoplasia. Of the 85 patients included in the study, 15 (17%) had aortic hypoplasia, 10 (66%) patients had hypoplasia in the middle of the aortic arch, and 5 (33%) patients in the isthmus. The patients with aortic hypoplasia were treated surgically.

A total of 54 patients underwent surgery, 47 patients in the initial treatment and seven patients in the second treatment. In terms of the preferred surgical technique, 26 (48%) patients were treated with subclavian flap aortoplasty, 24 (44%) patients with patch plasty, and 4 (7%) patients with end-to-end anastomosis.

The patients were followed up with a difference in upper-lower limb blood pressure, and echocardiographic evaluation. Because of a difference of 15 mmHg between echocardiographic instantaneous peak pressure gradient and catheter-measured peak-to-peak pressure gradient values of patients who underwent intervention/surgery in clinical practice, an echocardiographic instantaneous peak pressure gradient of >35 mmHg was taken as reference in the recoarctation evaluation.

Of the treated patients, 17 (28%) developed recoarctation. It was found that these patients developed recoarctation after a median period of 1.8 years (5 months-4 years). It was found that according to the treatment groups, the median period to the development of recoarctation was 1.4 years (7 months-4 years) in the balloon angioplasty group and 0.9 years (5 months-3.5 years) in the group treated surgically. Considering the treatment groups, there was no significant difference between the post-interventional and surgical treatment follow-up periods in terms of recoarctation development ($p=0.57$).

Among the patients followed up after the treatment, 20% of those who underwent balloon angioplasty developed recoarctation, while 8% of those who were treated surgically developed recoarctation. Seven patients who underwent stent implantation had no recoarctation throughout the follow-up period. The presence of discrete coarctation ($p=0.00$), high pre-procedural peak-to-peak pressure gradient ($p=0.00$) and high post-procedural peak-to-peak pressure gradient ($p=0.00$), and performing balloon angioplasty ($p=0.02$) in the initial treatment were determined to be the factors leading to recoarctation development (Table 3).

Five out of 17 patients who developed recoarctation were followed up without treatment since the difference in upper-lower limb blood pressure was <20 mmHg and the peak-to-peak pressure gradient was <20 mmHg. In our study, 12 patients were treated for the second time. Before the second treatment, the median instantaneous peak pressure gradient measured by echocardiography was 50 mmHg (range: 40-64 mmHg). The median time between two treatments was 4 months (range: 3-9 months). In nine of the 25 patients treated with balloon angioplasty in the initial treatment and followed up, surgery was preferred for 7 (36%) patients and stent implantation for two patients. Of the seven patients who underwent stent implantation in the initial treatment, three were lost to follow-up after the second year and did not require a second treatment during this period, and none of the four patients who were followed up developed recoarctation. In the 27 patients treated surgically in the initial treatment and followed up, balloon angioplasty was used for 3 (11%) patients in the second treatment.

The patients who underwent interventional treatment for the second time had smaller pre-treatment isthmus, descending aorta and coarctation area diameters measured by cardiac catheterization and had higher post-procedural peak-to-peak pressure gradient at the coarctation level compared to those who underwent interventional treatment once ($p<0.05$); the pre-treatment Z-scores of the isthmus diameter and descending aorta diameter were not significant.

During this period, a total of 97 treatments were performed on 85 patients, of whom 10 developed procedure-related complications.

Table 3. Evaluation of patients who developed recoarctation

	Gradient <35 mmHg* (n=39)	Gradient >35 mmHg (n=17)	p-value
Age at diagnosis, n (%)			
1-29 days	10 (25.6)	3 (17.6)	0.298
1 month-1 year	19 (48.7)	6 (35.3)	
>1 year	10 (25.6)	8 (47.1)	
Body weight, median, (IQR)	6.1 (3.8-11.5)	11.0 (4.6-21.0)	0.310
Gender, n (%)			
Male	24 (61.5)	12 (70.6)	0.516
Female	15 (38.5)	5 (29.4)	
Location of coarctation, n (%)			
Juxtaductal	25 (64.1)	15 (88.2)	0.127
Preductal	10 (25.6)	1 (5.9)	
Postductal	4 (10.3)	1 (5.9)	
Coarctation type, n (%)			
Discrete	20 (51.3)	16 (94.1)	0.002
Tubular	19 (48.7)	1 (5.9)	
Aortic hypoplasia, n (%)			
Yes	6 (15.4)	2 (11.8)	0.722
No	33 (84.6)	15 (88.2)	
ECHO peak instantaneous gradient at diagnosis, (mmHg), mean ± SD	40.0 (28.5-52.5)	45.0 (35.0-58.0)	0.276
Initial procedure type			
Balloon	13 (33.3)	12 (70.6)	0.023
Stent	4[a] (10.3)	0	
Surgery	22 (56.4)	5 (29.4)	
Pre-procedural peak-to-peak gradient	23.0 (17.2-31.2)	31.0 (25.0-42.0)	0.009
Post-procedural peak-to-peak gradient	4.0 (0-6.7)	13.0 (2.0-20.0)	0.004

IQR: Interquartile range, ECHO: Echocardiogram, SD: Standard deviation, n: Number
**Because of a difference of 15 mmHg between the echocardiographic instantaneous peak pressure gradient and catheter-measured peak-to-peak pressure gradient values of patients who underwent intervention/surgery in clinical practice, an echocardiographic instantaneous peak pressure gradient of >35 mmHg was taken as reference in the recoarctation evaluation.*
[a]Three patients who underwent stent implantation were not included in this table because of loss to follow-up after the second year of treatment

Eight patients who underwent surgical treatment developed minor complications. Of them, six were minor bleeding from the drain that did not require reoperation. Of the patients who developed bleeding, five were in the neonatal period and one was an infant, and two neonates died. Of the patients who underwent stent implantation, one developed femoral artery occlusion which improved with low molecular weight heparin during the follow-up and one developed bleeding, while none of the patients who underwent balloon angioplasty developed early complications. None of the patients developed aneurysm during the follow-up.

