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How to make a "Heart Team" a "real" Team to Ensure Optimal Patient Care

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Introduction

Due to the ongoing ageing of the population with increased related co-morbidities, transcatheter interventions are spreading around the first world countries like an unstoppable firewall. Some (the tip of the iceberg) have already established in "normal clinical life" and became very safe procedures for the "modern high-risk patient" with acceptable outcomes over the last decade but many more are just evolving currently being under investigation with first in-man clinical trials.

In the initial phase of the clinical adoption of transcatheter valve therapies (2007/2008), different specialists with different professional backgrounds, skill-sets and personalities were "forced" to work together out of necessity. As a result, interventional cardiologists and cardiac surgeons started to work as a "Heart Valve Team" in order to overcome the respective lack of knowledge (ie. wire skills for surgeons and valvular anatomy and well-established surgical valve therapies for interventionalists) and to merge in a complementary way to offer the best possible treatment. The establishment of a "Heart Team" was a need, which was desired and perceived by the physicians themselves. But with the progressive fast establishment of a complementary "hybrid" culture, the need for such a "Heart Team" became soon lees stringent, and many individual conflicts emerged, mainly due to not shared targets and willingness to be the predominant leader of the team.

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Therefore, the ESC/EACTS have recommended in the 2012 guidelines as a mandatory prerequisite for a Valve Centre performing transcatheter therapies to establish a "Heart Team" consisting of multiple specialists in order to be capable to discuss the cases interdisciplinary and to decide the optimal individual treatment option. The presence of the "Heart Team" became a "condition sine qua non" (in the interest of the patients) for every centre to be allowed to be part of the game (modern transcatheter therapies). In the last 2017 Guidelines the presence of a multidisciplinary "Valve Team" has reached a Class IC level of evidence recommendation, and today in many countries formal "Heart Team" discussions are even mandatory for reimbursement.

How to build a functional and functioning "Heart Team"?

While trying to establish this suggested "Heart Team", the following questions arise: who is the leader in an interdisciplinary team and how are decisions made in the presence of hierarchy, unbalanced information sharing and hidden agendas? Or is the "Heart Team" doomed to fail before it could be established in clinical practice? At present, there is no defined "standard" for the performance of a "Heart Team Meeting" which can result in biased decision making in a "Team of Experts" who do not share common goals.

Therefore, before answering the questions above, we first have to become aware of the definition of "Team": in a team, all members have shared goals, there is interdependency and reflexivity. If these criteria are not met, quality of decision-making suffers.[2-5] Are there shared goals in a "Heart Team" besides the well-being of the patient? Is there interdependency and reflexivity within a "Team of Experts" who ultimately aim to support their own specialty? Without standards, the final decision of a "Heart Team" may depend on status, individual points of view and decision-making habits rather than on integration of interdisciplinary expertise, which might result in less optimal treatment decisions.

In order to create a functioning unbiased "Heart Team", the following should be considered:

First of all, a shared "basis" or "goal" has to be created for the different specialties involved within an institution. A team of experts of different specialties has to be rewarded as "one team": the establishment of an official "Heart Centre" is advisable.

Secondly, the performance of a "Heart Team Meeting" has to be standardised with defined timeframe, leadership, role of team members, discussion culture and decision making process.

Thirdly, while conducting the "Heart Team Meeting", the members have to be aware of various team interaction phenomena, types of leadership with their respective consequences and discussion culture, which have a tremendous influence on the outcomes of decision-making.

Typical pitfalls of biased decision-making and evidence-based suggestions how to overcome them are the following:

- Lack of "speaking up": important information or concerns are not automatically integrated into decisions because team members do not necessarily dare to voice them.[6] This results in impaired quality and safety of patient care.[7,8] Team leaders can avoid this pitfall by inviting and encouraging to speak up by establishing process rules to make sure that team members can share their unique expertise without negative consequences.[9]

- "Groupthink" is a common "silent consensus phenomenon" within a team that does not reflect the individual team members' true beliefs but has been found to result in catastrophic decisions (i.e. Bay of Pigs invasion in Cuba.[10]) This phenomenon can be controlled when team leaders are open for new information and exclusively invite team members to dissent.[11,12]

- "Anchoring and confirmation bias": preferred opinions are usually "anchored" in one's mind, its advantages are overemphasized, weaknesses are not mentioned and evidence is sought to confirm them.[13] Team leaders can avoid this pitfall by inviting and allowing dissent, sharing information instead of opinions, and inquire instead of argue.[4,11,12,14]
- "Majority rule": makes decisions less time consuming but focuses rather on compromise instead of discussing important differing viewpoints. Decision-making is improved when team members discuss instead of vote.[15]
- "Leadership style": has a crucial impact on the decision-making process and decision quality (outcome can be biased by the leaders opinion):[16] leaders can be the main reason for the lack of speaking up by demonstrating hierarchy.[17] To avoid this they should ask instead of instruct, create a safe atmosphere that allows open discussion, take responsibility for the decision-making process by inviting team members to share their unique expertise and initiate reflections on the team's decision-making.[13,14,18-20]

Conclusion

In a "real" team all members have shared goals, there is interdependency and reflexivity which is not easily achievable when multiple specialties are involved. For that reason a "Heart Team" can only perform its purpose properly if it is deliberately forced to become a "real" Team whose decisions are not biased by hierarchy, unbalanced information sharing and hidden agendas. On the basis of the establishment of a "Heart Centre", we suggest the implementation of a standardized "Heart Team Meeting" protocol with defined timeframe, leadership, role of team members, discussion culture and process of decision making. If these evidence-based recommendations can be adopted, optimal decision-making and patient care can be achieved for the modern ageing high-risk population.

In order to achieve the education needed for the establishment and running of a functioning "Heart Team", the University of Zurich has initiated the worldwide very first "Certificate of Advanced Study (CAS) in Structural Heart Intervention" courses.

The education not only includes clinical and innovational elements, but most importantly communication, financial and leadership skills, along with elements of conflict solving in different scenarios. We believe that in the future, all members (especially leaders) of a "Heart Team" must undergo such an officially certified education in order to guarantee optimal patient care.

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Retrospective Evaluation of the First 150 Patients with Vascular Surgery in A New Cardiovascular Surgery Clinic

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Abstract

Objective: This study aimed to retrospectively evaluate the data of patients undergoing peripheral arterial vascular surgeries and to present our approach to peripheral arterial disease (PAD) in our clinic, which was put into service as of September 2014.

Methods: Data on 151 patients undergoing peripheral arterial vascular surgery between September 2014-December 2016 were retrospectively evaluated. Of the patients, 45 (29.80%) underwent emergency surgery and 106 (70.19%) underwent elective surgery. Of emergency surgeries, 31 (68.88%) patients had acute embolism. Among elective surgeries, femoropopliteal bypass was the most common procedure in 52 patients. While above-knee femoropopliteal bypass was performed in 40 (76.92%) patients, vena saphena magna (VSM) could be used as a graft in 31 patients. VSM could be used in 9 of 12 patients undergoing below-knee femoropopliteal bypass.

Results: Of 151 patients, 14 (9.27%) were admitted for revision during the postoperative period. Among 52 patients undergoing femoropopliteal bypass, 7 were re-operated (4 underwent above-knee and 3 underwent below-knee femoropopliteal bypass). While the polytetrafluoroethylene graft was used in all of these patients, none of the patients with VSM graft required revision. The patient with Shamblin type-III tumor, who was operated due to glomus caroticum, developed graft occlusion and was re-operated; however, hemiplegia was developed postoperatively. Mortality occurred in 4 patients (2 with abdominal aortic aneurysm rupture and 2 with penetrating injury). All of them had hypovolemic shock prior to the surgery.

Conclusion: There is a need for an experienced team for PAD and the treatment method to be applied should be patient-based.

Keywords: Peripheral arterial disease, vascular surgery, morbidity, mortality

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Introduction

Peripheral arterial disease (PAD) due to atherosclerosis is a significant cause of morbidity and mortality. PAD is an important health problem with a gradually increasing prevalence. It has been estimated that more than 30 million people worldwide are affected by PAD. The frequency of PAD over the age of 65 years has been reported to be 17% among females and 20% among males. According to the non-invasive criteria, while the prevalence of PAD is 3%-7% under the age of 60 years, it reaches to 20% in the population aged over 70 years. Additionally, one-third of these people are asymptomatic.[1] The treatment of PAD may be medical, endovascular or surgical. In the present study, we aimed to retrospectively evaluate the data of patients undergoing PAD surgeries and to present our approach to PAD in our clinic, which was put into service as of September 2014.

Methods

Data on patients undergoing PAD surgery between September 2014 and December 2016 in our clinic were retrospectively evaluated. The study was approved by the Ethics Committee of Training and Research Hospital and informed consents of patients were obtained. Absence of distal pulses detectable by palpation or by a hand-held Doppler was considered adequate for the diagnosis of PAD. In addition to the clinical and physical examination, patients also underwent vascular Doppler ultrasonography. While patients who were admitted with acute arterial embolism were operated based on the Doppler ultrasonography findings, computed tomography angiography and/or conventional angiography was used as the diagnostic method in the patients with PAD. Conventional angiography was performed in patients for whom endovascular surgery was planned or who required coronary angiography. Among the 31 patients who underwent concurrent coronary angiography, 13 had coronary lesion and coronary artery bypass graft (CABG) surgery was primarily performed in 8 of these patients.

Surgical Strategy and Techniques

Femoropopliteal Bypass

Patients underwent venous Doppler ultrasonography prior to the surgery. The wall structure and the diameter of the vena saphena magna (VSM) were examined. Polytetrafluoroethylene (PTFE) grafts were used when the VSM had a diameter of <3 mm or with packet formation, or had fibrotic valves. VSM was excised segmentally by intermittent skin incision in patients for whom VSM could be used and a reverse bypass was performed.

Glomus Caroticum (GC)

Two patients were operated due to GC; one with Shamblin type II tumor and the other with Shamblin type III tumor. In the patient with Shamblin type II tumor, the tumor was removed preserving the integrity of carotid artery. In the patient with Shamblin type III tumor, the tumor was removed together with the external carotid artery and the internal carotid artery and PTFE graft was used to maintain the continuity of internal carotid artery .

Carotid-to-Subclavian Bypass

A left supraclavicular transverse incision extending lateral to the clavicular head of the sternocleidomastoid muscle was performed. This provides excellent exposure for both carotid artery and subclavian artery. The subclavian artery was exposed by dividing the inferior insertion of the anterior scalene muscle (on the first rib). We took care to identify and protect the phrenic nerve. We ligated the thoracic duct and all its tributaries. We performed the carotid-to-subclavian bypass with 6 mm ringed PTFE graft. Carotid-to-subclavian bypass was performed concurrently with thoracic endovascular aneurysm repair in 2 patients with type III dissection involving the left subclavian artery.

Popliteal Artery Entrapment Syndrome

Four patients were operated due to popliteal artery entrapment syndrome; 2 with type I and 2 with type II. Popliteal artery was approached posteriorly using S incision. Myotomy of the medial head of the gastrocnemius muscle was performed. Despite the relieving of the compression, the vessel wall integrity was not preserved. All patients underwent graft interposition using the saphenous vein.

Statistical Analysis

Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean

and standard deviation for numerical variables.

Results

Of the 151 patients underwent peripheral arterial vascular surgery, 114 were males and 37 were females. The mean age of the patients was 56.5±13.3 years (range, 17-78 years). Of the patients, 37.74% had a history of smoking. The most prevalent comorbidity was diabetes mellitus followed by coronary artery disease (CAD) and chronic obstructive pulmonary disease **(Table 1)**. Of the 151 patients, 45 (29.80%) underwent emergency surgery and 106 (70.19%) underwent elective surgery. Of these 45 patients, 31 (68.88%) presented with a clinical picture of acute embolism and the most common site of occlusion was femoropopliteal region in 21 (67.74%) out of 31 patients. The leading etiological factor was arterial embolus resulted from atrial fibrillation.

Among elective surgeries, the femoropopliteal bypass was the most common procedure performed in 52 patients. While the femoropopliteal bypass was performed above the knee in 40 (76.92%) patients, VSM could be used as a graft in 31 patients. VSM could be used in 9 of 12 patients who underwent below-knee femoropopliteal bypass.

Seventeen patients, who were not suitable for endovascular treatment or required urgent intervention, were operated due to traumatic arteriovenous fistulas (AVFs). Primary repair of the artery and vein after ligation was performed in 2 patients, graft interposition in the artery and primary repair of vein were performed in 5 patients, and graft interposition to the artery and vein was performed in 10 patients. Saphenous vein was used as the graft in all patients **(Table 2)**.

There were 8 patients who were planned to undergo peripheral arterial surgery and had indication for concurrent CABG. In these patients, CABG was primarily performed since their coronary lesions were serious and the peripheral arterial surgery could be postponed. The left internal mammary artery (LIMA) was not used in 1patient with Leriche syndrome. Peripheral arterial surgery was performed in the patients in the 1st month after discharge. Among these patients, 7 underwent femoropopliteal bypass and 1 underwent aortobifemoral bypass. Coronary bypass and carotid endarterectomy were performed in the same session in 6 patients.

