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RESEARCH ARTICLES

CASE REPORT

HEART AND HEALTH FOUNDATION OF TURKEY

galenos yayınevi

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

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

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

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

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Correspondence

Heart and Health Foundation of Turkey

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

Phone: +90 232 464 19 63

Fax: +90 232 464 24 70

E-mail: info@tksv.com

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The Efficiency of Magnesium Supplements for the Symptomatic Relief of Patients with Superficial Venous Reflux Disease

Burak Önal[1], Didem Melis Öztaş[2], Burcu Bıçakhan[3], Aykun Hakgör[4], İbrahim Erdinç[5], Yahya Yıldız[6], Murat Uğurlucan[2]

[1]Biruni University Faculty of Medicine, Department of Medical Pharmacology, İstanbul, Turkey
[2]Biruni University Faculty of Medicine, Department of Cardiovascular Surgery, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Gaziosmanpaşa Training and Research Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey
[4]İstanbul Medipol University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
[5]University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Clinic of Cardiovascular Surgery, İzmir, Turkey
[6]İstanbul Medipol University Faculty of Medicine, Department of Anesthesia and Reanimation, İstanbul, Turkey

Abstract

Objectives: Patients with superficial venous reflux disease admit to the outpatient clinics with a wide range of symptoms. Although none of the marketed medications disappear the varicosities, they are helpful to relieve the symptoms of the patients to a certain degree. We investigated the influence of the addition of magnesium oxide (MO) to the standard symptomatic treatment of patients with superficial venous reflux disease.

Materials and Methods: Thirty-two consecutive patients who were diagnosed with chronic superficial venous reflux disease were randomly divided into 2 groups. The first group (n=16) was treated with a Horse chestnut seed extract

Address for Correspondence: Didem Melis Öztaş, Biruni University Faculty of Medicine, Department of Cardiovascular Surgery, İstanbul, Turkey
e-mail: didem_mls@hotmail.com **ORCID:** orcid.org/0000-0002-1093-2659
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(HCSE)-calcium dobesilate combined therapy, whereas the second group was treated with HCSE-calcium dobesilate combined plus MO therapy.

Results: The scores of symptoms including mean burning sensation, heaviness, cramps, edema, restlessness on the affected leg, and visual analog scale improved significantly in the second group with additional MO uptake at the end of the 2-week treatment period ($p<0.05$).

Conclusion: The addition of MO into the symptomatic treatment regime of patients is associated with a more efficient relief in symptoms and associated with a significant decrease in edema when combined with other anti-varicose vein agents.

Keywords: Superficial venous reflux disease, visual analog scale, magnesium, horse chestnut seed extract, calcium dobesilate

Introduction

Lower extremity venous insufficiency is a well-known, common health issue in the human population. Historically, it was described in ancient texts in China and Egypt. Pathology may be encountered among all age groups in the community worldwide, with a prevalence estimated between 30-40% in the general population[1-3]. The data regarding the incidence of varicose veins are indefinite; however, approximately 50% of people over 40 years are estimated to have varicose veins or telangiectasias in America and Europe[4]. Chronic venous insufficiency (CVI) is one of the most common causes of lower extremity discomfort, cramps, pain, edema, discoloration, and ulcer formation[4,5]. It is an important clinical condition leading to epidemiologic and socioeconomic consequences affecting the quality of life of patients. Increased incidence, diagnosis, and treatment costs result in a serious burden on the economy through medical costs and loss of work and attenuated quality of life[6,7].

The most common clinical findings related to long-standing venous insufficiency are telangiectasis, reticular, and/or varicose veins, whereas common symptoms are pain, cramping, itching, and complications related to venous ulcers, which are secondary to increased venous pressure due to valve insufficiency or venous obstruction[5]. Various treatment alternatives have been described for treating CVI as well as for the symptomatic relief of the affected patients. They include interventional and supportive methods. Compression stockings and medical therapy are supportive measures for pathology. The stockings act against the hydrostatic pressure of venous hypertension. Venoactive drugs relieve these symptoms by improving venous tone and capillary permeability[7].

Venoactive agents are the mainstay of standard symptomatic therapy in patients with venous reflux disease in addition to compression stockings which may be combined with various herbal and/or ionic mineral compounds. Among these, horse chestnut seed extract (HCSE) is a herbal agent frequently added to the regime of patients with venous disorders[8]. On the other hand, magnesium (Mg), which is an essential mineral for the body, has been suggested to improve vascular function[9] as well as act in the modulation of pain[10]; both of which are among the components of CVI.

In this research, we sought to investigate the efficiency of oral Mg supplements for the relief of symptoms in patients with chronic superficial venous reflux disease.