Discussion

Different first-choice treatment options for patients with CoA include interventional and/or surgical procedures. In this study aiming to determine the efficacy, frequency of reinterventions, and associated factors for different first-choice treatment options, the male/female ratio was 1.8 in line with the literature[3]. In our study, the mean age at diagnosis was 2.5±4.1 years and the median age was 3 months. In their study, Rao et al.[11] reported the mean age at diagnosis as 3.4±4.3 years and the mean body weight at the time of diagnosis as 3.5±0.9 kg in the surgical group and 3.8±1 kg in the balloon angioplasty group. In our study, the body weights of the patients ranged from 2 to 90 kg, and the median body weight at diagnosis was 5 kg (3-17 kg).

Studies have suggested that the widespread use of fetal echocardiography, knowing that conditions such as enlargement of the right structures on fetal echocardiography may be a warning sign for CoA, increased diagnosis, treatment opportunities, and awareness, makes it possible to diagnose and treat younger and lower weight patients, resulting in a decline in age and body weight at diagnosis.

In our study, the rates of juxtaductal, preductal, and postductal CoAs were 68%, 24%, and 7%, respectively. Similarly, in their study on 298 infants, IJsselhof et al.[12] found the rate of juxtaductal discrete coarctation as 40%. Considering the age groups of the patients, 60 (70%) of the 85 patients were infants, and this was associated with an increase in the incidence of aortic hypoplasias and preductal coarctation in these patients.

Numerous studies have reported that the echocardiographic peak instantaneous gradient is correlated with the catheter-measured peak-to-peak pressure gradient in the diagnosis of CoA, but the echocardiographic measurement is higher[13-17]. In our study, the peak instantaneous gradient measured in the coarctation area by echocardiography was 45.0±16.4 mmHg, and the peak-to-peak pressure gradient measured by cardiac catheterization at the coarctation level was 31.0±14.7 mmHg. In our study, there was a significant difference between the two measurement methods, and the gradient was measured higher by Doppler echocardiography ($p<0.001$).

In their study, Rao et al.[11] reported the mean diameter of the coarctation area as 1.7±0.6 mm [minimum (min)-maximum (max): 0.5-2.8 mm]. In our study, the diameter of the coarctation area was 6.3±3.4 mm (min-max: 4.1-8.0 mm) in patients with native coarctation, while it was measured as 4.1±1.4 mm (min-max: 3.2-5.0 mm) in patients with recoarctation before the second procedure.

In patients who require a second treatment and those who do not, studies have reported no significant difference in the Z-score of the isthmus diameter between the two groups[18]. In our study results, the Z-scores were -0.86±1.34 and -0.13±0.92, respectively ($p>0.05$).

In their study on patients younger than one year of age with the diagnosis of CoA, Wood et al.[19] reported that all 181 patients were treated surgically and this number was reported as 83 in the study of Wright et al.[20]. Surgical treatment is thought to be used in the foreground since it is technically more challenging to perform interventional treatment methods on neonatal patients, and cardiac anomalies are more common in these patients. In our study, 21 of 23 patients in the neonatal group were treated surgically, and balloon angioplasty was preferred to aid clinical improvement for two patients whose clinics were not suitable for surgical treatment.

In different studies, the peak-to-peak pressure gradient measured after balloon angioplasty treatment has been found as 11.0±5.0 mmHg and 13.0±11.0mmHg, which was 8.2±7.2 mmHg in our study[8,11]. In different studies, the peak-to-peak pressure gradient measured after stent treatment was 15.9±13.4 mm Hg and 2.1±2.4 mmHg, which was 2.7±6.5 mmHg in our study[21,22]. In our study, a significant decrease was shown in the peak-to-peak pressure gradient with balloon angioplasty and stent treatments (balloon angioplasty $p<0.001$, stent $p=0.02$). However, there was no difference between the two treatments ($p=0.57$). In patients treated surgically, the peak instantaneous pressure gradient achieved in the distal left subclavian artery decreased from the median value of 40 mmHg [interquartile range (IQR): 30-50.7 mmHg] to 12 mmHg (IQR: 10-19.2 mmHg) ($p<0.001$).

Dijkema et al.[3] reported that they found no difference between the two treatment methods in terms of the decrease in the pressure gradients of 48 patients (19 balloon angioplasty, 29 surgery) who were treated with balloon angioplasty or surgical technique for CoA and followed up for an average of 7 years.

A meta-analysis by Hu et al.[7] comparing balloon angioplasty and surgical treatments for the treatment of CoA evaluated complications that developed in 623 patients (245 balloon angioplasty, 378 surgery) in nine centers, and reported that balloon angioplasty was less invasive, resulting in a reduction in severe complications. When the post-treatment first year was grouped as short term, 1-5 years as midterm, and after 5 years as long term, the risks of post-treatment short-term recoarctation and mid-term and long-term aortic aneurysm were shown to increase significantly.