After sternotomy, LIMA was prepared and carotid exploration was performed by leaving the LIMA in the chest wall. Carotid endarterectomy was performed following heparinization and the standard CABG was then performed. Of the 151 patients who were operated for peripherial vascular diseases, 14 (9.27%) were admitted for revision during the postoperative monitoring period. Among these patients, 7 patients underwent

Table 1. Demographic and clinical characteristics of the patients

Characteristics	Data
Age, years (mean±SD)	**56.5±13.3**
Gender, n (%)	
Female	37 (24.50)
Male	114 (75.49)
Smoking, n (%)	57 (37.74)
Comorbidities	
Diabetes mellitus, n (%)	32 (21.19)
Coronary artery disease, n (%)	22 (14.56)
Chronic obstructive pulmonary disease, n (%)	9 (5.96)
SD: *standard deviation*	

Table 2. Surgical procedures

Surgery	n (%)
Femoropopliteal bypass	52 (34.43)
Embolectomy	21 (13.90)
Aortobifemoral bypass	20 (13.33)
Traumatic arteriovenous fistula	17 (11.25)
Carotid endarterectomy	13 (8.60)
Femorofemoral bypass	8 (5.29)
Left aortofemoral bypass	7 (4.63)
Abdominal aortic aneurysm repair	5 (3.31)
Popliteal artery entrapment syndrome	4 (2.64)
Glomus caroticum	2 (1.32)
Caroticosubclavian bypass	2 (1.32)

femoropopliteal bypass, of whom 4 underwent above-knee femoropopliteal bypass and 3 underwent below-knee femoropopliteal bypass. While the PTFE graft was used in all of these patients, none of the patients with VSM graft required revision. During the revision, graft embolectomy was performed in 2 patients and distal anastomosis was re-performed in 5 patients, in which the Miller cuff was used. While the earliest revision was required in the 7th month in 1 patient who underwent below-knee femoropopliteal bypass using the PTFE graft, the average time for revision was 12 months (mean, 12±4.5 months). Two-year patency rate was 75% in the patients undergoing below-knee femoropopliteal bypass and 90% in the patients undergoing above-knee femoropopliteal bypass.

Femoral wound site revision was performed in 4 patients due to tissue infection. Of these patients, 3 underwent femoropopliteal bypass and 1 underwent aortobifemoral bypass. None of the patients developed graft infection. In 1 one patient who underwent femoropopliteal bypass, an early revision was performed due to postoperative bleeding.

One patient who underwent revision presented to our clinic 4 days after the onset of symptoms. The graft patency was achieved after embolectomy; however, the below-knee amputation had to be performed. The patient, who was operated due to GC and surgically classified as the Shamblin type-III tumor, developed graft occlusion and hemiplegia was occurred **(Table 3).**

Mortality occurred only in 4 patients, of whom 2 were diagnosed as abdominal aortic aneurysm rupture and 2 had penetrating injury. All of these patients had hypovolemic shock prior to the surgery.

Discussion

The main principles of vascular surgical approaches were first defined by Carrel a century ago.[2,3] After the experiences on the vascular injury gained during the World War I and II, rapid deceleration has been provided in the incidence of amputations following reconstructive vascular interventions.

Peripheral artery disease is encountered in 13% of the people aged over 50 years. The frequency of symptomatic PAD in the Western populations has been reported to be 5% in the55-74age group.[4]

Peripheral artery disease is considered as a predictor for CAD. In the study by Poredos and Jug,[5] symptomatic atherosclerosis was reported in 821 (86.2%) of 952 subjects, who were at high risk for cardiovascular disease and the asymptomatic patients had at least two risk factors. Moreover, PAD was detected in 42% of the patients with CAD and there was no significant difference between the CAD and PAD groups in terms of the risk profiles.[5] In the present study, the patients who underwent elective surgeries were evaluated for cardiac diseases and coronary angiography was performed, when required. CABG was primarily performed in 8 of these patients.

In the Guideline for the Treatment of Peripheral Artery and Vein Diseases published in 2008 by the Turkish Society of Cardiovascular Surgery, aortoiliac and femoropopliteal lesions were classified from simple to complex using the Trans-Atlantic Inter-Society Consensus (TASC) Classification System as TASC A, B, C,

Table 3. Morbidity

Morbidity	Surgery	n (%)
Graft occlusion	Above-knee femoropopliteal bypass	4 (10)
	Below-knee femoropopliteal bypass	3 (25)
Wound-site infection	Femoropopliteal bypass	3 (5.76)
	Aortobifemoral bypass	1 (5)
Bleeding revision	Femoropoplitealbypass	1 (0.72)
Cerebrovascular accident	Glomus caroticum	1 (50)
Extremity loss	Femoropopliteal bypass	1 (1.92)

and D and in general, endovascular treatment was recommended for type A and B lesions and open surgery was recommended for type C and D.[6]

An update summarizing the literature on endovascular and open surgery procedures but not including definite recommendations was published in 2015.[7] In this update, definite treatment recommendations were not included as was in the TASC II. The main reason of this might be the facts that comparative studies have not been adequate in quality and in number to support the "endovascular approach at first" and that no consensus could have been provided. In this update, the common point is that life style changes, drug therapies, and exercises prior to the invasive procedure are still valid.

In the present study, the treatment modalities were identified based on age, occupation, and range of claudication. Medical therapy was preferred in the patients with long-distance claudication, advanced-age, and concomitant cardiac and pulmonary problems and in the inactive patients. The indication for invasive procedure was determined based on clinical picture of the patients and using the Fontaine classification.

Invasive procedure was planned, if a young patient with active life style had serious claudication and could not eliminate this problem by changing his/her life style, or if resting pain could not be relieved by conservative methods, or if refractory ulcer was present. Surgery, as a treatment method, was considered in the young patient group without high-risk for surgery. The remaining patient group was discussed in the cardiology clinic in the case-discussion meeting organized weekly. Endovascular treatment was performed in the patients considered appropriate.

Among graft materials, autologous vein grafts are still the most popular in femoropopliteal bypass.[8,9] For this reason, VSM should be considered as the optimal graft material. Autologous veins remain vital for a long time after implantation, are not rejected, and continue to be nourished by diffusion. However, endothelial damage may occur while preparing autologous vein grafts; this endothelial damage likely to occur during surgery is the most important factor influencing the graft patency.[8-10] Other factors that influence the patency of VSM include wall structure, diameter (>3.5 mm), and presence of varices and fibrotic valves.[11] In the present study, the diameter and wall structure of the VSM were evaluated by the venous Doppler ultrasonography. VSM was excised segmentally by intermittent incisions in all patients with the vein suitable for using as graft.

It is emphasized that while the primary goal of the treatment of a patient with acute arterial thromboembolic occlusion is to keep patient alive, the second goal is to enable the vitality of extremity.[12] In patients diagnosed with arterial embolism, arterial embolectomy is the first choice of treatment method. The study by Taviloğlu et al.[13] reported the amputation rate after embolectomy as 2.1% and mortality rate as 12.5% for the interventions performed within the first 12 hours, whereas these rates were found to be 39.2% and 37.7%, respectively for the interventions performed after the 12th hour. In the present study, intervention was performed after 12 hours in 3 of 21 patients who underwent embolectomy. Mortality or amputation was not encountered in none of the patients.

Traumatic AVFs may usually occur due to penetrating injuries or fractures of the regions where the artery and vein exist together or closely. More than 50% of traumatic AVFs are seen in the lower extremities. It is encountered in the femoral artery by 29% and in the popliteal artery by 16%.[14] In the present study, AVFs developed in the lower extremities of 16 of 17 patients. Treatment options for traumatic AVFs include surgical and endovascular (graft-coated stent or coil embolization) approaches. The advantages of endovascular treatment are lower complication rate as compared with surgical treatment and being non-invasive.

Patients undergoing endovascular treatment are usually discharged within a day; thus, hospital cost and workforce loss are minimized. In addition, intervention site is small and blood loss is minimum.[15] In the present study, endovascular treatment was primarily preferred. Surgery was performed in the patients with hemodynamic instability, endovascular failure, and lesions in the mobile regions.

Primary repair of the artery and vein after ligation was performed in 2 patients, graft interposition in the artery and primary repair of vein were performed in 5 patients, and graft interposition to the artery and vein was performed in 10 patients. Saphenous vein was used as the graft in all patients.

Conclusion

Peripheral artery disease is an important problem all over the world as it is quite common in advanced ages, has increasing prevalence, and carries potential risk factors. In our clinic, 151 arterial vascular surgical procedures were performed with acceptable rates of mortality and morbidity between 2014 and 2016.

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The Tactics of Safe Removal of Heart Myxomas; The Experience of 796 Operations

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Abstract

Objective: In the structure of cardiac new formation, myxoma constitute 80-90% of benign heart tumors. The aim of the study was to determine the features of diagnosis and to search the tactics of optimal and the safe surgical treatment of myxoma of the heart.

Material and methods: In N.M. Amosov Institute of Cardio-Vascular surgery of the Academy of Medical Sciences of Ukraine for period from 1.01.1969 to 1.01.2017 889 patients with primary heart tumors had surgical treatment. The myxomas of heart (MH) was founded in 796 (89,5%) cases, from them in 696 (87,4%) cases – MH of left atrium (LA). The other benign heart tumours were observed in 33 (3,7%) cases, malignant heart tumours – in 60 (6,8%) cases.

Results: Hospital mortality in the surgical treatment of MH was 4.9% (39 cases).

Conclusions: Over the past 16 years, 433 operations have been performed without lethal results, due to the peculiarities of the tactics of emergency diagnosis and surgical treatment, and radicality of removal of heart tumors.

Keywords: Myxoma, benign heart tumors, surgical treatment.

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Introduction

The primary tumours of heart (PTH) show up a various clinical picture, imitating other diseases of heart. In a structure cardiac tumours myxomas make 80 - 90% of benign tumours of heart. Frequency of diagnostics of primary heart tumors (from which more than 80% are morphologically of benign tumours) in relation to the acquired heart diseases makes from 1,5% to 2 %, or from 0,09% to 1,9% from the incurrence of the hospitalized patients.[1,2] Clinical displays come to light mainly in the late stages of disease, in addition, a prognosis at this pathology remains unfavorable.[1,2] Questions of diagnostics of new formations of heart and their adequate, quite often urgent surgical treatment are actual.[3,5]

Purpose of the research – to determine the peculiarities of diagnostics and to search the tactics of optimal and the safe surgical treatment of myxoma of the heart.

Material and methods

In N.M. Amosov Institute of Cardio-Vascular surgery of the Academy of Medical Sciences of Ukraine for period from 1.01.1969 to 1.01.2017 889 patients with the verified primary tumours of heart. Nonmyxomas benign tumours of heart (NBTH) were observed in 33 (3,7%) case, malignant tumours – in 60 (6.8%). Rabdomiomas were observed in 9 (27,3%) cases, 5 (15,2%) - hemangiomas, in 8 (24,2%) - papillarus fibroelastomas, for 3 (9,1%) cases were lipomas, fibromas, and lejomiofibromas; and for 1 (3,0%) cases were exposed fibroma and immature teratoma. Age of patients formed from 1 day to 67 years (on the average 34,5 ± 4,3 years).

The myxomas of heart (MH) are exposed at 796 (89,6%) patients, from them in 696 (87,4%) cases – MH the left atrium (LA). The myxomas of right atrium (RA) were determined in 73 (9,2%) supervisions, MH in the left (LV) and in the right (RV) ventricles – for 8 (1,1%) cases accordingly. Multicentral growth of tumour with a defeat two or three chambers of heart was discovered at 11 (1,4%) patients. Age of patients with MH made from 3 to 78 years (on the average 47,5 ± 3,4 years), from them 577 (72,5%) in age from 31 to 60 years.

Results and discussion

At the analysis of supervisions the increase of frequency of registration of patients is exposed with MH in In N.M. Amosov Institute of Cardio-Vascular surgery: for period from 1969 to 1990 amount of patients with MH made 160 (20,1%) cases, and for period from 1991 to 2017 are 636 (79,9%) cases, that is conditioned by both wide introduction in diagnostics of ultrasonic research of heart and probable increase of frequency of this disease.

The leading clinical display of disease was stagnant cardiac insufficiency, that was conditioned by partial damming by the tumour of the valvular openings with subsequent development of violation of hemodynamics in the proper chambers of heart, which was determined for 736 (92,5%) patients with MH. By III and to the IV functional classes of NYHA classification were taken - 289 (36,3%) and 68 (8,5%) patients accordingly, that in these groups frequently required urgent surgical treatment. Diameter of foundation MH made from 0,5 to 7,5 sm. Thus in 688 (86,4%) cases by the prevailing area of fixing MH there was a interatrium septum (IAS).

The losses of consciousness and the attacks of dizzinesses which was determined at 172 (21,6%) patients were the important clinical symptoms of MH. For 112 (14,1%) patients appearance of these symptoms was related to certain position of body, that appeared characteristic for atrium localizations of tumours and not observed in the cases of ventricles localization MH.

Such a heavy complication of clinical flow of this disease, as an embolic syndrome was determined for patients with MH in 43 (5,4%) cases, thus on a background a sine rhythm. From these patients embolism of cerebrum vessels was took place in 34 (4,3%) cases from which in 9 (1,1%) – repeatedly. At 9 (1,1%) patients embolism of vessels of other organs was registered – kidney, vessels of lower and overhead extremities.

Pains in area of heart were registered at 298 (37,4%) patients with various localizations MH. More frequent than all pains showed up as sense of weight in a thorax and did not carry anginal character. In 696 (84,6%) cases duration of symptoms of disease did not exceed 1 year to the operation. Displays of insufficiency of circulation of blood at MH (shortness of breath, palpitation, dizziness, losses of consciousness) were to different expressed depending on position of body of patient in 216 (27,1%) supervisions.

At auscultation for patients with MH noises, similar with such at rheumatic heart diseases, came to light. Changeability of ?uscultations displays at a stably sine rhythm in course of time and at the change of position of body of patient was determining, that is conditioned by displacement of tumour in relation to the valves of heart and marked for 153 (19,2%) patients. Different violations of rhythm, as clinical displays MH, came to light for 237 (29,8%) patients. It is necessary to notice that at 178 (22,4%) patients they showed up proof are 111 (13,9%) cases, or parocsismal were at 67 (8,5%) cases tachycardias in combination with extrasystole.