Materials and Methods

We included 32 consecutive patients who were diagnosed with chronic superficial venous reflux disease and were not amended for interventional treatment between November 11 and December 31, 2022, in this prospective study. All the patients were informed about

the study protocol in detail and researched following their consent. The study was approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee on November 10, 2022, with a decision number: 948.

The patients were randomly divided into two groups. Randomization was performed according to http://www.tufts.edu/~gdallal/PLAN.HTM, which revealed a sequence of 0100001100111001 and 0101010010101111, where 0 stands for allocation in Groups 1 and 1 in Group 2. The patients in Group 1 (n=16) received dobesilate calcium (Doxium 500 mg, twice daily) and HCSE (Venotrex Retard 50 mg, twice daily), and in Group 2 (n=16), patients were prescribed magnesium oxide (MO) (Magnorm 365 mg, once daily, before bedtime) in addition to the medications in Group 1. Age, gender, weight, symptoms, occupation, duration of staying still, and performance of any kind of sport were recorded. The diagnosis of superficial venous reflux disease was made by visual examination of the legs of the patients and confirmed with Doppler ultrasonography. Superficial venous reflux disease was categorized according to the 2020 updated version of the CEAP classification that stands for Clinical (C), Etiological (E), Anatomical (A), and Pathophysiological (P)[11].

The questioned symptoms were burning and heavy sensations in the legs, restless legs, cramps, and edema. Each symptom was graded between 0-10. All the patients were requested to fill out the visual analog scale (VAS). Patients were instructed regular medication use for a period of 2 weeks and re-investigated regarding the alteration of questioned symptoms at the outpatient clinic at the end of the study period. None of the patients used compression stockings on an outpatient clinic admission and were not prescribed compression stockings, at least during the research. Improvement in symptoms in Group 1 and Group 2, as well as the efficiency of the addition of MO preparation to the treatment, were analyzed and compared.

Patients with deep or superficial venous thrombosis or insufficiency, systemic or peripheric arterial diseases, immobile and seriously movement compromised patients, pregnant patients, patients who received surgical or interventional treatment against superficial venous reflux disease, or patients with short life expectancy, use of anticoagulants, pain killers, or any kind of any other medications, and patients who could not tolerate any agent prescribed against symptoms of superficial venous reflux were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, Illinois, USA) 16.00 Inc.. Continuous variables are presented as mean ± standard deviation (mean ± SD). Categorical variables are given as number and percentages. The distribution of the data was analyzed by the Kolmogorov-Smirnov test. Normally, distributed continuous variables were analyzed with Paired-Samples t-test. Continuous values without a normal distribution were analyzed with the Wilcoxon-Signed rank test. Proportional analysis and changes in parameters at different time intervals were evaluated using the chi-square test and Fisher's exact test. Pearson correlation was used for the analysis of the correlation between the variables. Statistical significance was defined as $p<0.05$.

Results

There were 16 patients in each group. The mean age of the patients was 46.1±15.9 in Group 1 and 53±11.7 in Group 2. Female/male ratio in Group 1 was 3 whereas, in Group 2, there were 12 females and 4 males. Patients seldomly performed routine sports activities in both groups. Mean scores for each symptom i.e. burning and heavy sensations on legs, restless legs, cramps, and edema, and VAS scores of the patients in both groups as well as the demographic features of the patients, are presented in Table 1. Except for the burning sensation in the legs (Group 1: 5.06±1.81 vs. Group 2: 2.44±1.78, p=0.02), none of the other symptoms and VAS scores differed significantly between both groups.

Mean scores for burning sensation, heaviness, cramps, edema, restlessness on the affected leg, and VAS scores on admission were 5.06±1.81, 3.38±3.07, 7.31±1.88, 1.88±2.65, 7.13±2.15, and 6.81±0.98 respectively in Group 1. The values at the end of 2-week treatment period changed to 2.44±1.98 for burning sensation, 1.31±1.91 for heaviness, 3.56±2.22 for cramps, 0.56±1.24 for edema, 3.18±2.11 for restless leg and, and 3.43±2.89 for VAS score. Except for the edema symptom (p=0.06), all the other symptoms in patients improved significantly in patients (Table 1).

In Group 2, mean burning sensation, heaviness, cramps, edema, restlessness on the affected leg, and VAS scores on admission were 6.52±2.18, 4.05±3.17, 7.23±1.85, 2.47±2.85, 6.88±2.05, and 6.82±1.07, respectively. The symptom scores of the patients improved significantly in Group 2 at the end of the 2-week treatment period (1.76±1.85 for burning sensation, 1.47±2.25 for heaviness, 1.23±1.52 for cramps, 1.05±1.47 for edema, 2.47±2.18 for restless leg and 5.05±0.82 for VAS score) including edema (pre-treatment edema score: 2.47±2.85, post-treatment edema score: 1.05±1.47, p=0.03) (Table 2).