Given the complications in our study, bleeding was detected in seven patients, including six patients who underwent surgical treatment and one patient who underwent stent implantation, and femoral artery occlusion was detected in one patient who underwent stent implantation. None of the patients who underwent balloon angioplasty developed complications, except for recoarctation. None of the patients developed aneurysm during our follow-up.

The study by Forbes et al.[5] comparing surgery, balloon angioplasty and stent implantation techniques for the treatment of 350 patients with CoA found the rate of recoarctation development as 19%, 32%, and 15%, respectively. In our study, 20% of patients treated with balloon angioplasty and 8% of patients who underwent surgery developed recoarctation. None of the patients who underwent stent implantation developed recoarctation.

Conclusion

The main goals of treatment for CoA are to eliminate coarctation and minimize complications. In untreated CoA patients, it is known that life expectancy is shortened, systemic arterial hypertension develops and progresses more seriously, and mortality and morbidity increase with a decrease in left ventricular function. Early diagnosis and immediate treatment are important to reduce the risk of early and late morbidity and mortality[23].

Interventional treatments are increasingly used for the treatment of CoA compared to surgical treatment. Given the acute complications by treatment preferences in our study, it was found that bleeding was higher in patients who underwent surgical treatment and these patients were especially in the neonatal group. Non-occurrence of any procedure-related complications in patients who underwent balloon angioplasty showed that the procedure could be a more reliable method. However, considering more satisfactory long-term outcomes of surgical treatment, it was concluded that the patient's age, clinical characteristics, and anatomical features of coarctation should be evaluated thoroughly in the treatment selection.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Dr. Behcet Uz Children's Diseases and Surgery Training and Research Hospital Ethics Committee (decision no: 2018/16-11, date: 08.11.2018).

Informed Consent: It was obtained.

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Authorship Contributions

Surgical and Medical Practices: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z., Concept: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z., Design: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z., Data Collection or Processing: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z., Analysis or Interpretation: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z., Literature Search: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z., Writing: C.Ö., T.M., M.M.Y., M.K., E.G., C.Z.

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References

1. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. J Pediatr 2008;153:807-13.
2. Torok RD, Campbell MJ, Fleming GA, Hill KD. Coarctation of the aorta: Management from infancy to adulthood. World J Cardiol 2015;7:765-75.
3. Dijkema EJ, Sieswerda GT, Takken T, et al. Long-term results of balloon angioplasty for native coarctation of the aorta in childhood in comparison with surgery. Eur J Cardiothorac Surg 2018;53:262-8.
4. Rudolph AM, Heymann MA, Spitznas U. Hemodynamic considerations in the development of narrowing of the aorta. Am J Cardiol 1972;30:514-25.
5. Forbes TJ, Kim DW, Du W, et al. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). J Am Coll Cardiol 2011;58:2664-74.
6. Brown ML, Burkhart HM, Connolly HM, et al. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol 2013;62:1020-5.
7. Hu ZP, Wang ZW, Dai XF, et al. Outcomes of surgical versus balloon angioplasty treatment for native coarctation of the aorta: a meta-analysis. Ann Vasc Surg 2014;28:394-403.
8. Ylinen MK, Tyni VE, Pihkala JI, Salminen JT, Sairanen H, Sarkola T. Procedural risk factors, incidence and timing of reintervention after treatment for native coarctation of the aorta in children: a population-based study†. Eur J Cardiothorac Surg 2019;55:564-71.
9. Toro-Salazar OH, Steinberger J, Thomas W, Rocchini AP, Carpenter B, Moller JH. Long-term follow-up of patients after coarctation of the aorta repair. Am J Cardiol 2002;89:541-7.
10. CAMPBELL M, POLANI PE. The aetiology of coarctation of the aorta. Lancet 1961;1:463-8.
11. Rao PS, Chopra PS, Koscik R, Smith PA, Willson AD. Surgical versus balloon therapy for aortic coarctation in infants < or = 3 months old. J Am Coll Cardiol 1994; 23:1479-83.
12. IJsselhof R, Liu H, Pigula F, et al. Rates of Interventions in Isolated Coarctation Repair in Neonates Versus Infants: Does Age Matter? Ann Thorac Surg 2019;107:180-6.
13. Carvalho JS, Redington AN, Shinebourne EA, Rigby ML, Gibson D. Continuous wave Doppler echocardiography and coarctation of the aorta: gradients and flow patterns in the assessment of severity. Br Heart J 1990;64:133-7.
14. Tan JL, Babu-Narayan SV, Henein MY, Mullen M, Li W. Doppler echocardiographic profile and indexes in the evaluation of aortic coarctation in patients before and after stenting. J Am Coll Cardiol 2005;46:1045-53.
15. Nihoyannopoulos P, Karas S, Sapsford RN, Hallidie-Smith K, Foale R. Accuracy of two-dimensional echocardiography in the diagnosis of aortic arch obstruction. J Am Coll Cardiol 1987;10:1072-7.
16. Cyran SE. Coarctation of the aorta in the adolescent and adult: echocardiographic evaluation prior to and following surgical repair. Echocardiography 1993;10:553-63.
17. Seifert BL, DesRochers K, Ta M, et al. Accuracy of Doppler methods for estimating peak-to-peak and peak instantaneous gradients across coarctation of the aorta: An In vitro study. J Am Soc Echocardiogr 1999;12:744-53.
18. Hijazi ZM, Fahey JT, Kleinman CS, Hellenbrand WE. Balloon angioplasty for recurrent coarctation of aorta. Immediate and long-term results. Circulation 1991;84:1150-6.
19. Wood AE, Javadpour H, Duff D, Oslizlok P, Walsh K. Is extended arch aortoplasty the operation of choice for infant aortic coarctation? Results of 15 years' experience in 181 patients. Ann Thorac Surg 2004;77:1353-7.
20. Wright GE, Nowak CA, Goldberg CS, Ohye RG, Bove EL, Rocchini AP. Extended resection and end-to-end anastomosis for aortic coarctation in infants: results of a tailored surgical approach. Ann Thorac Surg 2005;80:1453-9.
21. O'Laughlin MP, Perry SB, Lock JE, Mullins CE. Use of endovascular stents in congenital heart disease. Circulation 1991;83:1923-39.
22. Thanopoulos BD, Giannakoulas G, Giannopoulos A, Galdo F, Tsaoussis GS. Initial and six-year results of stent implantation for aortic coarctation in children. Am J Cardiol 2012;109:1499-503.
23. Attenhofer Jost CH, Schaff HV, Connolly HM, et al. Spectrum of reoperations after repair of aortic coarctation: importance of an individualized approach because of coexistent cardiovascular disease. Mayo Clin Proc 2002;77:646-53.