Such clinical displays MH, as a general weakness, rapid fatigueability and indisposition - at 499 (62,7%) patients, middle increase temperature - in 449 (56,4%) cases; pains in the articulations and muscles – at 248 (31,2%), decline of mass of body - for 309 (38,8%) patients were considered, as a general reaction of organism on a tumour.

A basic diagnostic method in the complex of diagnostics of primary tumours of heart (PTH) is EkhoCG. From 796 patients with MH in 753 (94,6%) cases, since 1984, it was produced EkhoCG. Among these patients in 512 (68,2%) cases a tumour localized as heterogeneous on the structure by volume formation of cellular character with diffuse uneven contours which changed in the process of motion. In other 239 (31,8%) cases by volume new formation of homogeneous character was visualized with clear even edges. In 57 (7,6%) cases disseminations of calcium were determined as bright echo-signals of various localization. Foundation MH came to light for 612 (81,5%) patients from which in 389 (63,5%) cases location of attachment of tumour was determined the on the area of IAS.

Expressed clinical displays, related to damming of the valvular openings at preparation to the operation took place at 46 (5,8%) patients with MH, namely during transporting and piling of patients on an operating table. In such cases it was acknowledged by expedient to give to the patients halfsitting position with a turn on a right side at the beginning of surgical interference.

All operations, except for 15 (1,9%), which was executed on the early stage of surgery MH and 1 case of right ministernotomy in 2015, conducted access from middle sternotomy, that provided optimum conditions for the delete of tumours of any localization.

At a delete MH LA was used different surgical accesses which differed frequency of fragmentations of new formations at their delete. Application of LA access in 122 (15,3%) cases MH LA was accompanied by fragmentation MH for 47 (38,1%) patients. Traditional access appeared most comfortable to MH LA through RA and IAS, diminishing of frequency of fragmentation of tumour was here registered to 21,1% (109 patients on 521 operations). For 8 (1,0%) patients with the myxomas of LA we were forced to apply the combined access of right atriotomy and septotomy with left atriotomy, that allowed safely to make off an operation. In 48 (6,1%) cases, at the exposure of large (to 8 – 12 sm) myxomas of LA was used access from both atriums which allowed practically fully to avoid fragmentation of tumour.

At macroscopic research MH it was certain that tumours it was been: villiferous – in 459 (57,7%) cases and compact new formations of ovoid or rounded form, with a brilliant smooth, sometimes hilly surface – in 337 (42,3%) accordingly.

Pathology of valves, wich accompany at MH, determined at 57 (6,9%) patient. There was the isolated defeat of mitral valve (MV) in 36 (4,5%) cases, in 18 (2,3%) – tricuspid valve (TV), for 1 case (0,1%) is the accompany defeat mitral and aortic, and the isolated defeat of aortic valves (AV). Among them the mechanical damage of valvular structures found out a myxoma at 23 (2,9%) patients. Other pathology of valvular apparatus showed up relative insufficiency of valve due to the expressed expansion of fibrotic ring: tricuspid – in 17 (2,1%) and mitral – in 13 (1,6%) cases accordingly.

Engaging of valvular apparatus in a tumour process was observed at 8 (1,0%) patients. Thus for a 1 (0,1%) patient the myxoma of RV attached to the papillars muscles and chords of TV, and in 7 (0,9%) cases of myxoma of LA struck the front leaflet of MV. The surgical correction of valvular defeats was executed at 54 (6,8%) patients: in 12 (1,5%) cases is replacement of valves (9 – MV, 1 – TV, 1 - AV, 1 – AV + MV), in 43 (5,4%) are repair operations with a positive functional effect.

At surgical treatment MH hospital mortality was

5% (39 cases). In the last 16 years 433 operations were executed without fatal outcomes. Reasons of fatal outcomes it was been: neurological complications – at 16 (46,2%) patients; material embolism - in 7 (17,9%) cases, infarct of myocardium – in 3 (7,7%) cases; septic complications – in 1 (2,6%) case; errors of operations – in 5 (12,9%) cases.

In a follow-up period the results of surgical treatment MH were studied for 679 patients (89,8% written) in terms from 6 months to 46 years (on the average 19,5±4,2 years). Survivability in terms to 20 years was 79,8%. In a follow-up period in I functional classes of NYHA classification were 532 (78,4%) patients, in II functional classes of NYHA – 101 (14,8%). Relapses MH discovered for 16 (2,1%) patients in period from 2 to 12 years (on the average 3,5±0,4 years) after a primary operation. Thus in 4 cases of relapse MH (25%) the myxomas syndrome took place.

At surgical treatment of NBTH hospital mortality was 3,0% (1 case). 2 patients died in a follow-up period, the relapse of disease in the first years after an operation was not exposed.

Conclusions

1. In the last 16 years 433 operations were executed on an occasion MH without fatal outcomes, that is conditioned by optimum tactic of diagnostics and urgency of surgical treatment, which reduce frequency of the preoperated complications and provide safety and radicalism of delete of tumours of heart.

2. The adopted tactics ensure the effectiveness of surgical treatment MH, confirmed by given follow-up results: in I functional classes of NYHA classification were 532 (78,4%) patients, in II functional classes of NYHA – 101 (14,6%) patients accordingly; survivability in terms to 20 years was 79,8%.

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Synchronous off-pump coronary artery bypass grafting and carotid endarterectomy (*an initial experience*)

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Abstract

Aim: To find out safety and efficacy of synchronous CEA in patients undergoing CABG.

Methods: Out of 711 patients who underwent CABG, 48 were found to have severe carotid stenosis of >70%. Out of this, 18 patients with >70% stenosis (thirteen symptomatic and five asymptomatic) and one patient with >70% symptomatic carotid stenosis (TIA within last 2 weeks) were taken for simultaneous CEA along with CABG. These three symptomatic carotid patients suffered from stroke within last 6 months.

Results: None suffered from myocardial infarction (MI) during perioperative period.Postoperative recovery period - 13,5 ± 0,8 days. During the follow-up period of 12 months, one patient died of cardiovascular causes (stroke).

Conclusion: Combined carotid and coronary arteries disease's incidence in this series was 6,3%. Simultaneous carotid and off-pump coronary artery bypass surgery is safe and effective method of treatment patients with severe concomitant carotid artery stenosis and ischemic heart disease with relatively low mortality rate.

Keywords: Carotid endarterectomy, coronary artery bypass graft surgery, off-pump CABG, peri-operative stroke

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Introduction

Stroke is a serious complication after CABG surgery, occurring in up to 3% of patients, patients with significant carotid disease represent a particularly high-risk category of patients.[1] Approximately 8-10% of patients scheduled for coronary artery bypass graft (CABG) surgery, have significant but asymptomatic internal carotid artery (ICA) stenosis. Regarding to the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[2] and Asymptomatic Carotid Atherosclerosis Study (ACAS)[3] carotid endarterectomy (CEA) reduced the risk of stroke in patients with ICA stenosis. During the last decade CEA is increasingly being performed alongside of CABG surgery for stroke prophylaxis. During this procedure cardiac surgeons are aiming to minimize the risk of stroke either by revascularizing the stenotic carotid artery followed by CABG or in the reversed fashion.

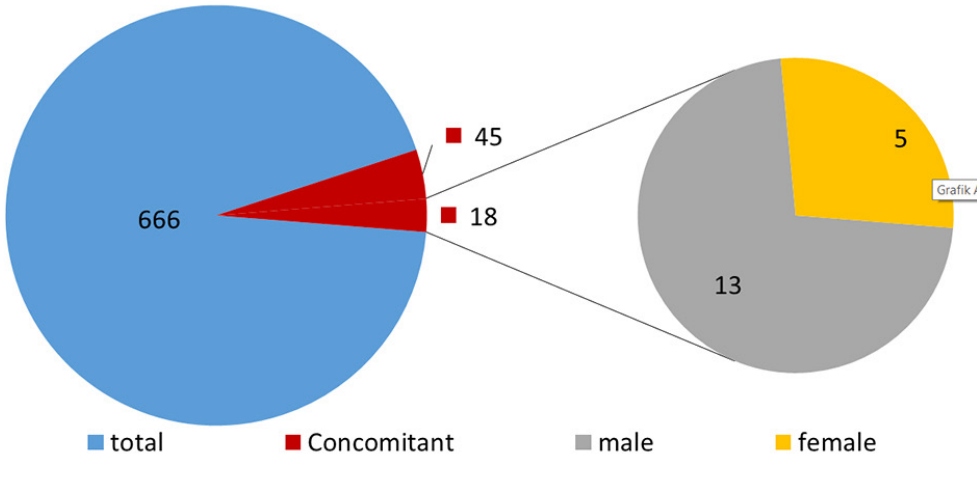
However, some authors consider that the patients who undergo CABG prior to CEA have increased risk of stroke. On the other hand patients undergoing to CEA prior to CABG, have higher risk of myocardial infarction (MI).[4] In order to decrease the rate of mortality and risk of MI and stroke, performing a CEA and CABG simultaneously (CEA/CABG), can be safe and effective alternative for staged approach. In this study we performed a retrospective analysis of safety and efficacy of CEA combined with CABG in patients with severe carotid stenosis requiring CABG surgery.

Materials and Methods

Data of all patients who underwent CABG in our hospital (total 711) from January 2013 to December 2017 were analyzed, of this 45(6,3%) patients had concomitant carotid and coronary artery stenosis, 18 (2,5%) of them needed simultaneous surgery **(Picture 1)**. In recent study only these 18 patients, operated simultaneously were included. Most patients had history of previous myocardial infarction or neurological disorders (patients characteristics are given in **Table 1**).

Table 1. Demographic and clinical characteristics of patients included in the study

Characteristics	Number of patients (n)	Percentage (%)
Gender		
Female	5	27.7
Male	13	72.3
Previous myocardial infarction	13	72.3
Neurological history		
Asymptomatic	5	27.7
Symptomatic	13	72.3
Hypertension	12	66.6
Smoking	10	55.5
Diabetes mellitus	12	66.6
Hyperlipidaemia	9	50
Peripheral artery disease	3	16.6
Mean age	64,8 ± 1,9 years	



Picture 1. The description of the design of the study (explained in the text).

To assess the degree of stenosis of ICAs, carotid Doppler was done preoperatively in all patients. Computed tomography angiogram (CTA) or magnetic resonance angiogram (MRA) was done to confirm the degree of stenosis in patients who had 50% or more stenosis of carotid artery on carotid Doppler.

Carotid stenosis was defined as severe if stenosis was >70% and symptomatic if there was any history of stroke or transient ischemic attack (TIA) within last 6 months involving same side. Near total occlusion was defined as severe stenosis of >95% with distal collapse of vessel. The main indications for simultaneous surgery were the need for myocardial revascularization with concomitant 1. More than 70% symptomatic stenosis of the carotid artery (with or without contralateral disease) or asymptomatic more than 70% bilateral carotid artery stenosis.

The eligibility for CEA along with CABG or isolated CABG was determined based on the joint decision of the cardiologist, cardiac surgeon, and neurologist. Patient with intracranial stenosis that exceeded the severity of the extracranial stenosis were excluded. Patients with total occlusion of internal carotid were also excluded. (characteristics of patients regarding to coronary and carotid artery stenoses described in **Table 2-3**).

All patients underwent carotid artery ultrasonography, coronary angiography, and neurological examination prior to surgery. In 45 of cases (6,3%) the concomitant carotid artery stenosis was diagnosed. Simultaneous intervention on the carotid and coronary arterial systems was performed in 18 patients (2,5%). The CEA was done prior to the median sternotomy and after harvesting the conduits; off-pump CABG was followed thereafter. CEA was performed by a vertical incision anterior to the sternocleidomastoid muscle, thus exposing the common carotid artery, ICA, and the external carotid artery. The patient was heparinized by giving 2 mg/kg heparin. The artery was opened through a longitudinal incision followed by an endarterectomy. The arteriotomy was closed either directly or by a saphenous vein patch **(Picture 2)**.

Care was taken to keep the systolic blood pressure above 120 mmHg and, inotropic agents were started if needed to maintain adequate blood pressure and cerebral flow. The neck wound was closed with a drain, followed by the median sternotomy, systemic heparinization and a off-pump coronary artery bypass grafting (17/94,4%), in one case (5,6%) due to unstable hemodynamics, the coronary artery bypass was performed on-pump. A stabilization systems were used for mechanical stabilization of the heart while performing all distal anastomosis. Intracoronary shunts were used in most of the patients **(Picture 3)** to maintain blood flow through the coronary arteries, at the end of procedure heparin was reversed by protamine.