Case Report

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Being on the Edge of Amputation: Vessel-sparing Approach and Biological Bone Reconstruction in a Toddler with Extremity Rhabdomyosarcoma

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Abstract

Vascular reconstruction leads to surgical difficulties such as acute occlusion and critical leg ischemia in childhood rhabdomyosarcoma (RMS) pressuring on the limb's vascular structures. Finally, amputation is inevitable. Also, use of prostheses to repair bone defects in these cases results in long-term failure or complications such as infection. To avoid a catastrophic problem such as amputation, a vessel-sparing approach and biological bone reconstruction may be a solution in these cases. Here, we present a case of total surgical tumor excision that keeps the native vascular and biologic bone reconstruction in a RMS case involving the left thigh in a two-year-old toddler.

Keywords: Rhabdomyosarcoma, limb-salvage, vessel-sparing surgery, soft tissue sarcoma

Introduction

Rhabdomyosarcoma (RMS), a soft tissue sarcoma, is very common in children and accounts for approximately 10% to 15% of solid malignant tumors[1-3]. The RMS is heterogeneous and has a rapid, invasive, and infiltrative growth pattern[4]. The outcome depends on primary involvement site, tumor size, histological structure, and the patient's age[5]. The limbs are invaded in 20%

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of the cases[6]. The cure chance of RMS increases with a multidisciplinary treatment approach that includes chemotherapy, radiotherapy, and wide excision surgery[2,7]. Today, limb salvage surgery is applied as standard treatment with the development of surgical techniques, imaging methods, and the presence of vascular grafts[8,9]. Autologous grafts are preferred in these cases compared to prosthetic grafts due to their superior patency[8,10,11]. However, the choice of vascular grafts in children is difficult due to the size limitations of autologous grafts, unusable small-diameter prosthetic grafts, and insufficient surgical experience. The difficulty is increased in toddlers, and limb salvage with vascular repair may be impossible[12].

Although synthetic bone grafts used to repair the extremity defect provide recovery in the short-term, they are not preferred due to infection and durability problems in the long-term. Biological reconstruction grafts obtained by processing tumor-containing bone tissues with liquid nitrogen may be a more natural and permanent solution[13,14].

A vascular-sparing surgical approach and the biologic bone autograft technique in childhood RMS will save the limb from amputation because of these difficulties.

Here, we present a case of total surgical tumor excision that keeps the native vascular and biologic bone reconstruction in the RMS case involving the left thigh in a two-year-old toddler.

Case Report

A two-year-old girl was admitted with a huge left thigh mass adjacent to the femoral bone's medial side. The patient had pain in her left thigh with stiffness and swelling for about five months. The patient did not have a family history of malignant disease or recent trauma. There was a mass of 6 cm x 12 cm in the left thigh on physical examination (Figure 1). No neurologic deficits were detected. On magnetic resonance imaging (MRI), a large mass of 6 cm x 12 cm was detected in the middle of the left thigh, compressing the neurovascular bundle (Figure 2a). The MRI showed that the femoral artery, femoral vein, and femoral nerve were compressed laterally by the tumor (Figure 2b). On positron emission tomographic imaging, the patient had a few small metastatic lesions in her lung. A tissue sample was taken from the patient with a trucut needle biopsy under ultrasound guidance with an anteromedial approach. Histopathological diagnosis was embryonal RMS. The lesion in the femoral bone segment persisted after preoperative chemotherapy.

Surgical Procedure

Two weeks after the diagnosis, the surgical procedure was performed with an anteromedial approach to protect the natural vascular structure and save the limb (Figure 3). Skin and subcutaneous incisions were made from the groin to the distal of the limb in a longitudinal fashion. The neurovascular bundle was exposed without touching the

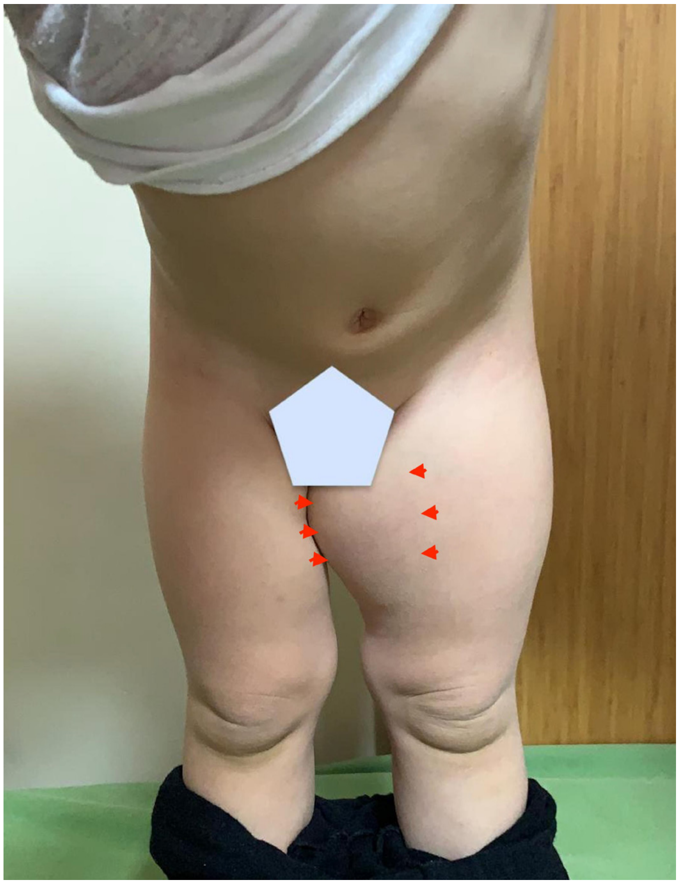

Figure 1. Preoperative view. The arrows show the soft tissue mass borders

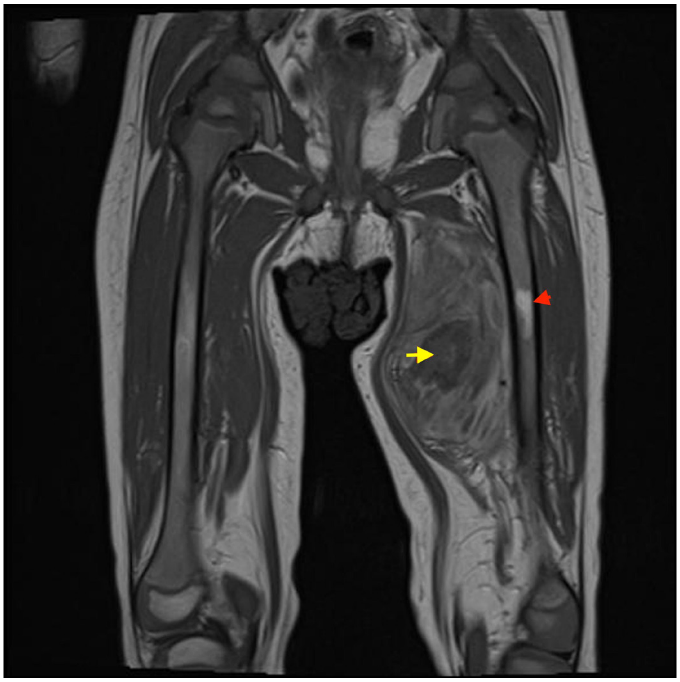

Figure 2a. On MRI, the yellow arrow shows the soft tissue mass in the left thigh's medial border, and the red arrow shows the bone involvement of the soft tissue mass

MRI: Magnetic resonance imaging

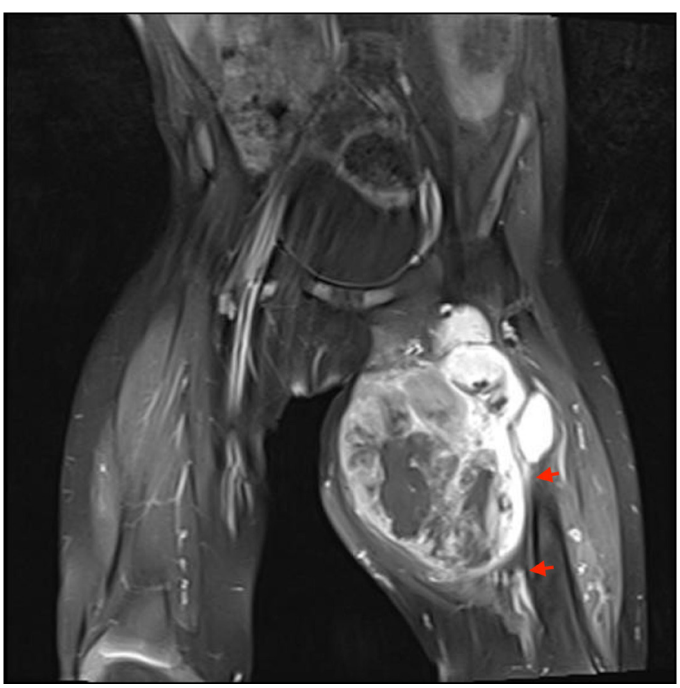

Figure 2b. Compressed neurovascular bundle on the MRI. The arrows show the compressed neurovascular bundle

MRI: Magnetic resonance imaging

tumor from the lateral of the tumor. The superficial femoral artery and vein and the femoral nerve were exposed and protected by making a gentle dissection. Since the most important factor for successful sarcoma surgery is wide resection, the deep femoral artery was ligated just below the femoral bifurcation and the deep femoral vein at the level of the saphenofemoral junction. Distal pulses were checked, and no ischemia was observed. Both arterial and venous flows were sufficient.