Results

In our center, all postoperative CABG patients undergo continuous cardiac monitoring for the first 2 postoperative days. A 12-lead electrocardiogram is also done daily for first 3 days after surgery in all patients. None suffered from perioperative ischemic stroke, but one patient with near total occlusion (asymptomatic)

Table 2. Characteristics coronary artery disease

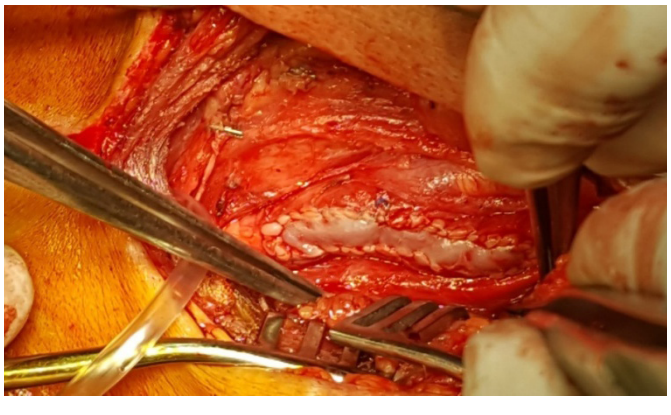
Patientscharacteristics, coronaryartery	Abs.(%)
Triple-vessel disease	15 (83,3%)
Double vessel disease	1 (5,6%)
Left main stem stenosis	2 (11,1%)
Reduced ejection fraction (lower than 40%).	9 (50%)
Previous myocardial infarction	13 (72,2%)
Unstableangina.	10 (55,6%)

Table 3. Characteristics of carotid artery disease

Patientscharacteristics, carotidartery	Abs.(%)
Internal carotid artery stenosis on the right side	5 (27,8%)
Internal carotid artery stenosis on the left side	6 (33,3%)
Bilateral carotid stenosis	7 (38,9%)
Previous stroke	13 (72,2%)
Asymptomatic	5 (27,8%)

suffered from hemorrhagic stroke on ipsilateral side following CEA. All the patients were followed-up till discharge from the hospital. None had any cardiovascular or cerebrovascular complication during this period. There were no any deaths from cardiovascular or any other cause. CT was done in three patients, who had delirium in the early postoperative period, and it did not reveal any fresh ischemic infarction. Their delirium was attributable to perioperative encephalopathy (pain, intensive care unit (ICU) setting). All the patients were discharged from the hospital in stable condition without any fresh neurological deficits **(Table 4).** Patient with perioperative hemorrhagic stroke following CEA also recovered well (mRS 0-1) at the end of 1 month.

Picture 2. After CEA.arteriotomy was closed by a saphenous vein patch



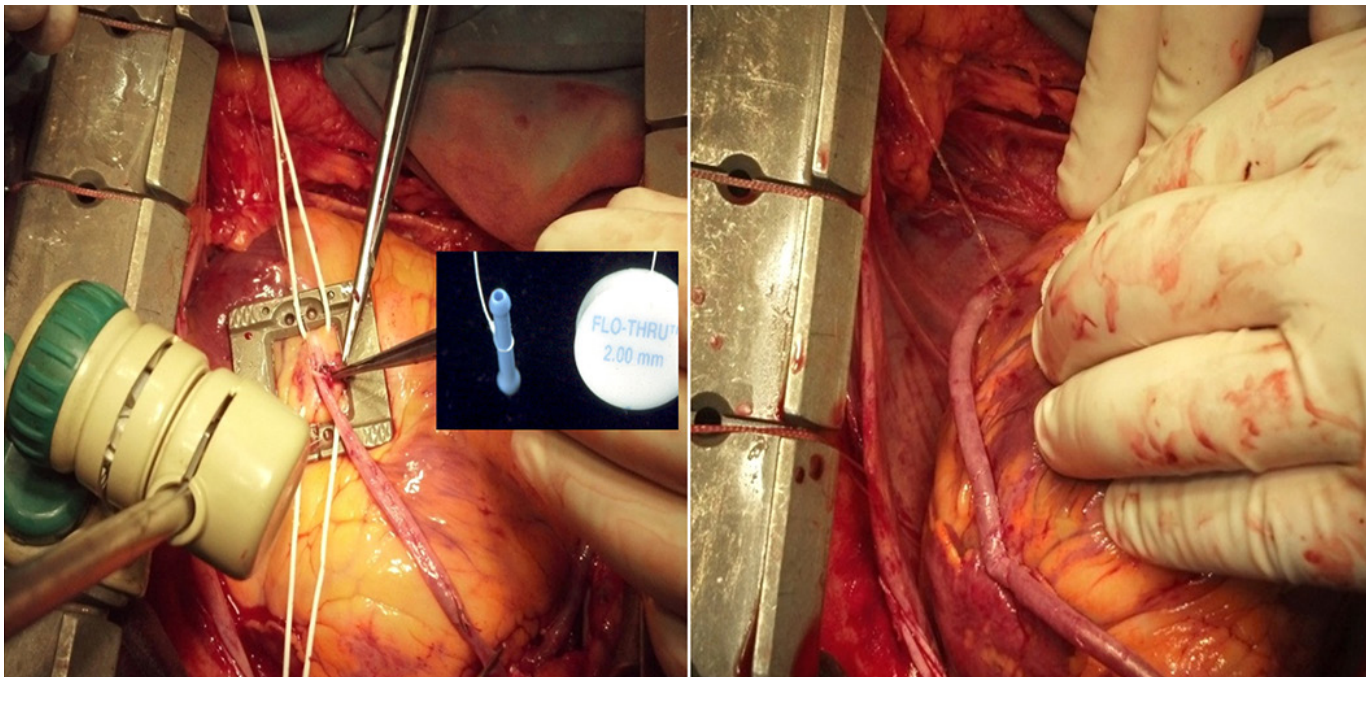
Discussion

The prevalence of haemodynamically significant (>50%) or severe carotid disease (>80%), in patients with severe coronary artery disease (CAD) scheduled for CABG has been estimated to be around 6 -17%. [1,2,3] Regarding to a systematic review, the risk of stroke after CABG was <2% in patients with no significant carotid disease, 3% in asymptomatic patients with 50-99% stenosis, increasing to 5% in those with bilateral 50-99% stenosis and 7-11% in patients with carotid occlusion. [8,12] Moreover, the risk of perioperative stroke in CABG patients suffered from previous TIA or stroke has been associated with a fourfold increased risk as compared to the risk for asymptomatic patients.[9,10] In our series

Table 4. Postoperative period, complications

Patients characteristics,	Abs.(%)
Intracranial hemorrhage*	1 (5,6%)
Reversible cerebral disorder (delirium)	3 (16,7%)
Ischemic stroke	0 (0%)
Mortality rate	0(0%)
Cerebral disorder during 6 month follow-up	0 (0%)
**after 1 month patient suffered ICH showed full recovery*	

Picture 3. Off-pump coronary artery bypass grafting. Heart stabilization during CABG. Intracoronary shunt.



the overall incidence of combined carotid and coronary artery stenosis was 6%. Carotid endarterectomy (CEA) has been well studied in the setting of both symptomatic (North American Symptomatic Carotid Endarterectomy Trial and European Carotid Surgery Trial) as well as asymptomatic (Asymptomatic Carotid Atherosclerosis Study and Asymptomatic Carotid Surgery Trial) individuals with isolated severe carotid disease.[5,6]

Nowadays CEA is routinely performed in the setting of CABG surgery in an attempt to improve perioperative outcomes. The operative strategies for combined severe carotid and coronary disease include: (1) CEA followed by CABG (staged); (2) combined CEA and CABG; and (3) CABG followed by CEA (reverse staged).[4,9,10] But there are still lack of data regarding to evaluating the safety and efficacy of CEA–CABG procedures. AHA recommends that for patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70-99%) CAS as documented by noninvasive imaging (CD, CTA, and MRA), CEA should be done, if the perioperative morbidity and mortality risk is estimated to be less than 6%.[14,16] All our patients were admitted primarily for symptomatic CAD and were planned for CABG based on joint decision of cardiologists and cardiothoracic surgeon.

Carotid Doppler was done as a part of routine screening in all these patients, which revealed carotid stenosis in 45 patients. Decision to do CEA along with CABG was done in 18 eligible patients on the basis of CTA findings. The combination of carotid Doppler and CTA is an acceptable method for the quantification of severe CAS in a substantial number of patients.[15] Decision was based on clinical data; 18 patients scheduled for CABG with concomitant 1. More than 70% symptomatic stenosis of the carotid artery (with or without contralateral disease) or asymptomatic more than 70% bilateral carotid artery stenosis, underwent to simultaneous CEA and CABG.

A recent RCT showed that patients undergoing prophylactic or simultaneous CEA + CABG had low stroke rates (0%), without significant perioperative mortality. Overall risk of all types of cerebrovascular complications (stroke, MI, and death) was low during and early after combined CEA + CABG.[11,12,13] Out of 18 patients opted for combined approach, none suffered from ischemic stroke after surgery. Only one patient with near total occlusion had ipsilateral ICH because of hyperperfusion syndrome. A rapid restoration of normal perfusion pressure following CEA may result in hyperperfusion in regions of the brain that have impaired autoregulatory capacity.[18]

Risk factors for this syndrome include long-standing hypertension and high-grade stenosis. This patient suffered from faciobrachial paresis, and made almost complete recovery within 1 month. Because carotid revascularization has proven its value in preventing risk of future ischemic stroke in patients with severe carotid disease, it seems appropriate to correct it in conjunction with CABG to achieve any additional protection from perioperative stroke that this approach may provide. Synchronous CEA/CABG also offers the economic benefit of avoiding two separate procedures/hospitalizations and advantage of patients being exposed to only one anesthesia.[19]

Conclusion

Combined carotid and coronary arteries disease's incidence in this series was 6,3%. Simultaneous carotid and off-pump coronary artery bypass surgery is safe and effective method of treating patients with severe concomitant carotid artery stenosis and ischemic heart disease with relatively low mortality rate.

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The authors declare no conflict of interest.

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The Effect of Benfothiamin and Vitamın D in Ischemia / Reperfusion Model of Rat Skeletal Muscle

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Abstract

Background: Benfothiamin is a highly potent form of vitamin B1 protecting endothelial function. On the other hand, vitamin D provides restoration of muscular tissue by inhibition of apoptosis and acceleration of cellular proliferation following muscle injury. We assumed that the administration of these vitamins in ischemia/ reperfusion (I/R) injury, could reduce the damage by alteration of the release of various oxidant and antioxidant mediators leading to cellular damage.

Materials and Methods: We assigned 30 Wistar Albino males rats into 5 groups. In the control group (n=6), rats were anaesthetized and total antioxidant capacity (TAS), total oxidant capacity (TOS), malondialdehyde (MDA), superoxide dismutase (SOD) and nitricoxide (NO) level were measured in lower extremity soleus muscle. Benfotiamin and D were given to the groups and the values of these parameters were evaluated in ischemia reperfusion muscle tissue specimens. All tissues were examined histologically.

Results: We detected a significant change in groups 3 and 4 for antioxidant NO level after ischemia and reperfusion. Therefore, we observed that the administration of vitamin D and benfothiamin increased NO levels in muscle especially during reperfusion. The level of other oxidants TOS and MDA and antioxidants TAS and SOD were not significant during I/R at given periods. Overall vitamin D and benfothiamin have acute beneficial effects especially in improving I/R injury of lower extremity, even at non-critical periods.

Conclusion: Acute term effects of benfothiamin and vitamin D can be useful during where changes due to I/R. The effects can be evaluated during long term I/R.

Key Words: Benfothiamin, vitamin D, ischemia / reperfusion injury, skeletal muscle, rats

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Introduction

Lower extremity can be subjected to ischemia due to certain conditions such as injuries, acute peripheral occlusive diseases and surgical intervention with prolonged tourniquet period. Following reperfusion of ischemic extremity by oxygenized blood, reactive oxygen species including free radicals such as hydroxyl ions (OH-), superoxide anion (O2-), oxygen (O2), hydrogen peroxide (H2O2) and nitric oxide (NO) are produced. These products within the circulation, lead to ischemic injury of the extremity.[1,2] However the organism develops an antioxidant defense system in order to prevent cellular damage due to free radicals. This system includes superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) antioxidant enzyme systems, which are "free radical scavengers" of indirect pathway.[3]

Superoxide dismutase (SOD) is an antioxidant enzyme catalyzing the transformation of superoxide free radical (O2-) to hydrogen peroxide(H2O2) and molecular oxygen (O2). It provides the alteration of reactive O2 metabolites and eliminate them from the cell.

The most important and harmful triggering effect of free radicals within the cell, is lipid peroxidation. Lipid peroxidationis defined as oxidation of polyunsaturated fatty acids by free radicals. Malondialdehyde (MDA) is one of the end products of lipid peroxidation and leads to polymerization of membrane components and their cross linking. In turn, this may affect the status of cellular surface, enzyme activity and ion transport.[4,5]

I/R injury leads to endothelial cell activation and dysfunction. Endothelial cells are potential target of superoxide radicals and also production site of superoxide radicals. Endothelium produces NO and endothelin (ET) which are responsible from microvascular hemostasis. NO tends to reverse the vasoconstrictor effect of ET in arterial circulation. The opposite is true in veins. In I/R injury, ET/NO ratio is impaired in favor of ET. Therefore arterial vasoconstriction and venous vasodilatation occurs.[6]

Total oxidant capacity TOS and antioxidant capacity TAS measurements show the oxidant and antioxidant status of serum and tissue.[7] Acute lower extremity ischemia is a clinical condition leading to significant morbidity and mortality even following elimination of ischemia. In case of delayed intervention, these risks are increased. In addition they may be seen in spite of extremity reperfusion. A clinical event chain leading to acute renal and respiratory insufficiency and dysfunction of heart, intestines and spleen, is initiated.[8] The initiation and development of these events should be identified in order to determine medical and surgical treatments to prevent this condition.

There are several studies showing the suppressive aspect of benfothiamin on reactive oxygen products.[9,10] In diabetic rats, benfothiamin normalized many oxygen species.[11] In addition, it reduces harmful oxidative effects in mice with streptozocin(STZ) induced diabetes.[12] Benfothiamin is fat-soluble form of thiamine and can easily pass from cellular membrane which is rich in fatty acid.