According to the concept of surgical margins, wide resection was made with soft tissue mass and 5-centimeter femoral bone resection (Figure 4). The tumoral mass was stripped from the bone segment, including the periosteum. Aggressive curettage was applied to the intramedullary cavity. Then, the bone segment was frozen with liquid nitrogen for 20 minutes. The bone segment was thawed at room temperature for 20 minutes and in distilled water for 15 minutes. Ultimately, a bone graft was obtained, which provided the best morphological matching from the bone segment. (Figure 5). Subsequently, the bone graft was fixed with a 3.5 mm reconstruction plate (Figure 6). The wound was irrigated and sutured in a standard fashion. The operation was completed successfully.

The patient's pedal pulses were checked regularly after surgery. The patient was discharged on the seventh postoperative day without any signs of ischemia.

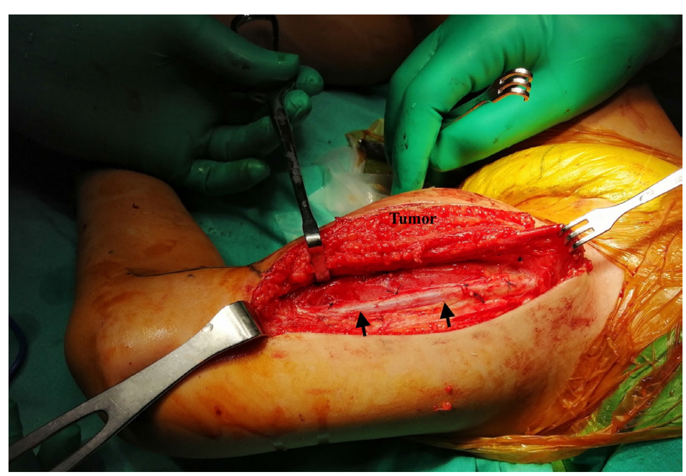

Figure 3. Intraoperative view. The arrows show spared-vascular structures during the surgery

The pediatric oncology clinic planned postoperative radiotherapy for lung metastasis and neo-adjuvant chemotherapy. Pathological samples confirmed the diagnosis and showed that all sides of the resected tumor mass were tumor-free.

Results

There was no loss of function in the left lower limb (Figure 7). In the postoperative second month's control examination, the patient was walking comfortably, and no neurological or orthopedic problems were detected. The patient continued the chemotherapy program.

Currently, the patient has had her five-month follow-up. The patient had no limb length discrepancy at her last follow-up. There was no problem with her bone growth and limb circulation. Finally, no tumor recurrence was detected in the left lower limb of the patient during the five-month follow-up.

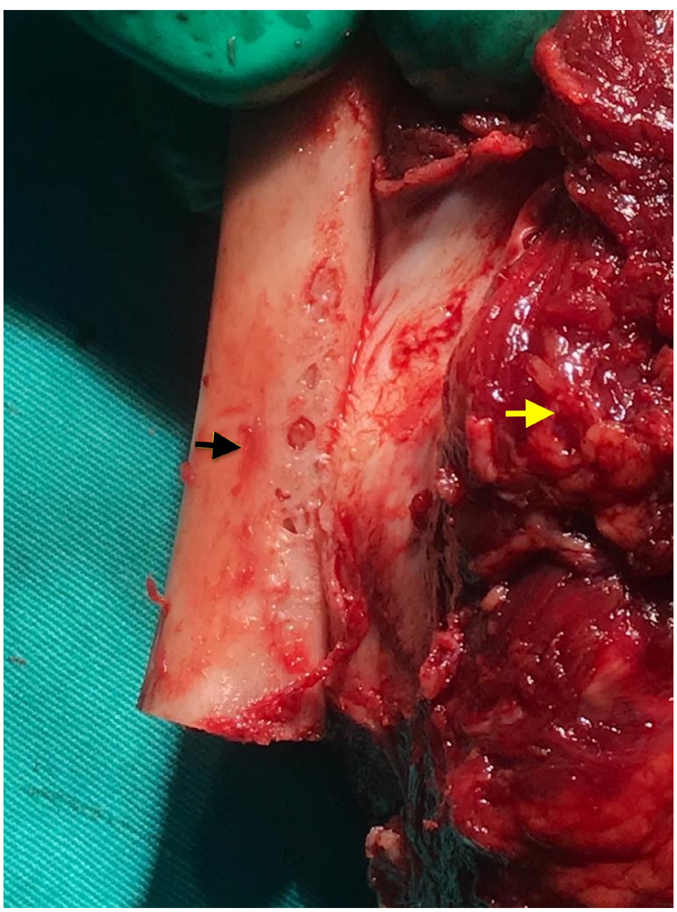

Figure 4. Perioperative view of the resected tumor involving soft tissue (yellow arrow) and the bone part (black arrow)

Discussion

Soft tissue sarcomas such as RMS is a rare condition in children[8]. Limb loss may occur because of vascular involvement by the tumor[15]. Vascular reconstructive surgery may be required in such cases[2]. However, in