There are clinical trials and animal experiment models showing that vitamins A,C,D and E prevent I/R injury. Vitamin D is fat-soluble and is considered to induce endogenous antioxidant pathways and to have neuroprotective properties by reducing inducible nitric oxide synthase. There are especially references on 1,25-dihydroxy vitamin D3.[13]

In our study, acute effects of administration of benfothiamin and vitamin D were investigated in experimental muscle I/R model. In assessment of this effect, levels of oxidant and antioxidant parameters at pre-determined ischemia and reperfusion periods as well as histopathological tissue samples were examined.

Materials - Methods

In this interventional animal study, 30 male Wistar Albino rats (aged 8-12 weeks and weighing 321±69 g) were included in the experiment, which received ethical approval from the laboratory Animal Unit of Giresun University. The animals were obtained from the same unit, and standard temperature (22±2°C) and humidity (50±5%) controlled rooms were used for preserving the rats until the start of the experiment. In addition, a standard diet and tap water were provided ad libitum for the rats.Following the intervention, all rats were sacrificed by obtainingintra-cardiac blood.

During the interventions, the rats were anesthetized with 50 mg/µl (8.5 cc) of ketamine hydrochloride (HCL) (Ketalar®, Pfizer, Inc., İstanbul, Turkey) and 23.32 mg/ml (1.5 cc) of Xylasine (Rompun®, Bayer Healthcare AG, Leverkusen, Germany) through an 0.3-0.5 cc intraperitoneal line. Vital parameters during anesthesia were considered observational. Lower extremity was ligated by silk number 0 at proximal level of femoral artery for lower extremity muscle ischemia **(Figure 1)**. Maintenance of cyanosis and coldness of the extremity was monitored during ischemia.

Following procedures were applied to the groups consecutively:

***Control group:** Rats were anesthetized and only a biopsy specimen of 1 cm was obtained from right leg soleus muscle and transferred into Eppendorf tube with 10% neutral formalin for histopathological examination. Blood samples were taken from each rat and then they were sacrified.

***Group 1:** Right lower extremity was ligated from femoral level and ischemia was maintained for 3 hours. Biopsy from soleus muscle was taken by vertical incision of 1 cm on the extremity. Following ischemia, extremity tourniquet was removed and reperfusion was maintained for 3 hours. Biopsy from soleus muscle was taken following reperfusion. Rats were sacrificed by obtaining 3 milliliters of intra-cardiac blood.

***Group 2:** In rats, ischemia was performed at right extremity and concomitantly subcutaneous 332.000 IU/kg (8.3 mg/kg) vitamin D (Devit 3 IM/Oral ampoule® 300.000IU/ml Deva İlaç) was administered; ischemia was maintained for 3 hours. Biopsy from soleus muscle was taken by vertical incision of 1 cm on the extremity. Following ischemia, extremity tourniquet was removed and reperfusion was maintained for 3 hours. Biopsy from soleus muscle was taken following reperfusion. Rats were sacrificed by obtaining 3 milliliters of intra-cardiac blood.

***Group 3:** Rats received diluted Benfothiamin (S-BenzoyithiaminO-monophosphate B9636-250 MG powder SIGMA-ALDRICH) 70mg/kg via oral route by gastric lavage tube **(Figure2)**. Following anesthesia, identical period of I/R was administered to rats and biopsy specimens from soleus muscle were taken. Rats were sacrificed by obtaining 3 milliliters of intra-cardiac blood.

***Group 4:** Rats received same amount of Benfothiaminvia same way. Following right leg ischemia, subcutaneous vitamin D ampoule was administered. Same period of I/R was done and biopsy specimens were obtained. Rats were sacrificed by obtaining 3 milliliters of intra-cardiac blood.

Tissue samples taken for TAS, TOS, MDA, SOD and NO were directly transferred into Eppendorf tubes and stored at -80°C. Tissue samples taken for histopathological examination were stored in 10% neutral formalin. SOD, MDA, NO, TAS, TOS determination was as following:



Figure 1



Figure 2

All tissues were homogenized atRel Assay laboratory. Following homogenization, SOD, MDA and NO tests were done manually according to micro-Elisa method by using Rel Assay Eliza kits on Biotec Elisa device. Other tests were done on Selectra full-automated biochemistry auto-analyzer.

Total Antioxidant Status (TAS)

TAS levels were measured using commercially available kits (Relassay, Turkey). The novel automated method is based on the bleaching of characteristic color of a more stable ABTS (2,2 ′ - Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) radical cation by antioxidants. The assay has excellent precision values, which are lower than 3%. The results were expressed as mmolTrolox equivalent/L.[14]

Total Oxidant Status (TOS)

TOS levels were measured using commercially available kits (Relassay, Turkey. In the new method, oxidants present in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction was enhanced by glycerol molecules abundantly present in the reaction medium. The ferric ion produced a colored complex with xylenol orange in an acidic medium. The color intensity, which could be measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of micromolar hydrogen peroxide equivalent per liter (µol H2O2 equivalent/L).[15] Parameters analyzed for ischemia and reperfusion are shown in **Table 1** and **Table 2**, respectively.

Table 1. TAS, TOS, SOD, MDA and NO concentration for ischemia.

Groups	TAS (mmol/lt)	TOS (µmol/lt)	SOD (ng/mlt)	MDA (µmol/lt)	NO (µmol/lt)	NO concentration
Total n=30	mean±SEM	mean±SEM	mean±SEM	mean±SEM	mean±SEM	mean±SEM
Control (n=6)	0.65±0.05	10.17±2.80	8.75±0.66	1.18±0.15	1.70±0.40	133.8±8.9
G1 (n=6)	0.65±0.05	14.66±3.82	5.5±0.51	1.05±0.19	1.42±0.18	189±41.3
G2 (n=6)	0.38±0.05	12.03±0.87	6.11±0.92	1.008±0.08	1.33±0.06	140.5±6.8
G3 (n=6)	0.53±0.03	11.14±1.07	5.41±0.66	622.36±281	**10327.9±2171.8***	125.3±8.8
G4 (n=6)	0.48±0.02	11.46±1.72	7.95±1.00	825.6±266.4	**15927.5±1276.8***	203.3±34.3

**NO values for ischemia were significant compared to control group (p<0.05).*

Table 2. TAS, TOS, SOD, MDA, NO and NO concentration for reperfusion.

Groups	TAS (mmol/lt)	TOS (µmol/lt)	SOD (ng/mlt)	MDA (µmol/lt)	NO (µmol/lt)	NO concentration
Total n=30	mean±SEM	mean±SEM	mean±SEM	mean±SEM	mean±SEM	mean±SEM
Control (n=6)	0.65±0.05	10.17±2.80	8.75±0.66	1.18±0.15	1.70±0.40	133.8±8.9
G1 (n=6)	0.65±0.05	14.66±3.82	5.5±0.51	1.05±0.19	1.42±0.18	189±41.3
G2 (n=6)	0.38±0.05	12.03±0.87	6.11±0.92	1.008±0.08	1.33±0.06	140.5±6.8
G3 (n=6)	0.53±0.03	11.14±1.07	5.41±0.66	622.36±281	**10327.9±2171.8***	125.3±8.8
G4 (n=6)	0.48±0.02	11.46±1.72	7.95±1.00	825.6±266.4	**15927.5±1276.8***	203.3±34.3

**NO values for reperfusion were significant compared to control group (p<0.05).*

According to the results of histopathological examination of tissue samples:

Muscle tissue samples taken during ischemia and reperfusion for histopathological examination were stained by hematoxylin-eosin (HE). In each group, the samples were examined for hyalinization, necrosis, inflammation and hemorrhage. Significant histopathological properties of groups were shown in **(Figure3)**. Severity score of histopathological examination was rated as 0: none, 1: mild, 2: moderate, and 3: severe. Mean values of groups were shown in **Table 3**. It was seen in **Figure 3**: G1: Focal congestion area in the control group, G2: The hyalinisation in muscle tissue . It was seen in figure 4: G4: Active chronic inflammation at the periphery of bleeding areas involved by neutrophils.

Statistics

All numeric data were presented as mean± standard error of mean(SEM). Two-ways ANOVA multi comparison test was used to compare the parameters between groups. The value $P<0.05$ was considered as statistically significant.

Results

All experimental subjects completed the study without mortality. In all groups, TAS, TOS, SOD, MDA, NO and NO concentration was statistically non-significant in control group and I/R group of 3 hours($p>0.05$). TAS, TOS, SOD, MDA, NO and NO levels of ischemic soleus muscle are shown in **Table 1**.

There was no statistically significant difference between groups in respect of TAS, TOS, SOD, MDA and NO concentrations for both ischemia and reperfusion at predetermined period. However there was a difference for NO values.

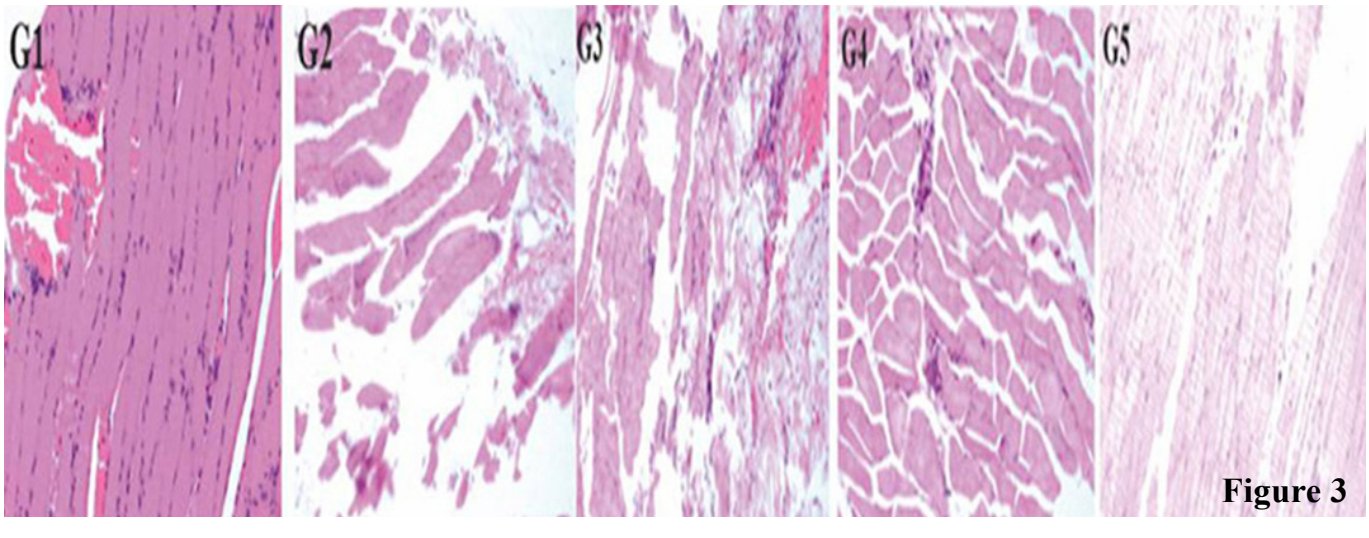


Figure 3

Table 3. Histopathological examination score of muscle.

Groups	Mean Hyalinization	Mean Necrosis	Mean Inflammation	Mean Hemorrhage
Control	1	0	0	0.83
G1	1.33	0	0.33	1.5
G2	1	0	0.16	1.16
G3	1.33	0	0.5	1.33
G4	1	0	1.16	1.33

***0:** none, **1:** mild, **2:** moderate, **3:** severe.*

NO value was significant in group receiving benfothiamin + vitamin D compared to control group during both ischemia and reperfusion. In group receiving only vitamin D, the significance was present only for reperfusion. This showed us benfothiamin considerably increased the acute protective amount of NO during given I/R period and that vitamin D increased remarkably the NO during reperfusion. Concomitant administrations of benfothiamin and vitamin D led also acute increase in NO. Muscle necrosis was not present in any of groups during I/R periods. Hyalinization, inflammation and hemorrhage were mildly present.

Discussion

Acute lower extremity I/R may lead to severe tissue damage and systemic complications. Rate of mortality and amputation due to this condition were reported as 15-52% and 12-22%, respectively.[16] Early diagnosis and early revascularization should be provided as soon as possible. During reperfusion, toxic free oxygen radicals are formed due to re-exposure of tissue to oxygen. [17] In addition to clearance systems developed by the organism to eliminate them, certain substances were also shown to be effective in preventing experimental IR injury. Studies showed that benfothiamin, one of these substances, has suppressive effect on reactive oxygen species.[18] In diabetic rats, benfotihamin normalized many oxygen species.[19] In addition, it reduced harmful oxidative effects in streptozocin (STZ)- induced diabetic rats.[20] There are several studies showing that Benfothiaminsupplement relieved neuropathic pain, vasodilator effect, demonstrated favorable effects on renal and cardiac systems and contributed to wound healing.[21-24]

Although there is evidence for effects of vitamin D on aspects of myogenesis, muscle cell signaling, muscle function, and muscle force[25,26] the mechanistic action of vitamin D on the injured muscle remains largely unknown. We planned this study by considering that benfotihaminand vitamin D could show protective effects on tissue in IR injury.

Thiamine is not a fat-soluble vitamin. Therefore its oral bioavailability is low. Excess amount of thiamine is eliminated via urine.[27] Benfothiamin is a fat-soluble form of thiaminan can easily penetrates cellular membrane rich in fatty acids. According to a study comparing Benfothiamin and Thiamin, overall bioavailability is 420% higher (420% more recovery in cellular plasma).[28] By considering these properties, acute effects were evaluated during I/R following oral administration in rats. Each rats received benfothiamin70 mg/kg by gavage tube and thus individual different dose administration has been prevented.

Biological maximal stimulating dose of vitamin D is 8.3 mg/kg (332.000 IU/kg) and this was subcutaneously administered.

Measurements of tissue oxidants and antioxidants were used to determine the damage caused byI/R in the tissue as well as the improving effect of benfothiamin and vitamin D. Total and individual parameters were analyzed during given I/R periods.

Histological changes were examined in soleus muscle specimens from experimental animals.

During I/R period of 3 hours, the oxidants TOS and MDA an the antioxidants TAS and SOD were not significantly affected by I/R statistically and their concentrations were not significantly changed by administration of both benfothiaminand vitamin D statistically. NO was not changed during given periods of I/R. However it was significantly increased by administration of benfothiaminand vitamin D.

In contrast to vasoconstrictor effect in the muscle due to ischemia, This increase in NO level is protective. The beneficial effect of vitamin D was more significant during reperfusion, while benfothiaminwas significantly effective during both ischemia and reperfusion upon its administration alone as well as in combination with vitamin D. The effect of benfothiaminand benfothiamin+ vitamin D may be clinically beneficial in order to induce protective effect against NO in any type of traumatic and degenerative vascular I/R conditions.

Acute and long term effects of benfothiamin and vitamin D can be investigated during more prolonged periods where irreversible changes due to I/R occurs.

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Serum Presepsin Levels in Patients with Decompensated Heart Failure

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Abstract

Objective: Recently, the soluble CD14 subtype; presepsin (PSP) has been suggested as a reliable marker for systemic inflammation, which has not been studied in decompensated heart failure (DHF) up to date. Our aim was to investigate plasma PSP levels and its diagnostic ability in patients with DHF.

Methods: Fifty patients with DHF and 51 controls without HF were included in our study. Besides routine clinical and laboratory data, N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) and PSP levels were measured in blood samples of all the participants.

Results: PSP levels were significantly higher in patients with DHF than controls (1107.98 ± 1001.15 vs. 540.47 ± 526.9 pg / mL, p = 0.001). Cut-off value for PSP was 442 pg / mL to detect HF with 76% sensitivity, 62.7% specificity, 66.7% positive predictive value and 72.7% negative predictive value (CI: 0.975 - 1.000). The diagnostic accuracy of PSP for DHF was not superior to that of NT-pro BNP (AUC: 0.99 vs. 0.74)

Conclusions: This preliminary study reveals that PSP levels are significantly elevated in patients with DHF but the diagnostic power of PSP for DHF is lower than NT-pro BNP. PSP may be a new marker for DHF.

Keywords: Decompensated heart failure, presepsin, inflammation

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Introduction

Decompensated heart failure (HF) is a clinical syndrome caused by many conditions resulting in reduced cardiac output.[1] There are many pathophysiological mechanisms of HF besides cardiovascular pathologies, and inflammation is one of them.[1] The correlation between C- reactive protein (CRP) and the severity and prognosis of HF is a good example for the role of inflammation in the development of HF.[1] Besides CRP many other inflammatory markers such as cytokines, tumor necrosis factor 6 (TNF-6), interleukin 6 (IL6), oxidative stress markers and leukocytosis have been shown to be involved in the onset and development of HF.[1,3] Recently, natriuretic peptides have been used for screening, diagnosis and prognosis of acute HF.[1]

However, their plasma levels are affected by some clinical situations such as renal failure and they may not be reflecting all of the pathophysiologies underlying HF.[1] Presepsin (PSP) is a novel inflammatory marker.[4] Several clinical studies suggest PSP as an acute phase reactant similar to CRP.[5] Monocytes, macrophages and neutrophils express a cluster of differentiation (CD) surface glycoprotein named CD14.[6] CD14 forms a circulating soluble subtype after activated by plasma proteases which is named as sCD14-ST, also known as PSP.[6] Although the diagnostic power, prognostic value and mortality predictive capacity of PSP have been widely evaluated and accepted in sepsis, almost no publications about the association between PSP and heart failure has been available in literature to date.[4,7,8]. Our aim in this study was to investigate plasma PSP levels and its diagnostic ability in patients with acute decompensated HF.

Methods

Study population

This observational comparative study was conducted in a tertiary referral center. In this study, we used the methods of our previous study.[9] Fifty patients admitted to coronary care unit with acute decompensated HF and 51 age-matched control group patients without HF as verified by echocardiography were enrolled in this study. The study protocol was approved by the local ethics committee review board. The study complied with the Declaration of Helsinki and informed written consent was obtained from all patients included in this study. The patient group was consisted of patients admitted to coronary care unit with symptoms and signs of acutely decompensated HF (New York Heart Association Classification 2 to 4) as in described by related European Society of Cardiology guideline and left ventricular ejection fraction lower than 40% as shown by echocardiography.[10] We included both de novo and previously known HF patients regardless of the etiology. We were excluded some specific cardiomyopathy phenotypes such as hypertrophic cardiomyopathy, peripartum cardiomyopathy and alcoholic cardiomyopathy.

Control group was consisted of age matched volunteers. All clinical available data at the time of initial visit were collected by two cardiologists from the medical records of each patient. Patients with diabetes mellitus and hypertension were not excluded from the study.[9] The glomerular filtration rate was estimated by using the Modification of Diet in Renal Disease (MDRD) equation at admission. Body mass index (BMI) was calculated due to World Health Organization criteria.[11] Patients with known inflammatory disease, serious valvular disease, uncontrolled hypertension, serious hepatic failure, fever, acute or chronic infection, receiving antibiotic therapy, muscle aches, immunoproliferative disease, osteoporosis, rheumatic disease, cancer, younger than 18 years old and older than 70 years old, estimated glomerular filtration rate (eGFR) < 60 mL / min / 1.73 m2 were excluded.[9]

Laboratory measurements

Blood samples for PSP and other biochemical measurements were taken from the patients once the diagnosis of decompensated HF was made and volunteers in the control group. All of the laboratory measurements of the study participants consisting of white blood cell count (WBC), high sensitive CRP (hsCRP) and creatinine were performed. Blood samples for PSP measurement were obtained by vein puncture into ethylene diamine tetra acetic acid (EDTA) blood collection tubes without additives and immediately centrifuged at 2500 rpm for 10 minutes.[9] The serum was collected and stored at -80 ºC until analysis up to six months. The samples were thawed out once. All the assays were performed according to the manufacturer's recommendations with the Pathfast® immunoassay analytical

system (Progen Biotechnik GmbH, Germany and Mitsubishi Chemical Medience Corporation, Japan) using plasma from EDTA tubes.[9] Heparinized whole blood samples were centrifuged at 1000 rpm for 5 minutes and NT-ProBNP measurements were performed using chemiluminescence method (Cobas e411, Roche Diagnostics, Basel, Switzerland).[9] Following centrifugation at 1000 rpm for 10 minutes of plain tubes, creatinine and hsCRP levels were measured according to the manufacturer's recommendations with using related methods (Cobas c501, Roche Diagnostics, Basel, Switzerland).[9]

Statistical analysis

Number Cruncher Statistical system (NCSS) (Kaysville, Utah, USA 2007) programme was used for statistical analysis. Study data were analyzed using descriptive statistical methods such as mean, standard deviation, median, frequency, ratio, minimum and maximum. Normally distributed quantitative data were analyzed by Student t test, and non-normally distributed data were analyzed by Mann Whitney U test. Comparisons of qualitative data were analyzed by Yates' Continuity Correction test.[9]

Diagnostic screening tests (sensitivity, specificity, positive predictive value, negative predictive value) and ROC (Receiver Operating Curve) curve test were performed for determining PSP and NT-proBNP cut-off values. Spearman's rank correlation was made to test the association of PSP with other laboratory parameters. Two tailed p values lower than 0.01 with 99% confidence level and lower than 0.05 with 95% confidence level were accepted as statistically significant.[9]

Results

Fifty patients with HF [27 (54%) male and 23 (46%) female)] and 51 voluntary controls [20 (39.2%) male and 31 (60.8%) female)] were included in the analysis. Baseline characteristics and laboratory findings are given in **Table 1**. Mean age, BMI, smoking and medical history were similar among groups. Left ventricular ejection fraction (LVEF) measurements were significantly lower in HF group than controls as expected (30 ± 9% vs. 63 ± 4%, p=0.001). PSP levels were significantly higher in HF group than controls (1107.9 ± 1001.1 pg / mL vs. 540.4 ± 526.9 pg / mL, p = 0.001). NT-proBNP levels were higher in HF group than control group as predicted (11227.2 pg / mL ± 11443.2 vs. 174.1 ± 207.9 pg / mL, p = 0.001). Levels of hsCRP did not show significant difference among groups (4.65 ± 10.9 mg / L vs. 3.9 ± 4.1 mg / L, p = 0.239). WBC count was also similar among groups (9.13 ± 2.97 vs. 9.01 ± 3.24 109 / L, p = 0.58). Likewise, creatinine levels were similar among groups.

Diagnostic screening test and ROC curve analysis for determining cut-off for NT-proBNP and PSP are given in **Table 2**. Cut-off value for NT-proBNP was 727 pg / mL to detect HF with 98% sensitivity, 96% specificity, 96.1% positive predictive value and 98 % negative predictive value (AUC: 99.1%, SD: 0.008) and cut-off value for PSP was 472 pg / mL to detect HF with 76% sensitivity, 62.7% specificity, 66.7% positive predictive value and 72.7% negative predictive value (AUC: 73.8%, SD: 0.049). PSP levels were not correlated with NT-proBNP, hsCRP and WBC ($p > 0.05$) **(Table 3)**. The diagnostic value of PSP levels to diagnose HF was statistically lower than NT-proBNP ($p = 0.001$) **(Table 2)**.

Discussion

In this study, we investigated the diagnostic ability of PSP in patients with decompensated HF. The results revealed that PSP was significantly increased in patients with decompensated HF compared to controls, but it was not correlated with NT-proBNP, hsCRP and WBC, and the diagnostic power of PSP to diagnose decompensated HF was statistically lower than NT-proBNP. Various cardiac and non-cardiac disorders may cause HF by different pathophysiological mechanisms.[1,12] Systemic inflammation plays a role in all steps of HF and could be the reason of HF onset or impairment of a previously stable HF.[1,12,13]

It is widely accepted that inflammatory mediators may deteriorate cardiac function Leukocytosis and monocyte or macrophage levels are correlated in post-myocardial infarction patients with HF.[3] Up to date, many inflammatory biomarkers have been identified to recognize and to make risk stratification in patients with HF.[1,13] Among them, hsCRP, TNF"α" and IL6

Table 1. Demographic features and laboratory findings of HF and control group

		Patient group (n=50)	Control group (n=51)	p value
Age (years)	Mean ± SD	69.1±12.2	65.6±10.3	[a]0.110
Sex n (%)	Male	27 (54.0)	20 (39.2)	[c]0.197
	Female	23 (46.0)	31 (60.8)	
BMI (kg/m2)	Mean ± SD	28.38±3.27	27.33±3.18	[b]0.112
	Min-Max	20-36	21-33	
	(Median)	(29)	(27.5)	
Smoking		24 (48.0)	32 (66.7)	[C]0.615
Hypertension n (%)		27 (54.0)	22 (43.1)	[C]0.372
Diabetes n (%)		11 (22.0)	10 (19.6)	[C]0.959
Hyperlipidemia n (%)		24 (48,0)	25 (49,0)	[b]0,918
History of CVA n (%)		1 (2.0)	0 (0)	[d]0.495
EF	Mean ± SD	0.30±0.09	0.63±0.04	[a]0,001**
	Min-Max	0.15-*-0.45	0.52-0.7	
	(Median)	(0.3)	(0.6)	
NT-proBNP (pg/mL)	Mean ± SD	11227.2±11443.2	174.1±207.9	[a]0.001**
	Min-Max	100-35000	20-1050	
	(Median)	(6610)	(85)	
Presepsin (pg/mL)	Mean ± SD	1107.9±1001.1	540.4±526.9	[a]0.001**
	Min-Max	147-5529	111-2722	
	(Median)	(684)	(341)	
hsCRP (mg/dL)	Mean ± SD	4.65±10.9	3.99±4.18	[a]0.097
	Min-Max	0.1-75.5	0.2-17.8	
	(Median)	(1.3)	(2.6)	
Creatinine (mg/dL)	Mean ± SD	0.78±0.17	0.87±0.25	[a]0.056
	Min-Max	0.42-1.03	0.41-1.13	
	(Median)	(0.68)	(0.74)	
WBC (x109/L)	Mean ± SD	9.13±2.97	9.01 ±3.24	[c]0.587
	Min-Max	5-15.9	5-17.6	
	(Median)	(8.5)	(8.3)	

[a] Student t test, [b] Paired chi square test, [c] Yates Continuity Correction Test, [d] Fisher's Exact test
***SD;** standard deviation, **BMI;** body mass index, **CVA;** cerebrovascular accident, **EF;** ejection fraction, **NT-proBNP;** N-terminal prohormone of brain natriuretic peptide, **hsCRP;** high sensitive C reactive protein, **WBC;** white blood cell, **p<0,01*

are the mostly studied ones.[1,12,13] However, traditional laboratory tests could not efficiently reflect the progression of HF.[12] One of the receptors of monocyte / macrophage specific cluster of differentiation and lipopolysaccharide (LPS) / LPS-binding protein (LBP) complexes is CD14.[4,7] Cleaved N- terminal fragment of CD14 is called PSP glycoprotein.[4] PSP normally exist in healthy people's blood for a certain amount and increase in response to inflammation.[4,7]

We showed median serum PSP level 341 pg / mL ranging between 111 and 2722 pg / mL in the control group. This result is consistent with other studies which mostly report PSP levels as 55 - 600 pg / mL.[14,15] The wide range of PSP levels among studies may be due to the selection bias of the subjects or the method of PSP measurement.[2,16] We measured PSP with chemiluminescent enzyme immunoassay method which is the most used method in other studies.