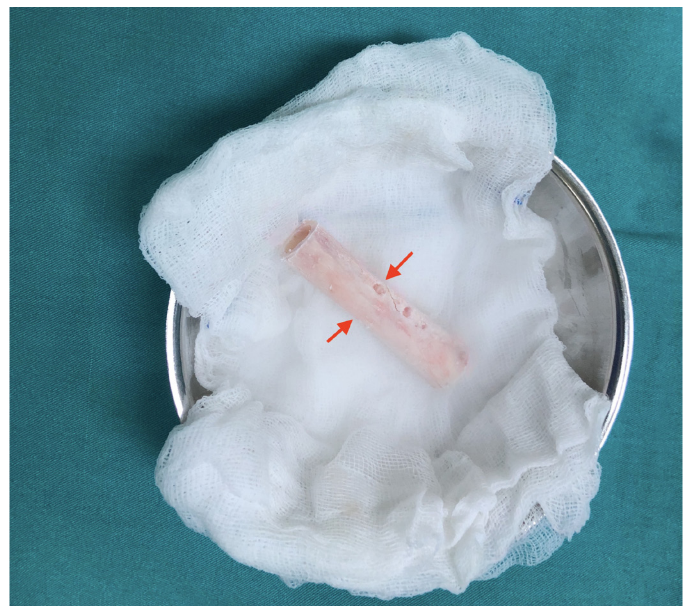

Figure 5. The biological bone graft prepared with the liquid-nitrogen application. The red arrows show the tumor-free bone graft

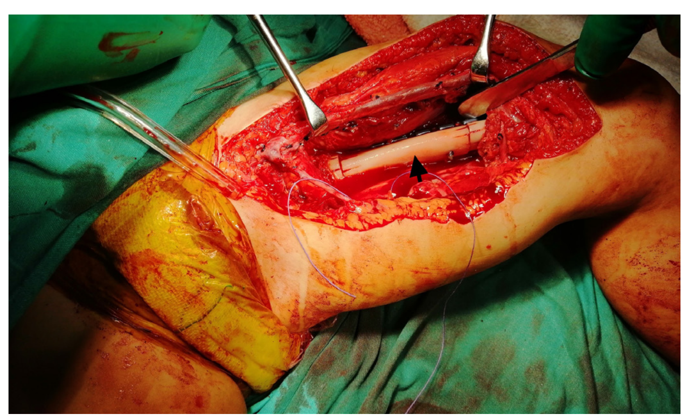

Figure 6. Perioperative view of the re-implanted biologic bone graft. The arrow shows the re-implanted bone segment

infants and toddlers, reconstruction is difficult due to small diameter vein grafts, or prosthetic grafts, which trend to thrombosis[12]. Vascular reconstruction surgery may be necessary to avoid catastrophic consequences such as amputation due to distal limb ischemia[15]. However, in toddlers, arteries or veins are of relatively small diameter[12]. Therefore, the vascular reconstruction procedure is often complicated due to small-sized native grafts or small diameter prosthetic grafts. Sometimes, amputation is mandatory because artificial grafts applied to small vessels are thrombosed[12].

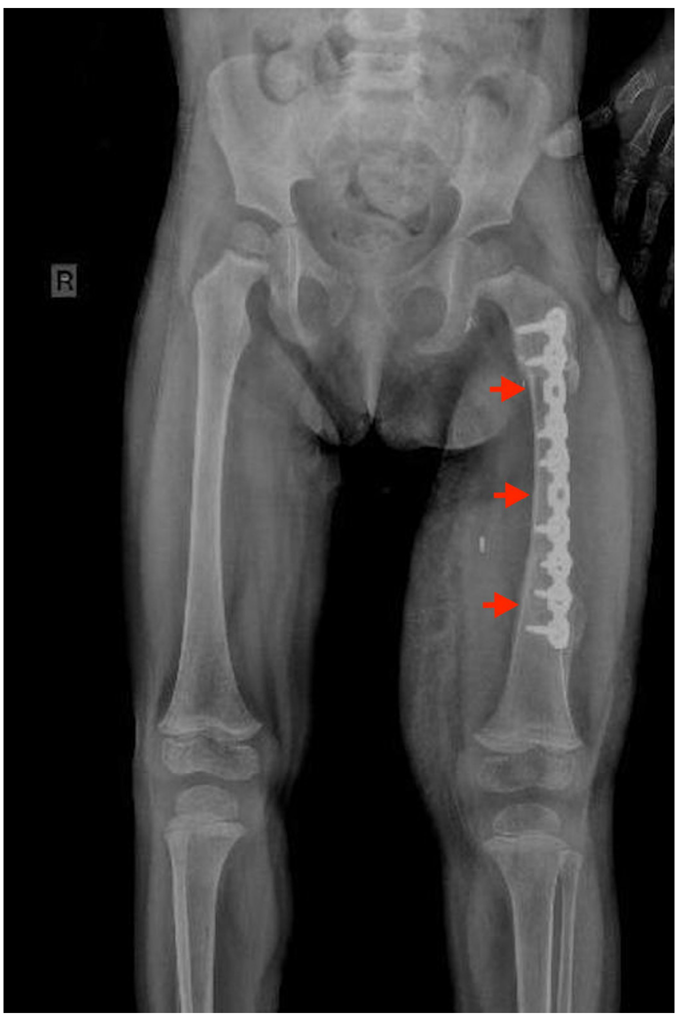

Figure 7. Postoperative second-month control X-ray image. The arrows show that the re-implanted biologic bone graft integrated with the host bone. The union of the bone graft and the host bone can be seen on the X-ray image

Furthermore, the neurovascular bundle is under pressure if the tumor invades the package[3,16]. There are various intervention scenarios to preserve the affected limb[16]. Although otherwise claimed[12], most surgeons cannot dare to ligate the main arteries in the toddlers in tumor operations with a high risk of amputation by trusting on collateral circulation. There are insufficient diameter and length of native grafts, such as a great saphenous vein in toddlers[12], and a high risk of thrombosis of prosthetic grafts complicates the surgical intervention to recover the affected limb[2,8,16]. There are two options back to recover the tumor invaded by the tumor; amputation or vessel-sparing surgery. Vessel-sparing surgery is possible only with an experienced surgical team and a rigorous tissue resection, and the results are excellent[1,4,6-9,15,16]. Today, limb salvage surgery is now accepted as a standard treatment method in limb sarcomas[8,9], and the number of surviving limbs is higher than the number of amputations[1,7]. This treatment model change was made possible by advancing surgical techniques, introducing new imaging methods, and developing vascular grafts[13].

Our team was ready before the operation for possible vascular reconstruction scenarios. In case of failure to protect the vascular structures, our first alternative was to create a new graft by opening the great saphenous vein of the patient with a diameter of 1.7 mm linearly and wrapping it around a Hegar dilator. In case this was not possible, we had planned to use a biological vein graft. Our worst scenario was transfemoral amputation.

Another goal of the treatment should also be to restore bone defects that preserve the affected limb's length and function. Arthroplasty is one of the choices, especially in adult patients. However, biological reconstruction is important, especially in children. We used the biological reconstruction technique "frozen autograft treated with liquid nitrogen" for this toddler[13,14].

Liquid nitrogen-inactivated autologous bone graft is a safe method for primary malignant extremity tumors. This method has a low complication rate and high bone healing rate, and also offers a satisfactory limb function[17].

In our case, the patient's age, clinical and radiographic findings have encouraged us to prefer a limb-sparing surgical technique that preserves native neurovascular bundle and bone structure. Our approach in toddlers with malignant limb soft tissue tumors adjacent to vascular structures can be applied successfully and it can prevent amputation. We believe that the vessel-sparing surgery can be the first choice for standard surgical technique in toddlers in terms of better cosmesis, low morbidity, and loss of function in huge sarcomas threatening the limb.

Ethics

Informed Consent: The informed consent forms were obtained for the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O., B.K.A., Concept: A.O., B.K.A., Design: A.O., B.K.A., Data Collection or Processing: A.O., B.K.A., Analysis or Interpretation: A.O., B.K.A., Literature Search: A.O., B.K.A., Writing: A.O., B.K.A.

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

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References

1. Kumta SM, Cheng JC, Li CK, Griffith JF, Chow LT, Quintos AD. Scope and limitations of limb-sparing surgery in childhood sarcomas. J Pediatr Orthop 2002;22:244-8.
2. McGoldrick NP, Butler JS, Lavelle M, Sheehan S, Dudeney S, O'Toole GC. Resection and reconstruction of pelvic and extremity soft tissue sarcomas with major vascular involvement: Current concepts. World J Orthop 2016;7:293-300.
3. Ng WK. Embryonal rhabdomyosarcoma in a young boy. Mcgill J Med 2007;10:16-9.
4. Wolden SL, Alektiar KM. Sarcomas across the age spectrum. Semin Radiat Oncol 2010;20:45-51.
5. Zhu L, Sun Y, Wang X, et al. Survival stratification in childhood rhabdomyosarcoma of the extremities: a derivation and validation study. Sci Rep 2020;10:5684.
6. Hosalkar HS, Dormans JP. Limb sparing surgery for pediatric musculoskeletal tumors. Pediatr Blood Cancer 2004;42:295-310.
7. Marchetti AA, Di Giulio L, Oddi FM, Davila BO, Ciattaglia R, Ippoliti A. Strategy to preserve function in lower limbs tumors resection. Vascular competence in multidisciplinary approach. 2020;1-12.
8. Khalefa S, El Bahaey A, El-Samadoni A, Eldmarany HA. Clinical outcomes after wide resection of lower extremity soft tissue sarcomas with femoral vessel reconstruction. Egypt J Surg. 2020;39:206-14.
9. Steinau HU, Daigeler A, Langer S, et al. Limb salvage in malignant tumors. Semin Plast Surg 2010;24:18-33.
10. Nishinari K, Krutman M, Aguiar Junior S, et al. Surgical outcomes of vascular reconstruction in soft tissue sarcomas of the lower extremities. J Vasc Surg 2015;62:143-9.
11. Nishinari K, Wolosker N, Yazbek G, Zerati AE, Nishimoto IN. Venous reconstructions in lower limbs associated with resection of malignancies. J Vasc Surg 2006;44:1046-50.
12. Aponte-Tinao L, Farfalli GL, Ayerza MA, Muscolo DL. Case report: Common femoral artery ligation after sarcoma resection in an infant. Clin Orthop Relat Res 2011;469:609-12.
13. Igarashi K, Yamamoto N, Shirai T, et al. The long-term outcome following the use of frozen autograft treated with liquid nitrogen in the management of bone and soft-tissue sarcomas. Bone Joint J 2014;96:555-61.
14. Yamamoto N, Hayashi K, Tsuchiya H. Progress in biological reconstruction and enhanced bone revitalization for bone defects. J Orthop Sci 2019;24:387-92.
15. Ramamurthy R, Soundrarajan JC, Mettupalayam V, Shanmugham S, Arumugam B, Periasamy S. Limb conservation in extremity soft tissue sarcomas with vascular involvement. Indian J Orthop 2009;43:403-7.
16. Song TK, Harris EJ Jr, Raghavan S, Norton JA. Major blood vessel reconstruction during sarcoma surgery. Arch Surg 2009;144:817-22.
17. Li Y, Yang Y, Huang Z, Shan H, Xu H, Niu X. Bone defect reconstruction with autologous bone inactivated with liquid nitrogen after resection of primary limb malignant tumors: An observational study. Medicine (Baltimore) 2020;99:20442.