It has been demonstrated that increased PSP levels are correlated with the existence, severity and prognosis prediction of systemic inflammation.[4,17,18] Masson et al demonstrated that PSP levels were higher in patients died as a result of severe sepsis or septic shock than survivors, and suggested to measure PSP for early risk stratification in these patients.[18]

The roles of PSP in different clinical situations have also been evaluated.[7,14,19] Klouche et al showed the usefulness of PSP in patients with severe sepsis, septic shock and severe community-acquired pneumonia and found that the level of PSP increase was different among subgroups .[19] Endo et al stated that PSP is one of the most predictive markers of sepsis and is more valuable than blood culture.[20] Shozushima et al reported that PSP is comparable to procalcitonin for the diagnosis of infections and clinical specificity of PSP is much higher than procalcitonin.[21] Hou et al reported that PSP is a sensitive predictor and a useful monitoring marker in patients with systemic inflammation and nephrolithiasis.[7] Olad et al measured PSP in patients with chemotherapy induced severe neutropenia and demonstrated that PSP was significantly higher in patients with culture positive infections but was not sensitive enough to detect culture negative bacteremia.[8]

In the present study, we demonstrated significantly higher PSP levels in patients with acute decompensated HF than the control group ($p = 0.001$). Similarly, Popov et al evaluated the prognostic value of PSP in patients operated for acquired heart diseases and revealed that PSP levels were increased in patients with acute HF and acute coronary syndrome without infection.[22]

In our study, median PSP level was 684 pg / mL ranging from 147 to 5529 pg / mL in the patient group. Liu et al declared median PSP levels as 787 pg / mL for severe sepsis and 1084 pg / mL for septic shock in an emergency department.[23] Behnes et al reported diagnostic PSP cutoffs as ≥ 530 pg / mL for sepsis, ≥ 600 pg/ mL for severe sepsis and ≥ 700 pg/ mL for septic shock (89% sensitivity, AUC: 0.77).[5] Diagnostic cutoff value of PSP was ≥ 472 pg / mL for HF in our study. Our results showed that PSP had the acceptable pooled sensitivity (0.76) and pooled specificity (0.63). Accordingly, the AUC was 0.74, indicating that the PSP had a moderate diagnostic efficiency. Zheng et al's meta-analysis reported the results of 8 studies conducted on the pa-

Table 2. Diagnostic screening tests and ROC curve analysis for NT pro BNP and Presepsin

	Diagnostic Scan					ROC Curve		p value
	Cut-off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	AUC	95% Confidence Interval	
NT-proBNP	≥ 727	98.0	96.08	96.1	98	0.991	0.975-1.000	0.001
Presepsin	≥472	76.0	62.75	66.7	72.7	0.738	0.642-0.835	0.001

ROC; *receiver operating characteristic,* ***AUC;*** *area under the curve,*
NT-proBNP; *N-terminal prohormone of brain natriuretic peptide*

tients with severe systemic inflammation and demonstrated the sensitivity range of PSP as 0.71-0.93 and the specificity range as 0.60-0.86.[17] Our study results are consistent with these ranges. PSP levels are affected by kidney function because of its low molecular weight.[14]

PSP is filtered by the glomeruli, reabsorbed and catabolized by proximal tubular cells.[14] Nagata et al studied PSP levels in patients with different stages of chronic kidney disease and demonstrated that PSP levels increase as eGFR decrease.[14] Behnes et al. showed the correlation between PSP and creatinine levels and the number of days on renal replacement therapy in patients in intensive care unit.[5] For that reason, we did not include the patients with eGFR lower than 60 mL / min / 1.73 m2 in the study. We did not include patients over 70 years old based on the study of Chenevier-Gobeaux et al.[24] They revealed significantly increased PSP levels in patients older than 70 years old compared to patients younger than 70 years old.[24]

Biochemical and hematological markers are important predictors in development and diagnosis of cardiovascular diseases (25, 26). In our previous study, we also reported that PSP levels were significantly elevated in acute ST elevation myocardial infarction patients together with high sensitivity troponins, which may be a novel supporting marker for acute myocardial infarction.[9] It has recently been reported that elevated preoperative plasma presepsin concentration is an independent predictor of postoperative mortality in cardiac surgery patients and PSP is a stronger predictor than other powered markers such as procalcitonin, NT-proBNP and cystatin C.[27] We also investigated PSP levels in well-controlled hypertensive patients and compared to healthy controls.[28] The results revealed that PSP levels were significantly lower in patients with well-controlled hypertension than healthy controls, which may be related to anti-inflammatory effects of antihypertensive agents.[28]

Table 3. Univariate correlations of presepsin with other markers

		PSP	
		Patients	Controls
NT-proBNP	r	0,021	0,128
	p	0,884	0,372
hsCRP	r	0,055	-0,175
	p	0,702	0,220
WBC	r	0,126	-0,027
	p	0,383	0,851

r: Spearman's Correlation Coefficient, ***NT-proBNP;*** *N-terminal prohormone of brain natriuretic peptide,* ***hsCRP;*** *high sensitive C reactive protein,* ***WBC;*** *white blood cell*

We also compared PSP with NT-proBNP being a biomechanical stress marker for HF recognized by the related guidelines.[10] A large body of evidence from clinical and experimental studies demonstrated NT-proBNP as a precise mortality and morbidity predictor for HF.[29,30] Although PSP levels were significantly increased in patients with HF, the results were not correlated with NT-proBNP levels in the present study.

Moreover the sensitivity, specificity and predictive value of PSP to recognize HF were lower than NT-proBNP. The diagnostic accuracy of PSP in HF was not superior to that of NT-proBNP. Our study does have some limitations. This study is a small, single centered, observational study. Biomarker follow-up during HF setting is of fundamental clinical importance. We were able to measure PSP once, so we may have missed the biological intra-individual variation over time. We were not able to compare PSP levels and NYHA class because the number of patients was not enough. Despite above limitations, the strength of this study comes from that it has revealed increased PSP levels in patients with decompensated HF up to date.

Conclusions

This preliminary study reveals that PSP levels are significantly elevated in patients with acute decompensated HF but the diagnostic power of PSP for decompensated HF is lower than NT-pro BNP. PSP may be a new marker for decompensated HF. Large scale studies are needed to reveal the importance of PSP in the diagnosis and prognosis of HF.

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Hybrid Treatment of Supravalvular Aortic Stenosis and Coronary Ostial Stenosis in Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant inherited metabolic disorder characterized with high levels of low-density lipoprotein (LDL) plasma cholesterol. Increased plasma LDL-cholesterol levels cause cutaneous and tendinous xanthomas, supravalvular aortic stenosis and coronary ostial stenosis in younger ages. Complications can be fatal if it is not diagnosed and treated in preliminary stages. We present a 22-year-old male patient with familial hypercholesterolemia and concomitant supravalvular aortic stenosis and coronary artery disease treated with hybrid coronary revascularization approach.

Key words: Familial Hypercholesterolemia, Coronary Ostial Stenosis, Supravalvular Aortic Stenosis, Hybrid Approach

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Introduction

Familial hypercholesterolemia (FH) is a metabolic disorder caused by the mutations in the low density lipoprotein (LDL) cholesterol receptor gene.[1] The incidence of autosomal dominant inherited familial hypercholesterolemia is 1 in 1.000.000.[2,3] Hypercholesterolemia not only affects the aortic root but also the aortic valve. Plaques formed by the accumulation of cholesterol particles lead supravalvular aortic stenosis along with the atherosclerosis causing severe ostial stenosis of coronary arteries.[4] Patients with this disorder might develop ischemic heart disease and myocardial infarction at early ages. In this case, we report a patient with autosomal dominant inherited familial hypercholesterolemia complicated with supravalvular aortic stenosis and coronary artery disease who was surgically treated with hybrid approach.

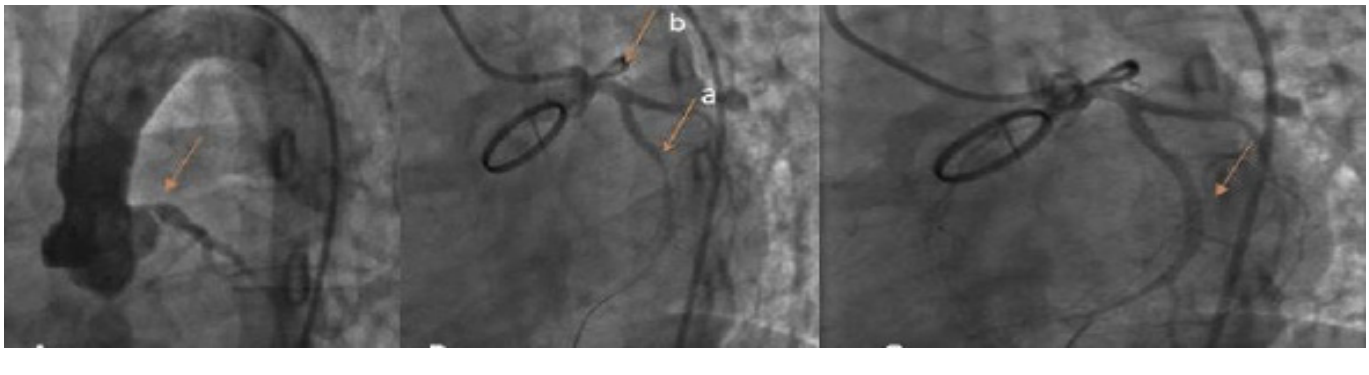
Case Report

A 22-year-old male patient was admitted to our department with symptoms of chest pain and dyspnea on exertion. He had been diagnosed with FH approximately 10 years ago. On admission he had xanthomas on his left elbow **(Figure 1)**. He was a child of a consanguineous marriage. Although the use of HMG-CoA reductase inhibitor, laboratory studies of the patient, whose body surface area was 0.93 m2, showed elevated serum total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride levels which were 560 mg/dl, 450 mg/dl, 41 mg/dl and 146 mg/dl, respectively. Transthoracic echocardiography (TTE) showed combined supravalvular aortic stenosis (peak/average gradient: 53/28 mmHg) and moderate aortic valve insufficiency. Angiographic examination revealed severe stenosis in the proximal left main coronary artery

Figure 1. Xanthomas on the left elbow.



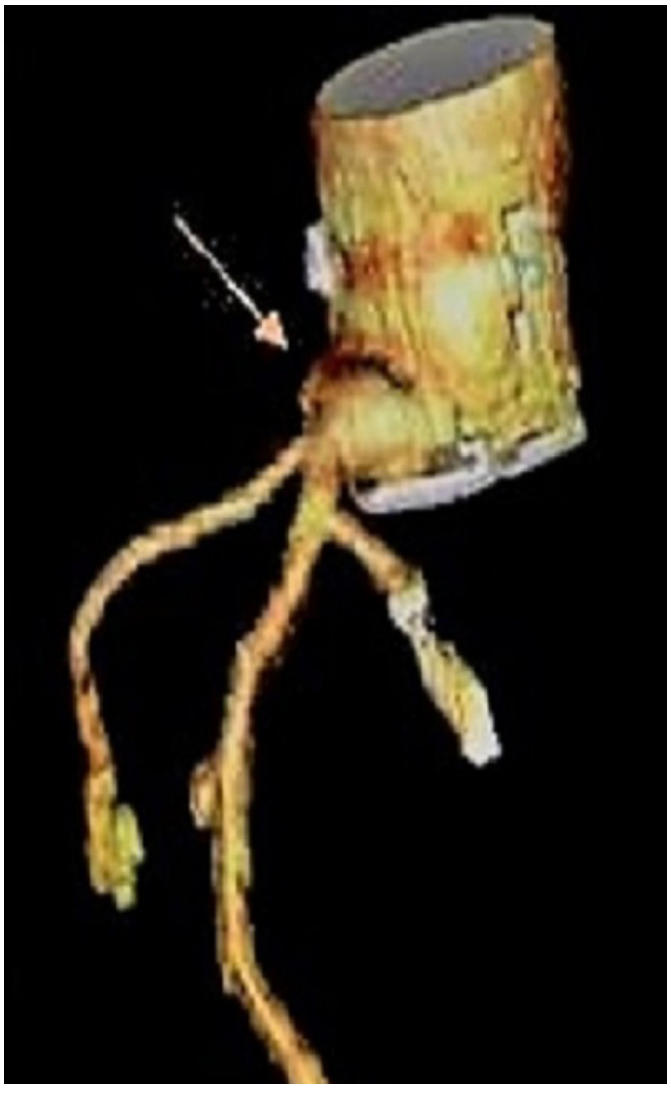
Figure 2. 90% osteal stenosis of LMCA, b. Stenosis (80%) in the mid portion of Cx artery.



(LMCA) and in the body of circumflex (Cx) artery as well as supravalvular aortic stenosis. **(Figure 2)**

Decision of surgical intervention was made according to these medical findings. Supracoronary ascending aorta and aortic valve were resected. Aortic valve replacement was performed with 21 mm St. Jude HP prosthesis. Then, osteal stenosis of LMCA was repaired with pericardial patchplasty and the patch was extended through the sinus of Valsalva. This surgical technique made the left sinus of Valsalva larger. **(Figure 3)** Subsequently, ascending aorta was replaced with a 26 mm Dacron graft. After two weeks of uneventful postoperative period, the cardiologist placed two metal stents to the Cx artery at cardiology unit. The patient was discharged with anticoagulant, antiplatelet and statin therapies without any complications on the postoperative 16th day. The patient is in the follow-up period without any problem presently.

Figure 3. BT angiographic view of LMCA ostium after osteal patchplasty.



Discussion

Hyperlipidemia, premature atherosclerosis causing coronary artery disease, supravalvular aortic stenosis, large vessel atherosclerosis and giant xanthomas can be seen familial hypercholesterolemia. Atherosclerotic plaque of the aorta mostly develops in the abdominal segment in elderly patients, whereas premature atherosclerosis is often found in the ascending aorta and coronary ostia in patients with homozygous familial hypercholesterolemia.[3,5] This condition leads to development of supravalvular aortic stenosis and ostial stenosis of the coronary arteries.

Treatment of homozygous FH consists of diet, medical therapy and apheresis. However, despite the medical treatment, majority of patients necessitate coronary revascularization and valve repair surgery. Coronary artery bypass grafting (CABG) with a full arterial grafting is a surgical option with longer patency rates in younger patients.[6] In selected left main coronary artery lesions (noncalcified isolated lesions of the proximal or midportion LMCA) surgical patch angioplasty might be an alternative to CABG.

Surgical patchplasty restores patency of the narrowed coronary artery segment and increases physiological antegrade coronary artery blood flow. In LMCA lesions, if the coronary arteries are buried intramyocardially, the surgical patch angioplasty may be the only viable surgical treatment. If we use LMCA patchplasty in younger ages, classical CABG surgery and percutaneous stent implantation are available for distal coronary artery disease that might come out in future. Also, in case of a reoperation, the anatomy of the coronary graft is prevented from deterioration.

Autologous pericardium and saphenous vein are the most preferred patch materials with sufficient width and ease to suture. Malyshev et al. reported the rate of restenosis for autologous venous material and autologous pericardium were 3.4% and 4.9%, respectively.[7] In our patient a young patient has osteal stenosis of LMCA and

stenosis of the Cx artery at the atrioventricular grove. In classic hybrid approach, minimal invasive LIMA to LAD bypass graft and percutaneous coronary intervention through to remaining lesions can be preferred.[8] In our patient, we provided anatomical coronary ostial patency with patchplasty and hybrid coronary revascularization to the Cx artery in case of a need to a reoperation in the future.

Close follow-up is important in patients with familial hypercholesterolemia since ostial coronary artery disease and ascending aorta disease with valvular involvement are likely to be seen at early ages of life. In LMCA lesions accompanying supravalvular aortic stenosis, ostial patchplasty combined with percutaneous coronary revascularization seems a better treatment option (especially in young patients) compared with conventional CABG, as there is no graft problem in redo surgery, the coronary anatomic plane is preserved and the higher capability of percutaneous interventions in concomitant distal coronary lesions.

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Rare Late Complications of Femoral Arteriovenous Fistulas Following Cardiac Catheterizations: Report of two cases

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Abstract

An arteriovenous fistula (AVF) is a vascular malformation with a direct communication between an artery and a vein and can lead to bleeding, thromboembolic events, aneurysm formation or heart failure. AVF is a rare but potentially harmful complication of cardiac catheterization. The sites of associated artery and vein are important for surgical exposure. We report two cases of femoral AVFs following diagnostic cardiac catheterizations with rather interesting extensions, originating from right deep femoral arteries and draining into right superficial femoral veins in both cases. The tracks were divided and the defects on deep femoral arteries and superficial femoral veins were primarily sutured. Symptoms of the patients, which were mainly edema and pain, relieved after surgeries. Both the patients were discharged without any complications. During cardiac catheterization, the cardiologist should master the anatomy of the femoral puncture site to avoid the complications which can be hazardous and life-threatening such as AV fistula.

Keywords: Arteriovenous fistula, Femoral artery, Femoral vein, Cardiac catheterization, Vascular malformations

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Introduction

Diagnostic and interventional cardiac catheterizations, by the most common site of arterial access being the femoral artery, have increased recently.[1] Arteriovenous fistulas (AVFs) are potentially harmful but curable complications of cardiac catheterization. Since these fistulas can cause congestive heart failure and may threaten limb circulation, prompt diagnosis and appropriate treatment are essential.[2] Here, we present femoral arteriovenous fistulas which were orginating from the right deep femoral arteries and draining into the right superficial femoral veins. Informed consent was obtained from both of the patients before surgery. Surgical repairs were successfully performed, and clinical signs and symptoms improved afterwards.

Case Report 1

A 48-year-old woman was admitted to our hospital due to leg pain and edema. A continuous bruit was audible in the right groin on auscultation. She had a history of diagnostic cardiac catheterization via the right femoral artery 3 years ago. AVF was detected via Duplex ultrasonography scan. Magnetic resonance angiography imaging (MRAI) was performed and extention of AVF was revealed **(Figure 1)**. AVF, which was from the right deep femoral artery to the right superficial femoral vein, was observed during surgical operation **(Figure 2)**. After division of the fistula track, both defects in femoral artery and vein were primarily repaired. Leg pain and edema improved following surgery.

Figure 1. MRA examination of the first patient. AVF site is showed with an arrow.



Figure 2. Arteriovenous fistula of the first patient is exposed; it is between deep femoral artery and superficial femoral vein (arrow).

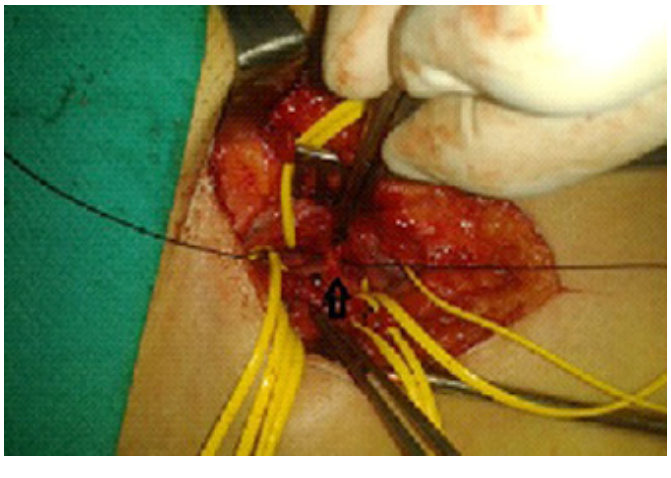
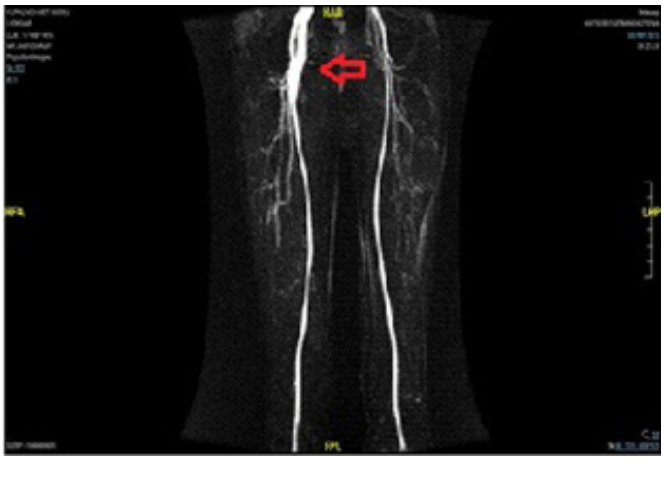


Figure 3. MRA examination of the second patient. AVF site is showed with an arrow.



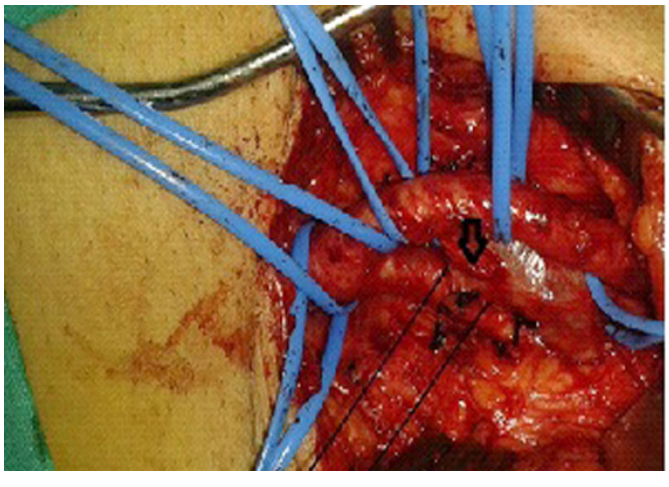
Case Report 2

A 59-year-old man admitted to our hospital with right-sided inguinal pain and leg edema. He had undergone over ten coronary angiograms via right femoral artery. Multiple puncture marks were seen related to cardiac catheterizations in the right groin with physical examination. Duplex ultrasonography and MRAI revealed a femoral AVF **(Figure 3)**. AVF which was originating from the right deep femoral artery to the right superficial femoral vein was seen intraoperatively and the defects were sutured following interruption of the communication **(Figure 4)**. The symptoms of the patient declined after the operation.

Discussion

The complications of cardiac catheterization are AVF, pseudoaneurysm (PSA), haemorrhage, arterial thrombosis and peripheral embolisation.[3] We present AVFs as a complication of cardiac catheterization which is fairly rare among the other reasons. According to a study of Perings et al., the rate of AVF after transfemoral cardiac catheteterization as 0,86%.[4] Ohlow et al. reported the rate of AVF and PSA after transfemoral cardiac catheterization as 2%.[5]

Figure 4. Arteriovenous fistula of the second patient is exposed; it is between deep femoral artery and superficial femoral vein (arrow).



Female gender, arterial hypertension, puncture side (left groin), anticoagulation therapy and emergency procedure are the risk factors for developing AVF.[4,5] Arterial complications usually occur when the arterial puncture was done through the distal segments of the common femoral artery.[6] In the both cases we present, the arterial puncture site was deep femoral artery rather than common femoral artery.

The potential adverse effects of traumatic AVFs can be reduction in distal arterial blood flow and heart failure,[7] but it has been reported that these adverse effects are rarely seen in patients with femoral AVFs following cardiac catheterization.[5]

A femoral AVF following cardiac catheterization is because of a puncture through both femoral artery and vein at a kissing site in which they lie behind one another.[8] When the femoral triangle anotomy is considered, deep femoral artery to supreficial femoral vein AVFs as in our cases are rather rare and interesting.

In conclusion, during cardiac catheterization, the cardiologist should master the anatomy of the femoral puncture site to avoid the complications which can be hazardous and life-threatening such as AV fistula.

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Chronic Leg Ulcer Due to Arteriovenous Malformation: A Case Report

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Abstract

Backround: Peripheral arteriovenous malformations are rare clinical situations and the clinical spectrum varies from asymptomatic birth spot to life-threatining congestive heart failure. Also, venous compression and insufficiency result in stasis, dermatitis and ulcer development. Leg ulceration as a complication of arteriovenous malformation has been reported after tibial arteriovenous malformation causing venous congestion or femoral arteriovenous malformation resulting in a steal syndrome. Symptomatic and progressive growing arteriovenous malformations should be treated.

Case Report: In this study we present a successful surgical and medical treatment of a fifty-four year old female patient with chronic leg ulcer due to newly diagnosed arteriovenous malformation.

Conclusion: One of the important causes of chronic leg ulcer is delayed diagnoses like arteriovenous malformation so correct diagnoses and adequate treatment including surgery is important in patients with chronic leg ulcer due to arteriovenous malformation.

Keywords: Arteriovenous malformation, leg ulcer, surgery.

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Case

A 54-year-old female patient was admitted to our clinic with symptoms of irregularly shaped chronic leg ulcer located on the lateral and pretibial side of the lower right leg. Ulcer formation started five years ago and didn't respond to medical treatment and enlarged. She noted increasing warmth, pain and eruptions without complete healing for three years.

The patient had no history of diabetes mellitus, hypertension and trauma. Laboratory findings showed no abnormality except a mild elevation in CRP (19,8 mg/L). There were no signs of deep or superfifcial venous insufficiency in lower extremity venous doppler usg. Patient was taken to hybrid operation room. Arteriography to the right lower extremity revealed multipl arteriovenous malformations related with vena saphena magna in the lower leg.

Successful therapy consisted of ligature of multipl arteriovenous connections, excision of vena saphena magna, ulcer and necrotic tissues (**Figüre 1-Figüre 2**). In addition to surgery, bed rest and adequate medical treatment including antibiotic, topical agents and venotonic drugs, the ulcer healed leaving a shallow scar and pigmentation after five mounths.

Discussion

Chronic leg ulcers are the clinical conditions that disrupt the quality of life and need long-term treatment. The most common cause is chronic venous insufficiency, but a number of different clinical conditions may play a role in the etiology . One of the important and rare causes is the arteriovenous malformations.[3]

Direct connection of arteries or arterioles to the venous system without any capillary bed can be described as arteriovenous malformation and it can be occured sporadically or as a component of inherited vascular malformation syndromes.[4] Arteriovenous malformations may exist for many years without symptoms.[5] Symptoms of fistulas due to malformation differ from congestive heart failure to distal leg ischaemia result to ulcer formation.[6]

Chronic leg ulcers may be evaluated as the result of

Figure 1. İntraoperative view after a portion of arterial and venous connections of arterio-venous malformation are attached



venous insufficiency in some patients for many years so treatment delays because of misdiagnosis. So accurate diagnoses and appropriate management is important because of long duration of asymptomatic period and serious symptoms that may occur.[7]

Patients with arteriovenous malformation that are symptomatic or have follow-up growth should be treated absolutely to avoid clinical complaints or prevent complications that may develop.[8]

As a conclusion, it should be kept in mind that arteriovenous malformation may be a cause of chronic leg ulcer. Correct diagnoses and adequate treatment including surgery is important in patients with chronic leg ulcer due to arteriovenous malformation.



Figure 2. Removed status of arterio-venous malformation after binding arterial and venous branches

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