The improvement in symptoms in both groups was also compared at the end of the study period. There were no statistically significant differences between burning sensation (Group 1: 2.44±1.98 vs. Group 2: 1.76±1.85, p=0.16), heaviness (Group 1: 1.47±2.25 vs. Group 2: 1.31±1.91 p=0.45), edema (Group 1: 1.05±1.47 vs. Group 2: 0.56±1.24, p=0.27), restlessness (Group 1: 2.47±2.18 vs. Group 2: 3.18±2.11 p=0.17) on the affected leg and VAS scores (Group 1: 5.05±0.82 vs. Group 2: 3.43±2.89, p=0.24); however, patients in Group 2 exhibited significant improvement in cramps (Group 1: 1.23±1.52 vs. Group 2: 3.56±2.22, p=0.0007) with the addition of MO to the treatment regime (Tables 1, 2).

Discussion

CVI is a condition in which the valves in the veins of the legs malfunction, causing blood to flow backward and pool in the legs. The symptoms of CVI may include aching, heaviness, fatigue, itching, burning, and cramping in the legs, as well as visible varicose veins and skin changes such as eczema and pigmentation. Long-term complications of CVI can include skin damage, ulceration, and blood clots[12].

Table 1. Pre- and post-treatment scores of superficial venous reflux disease symptoms for Group 1

Group 1	Pre-treatment	Post-treatment	p-value
Burning sensation	5.06±1.81	2.44±1.98	**<0.01**
Heaviness	3.38±3.07	1.31±1.91	**<0.01**
Cramps	7.31±1.88	3.56±2.22	**<0.001**
Edema	1.88±2.65	0.56±1.24	0.06
Restlessness	7.13±2.15	3.18±2.11	**<0.001**
VAS scores	6.81±0.98	3.43±2.89	**<0.001**

VAS: Visual analog scale

Table 2. Pre- and post-treatment scores of superficial venous reflux disease symptoms for Group 2

Group 2	Pre-treatment	Post-treatment	p-value
Burning sensation	6.52±2.18	1.76±1.85	**<0.01**
Heaviness	4.05±3.17	1.47±2.25	**<0.05**
Cramps	7.23±1.85	1.23±1.52	**<0.01**
Edema	2.47±2.85	1.05±1.47	**<0.05**
Restlessness	6.88±2.05	2.47±2.18	**<0.01**
VAS scores	6.82±1.07	5.05±0.82	**<0.01**

VAS: Visual analog scale

The most common cause of CVI in the lower extremities is venous wall weakening, which also contributes to concurrent valvular insufficiency and alterations in venous hemodynamics. Increased hydrostatic pressure, venous stasis, and dilatation are the characteristics of these alterations. Consequently, both directly and indirectly, the microcirculation is disturbed, resulting in diffuse edema, pain, night/day (or both day and night) cramps, paresthesia, or restless legs syndrome of the legs[13].

One of the CVI treatment elements, Calcium dobesilate (2,5-dihydroxy-benzenesulfonate) (CD), is an angioprotective drug that mitigates the platelet activity, blood viscosity, and vascular permeability, as well as alleviates microcirculation and hemorheological anomalies owing to its vasoprotective and antithrombotic properties to treat both CVI and diabetic retinopathy[14,15]. Supporting these findings, the CD is reported to reduce erythrocyte aggregation and suspension viscosity[16] and inhibits thrombus formation and platelet aggregation in vascular grafts[17], antagonizing the release of thrombin- and collagen-induced serotonin from platelets, which clarifies its effect on reducing capillary permeability[18].

However, the results of human studies on CD, however, have been inconsistent. Some trials involving over 600 patients found it to be effective in reducing lower leg pain and decreasing the size of lower limbs after 7-12 weeks of treatment, but other research found no overall benefits for lower limb pain[19-21]. In a randomized, double-blind, placebo-controlled clinical trial, the CD was shown to improve the lymph physiology and symptoms of patients with CVI[20]. The varying results and subjectivity of pain assessments may be due to the drug being more effective in more severe cases of the condition.

Escin is the active ingredient of HCSE, which is used for treating conditions such as hemorrhoids, venous insufficiency, hematomas, and venous congestion[22]. Clinical studies of the vascular activity of β-escin have shown improved microcirculation, increased venous tone, decreased vascular permeability, and venous return leading to reduced edema[23]. Several studies have shown that taking oral HCSE can lead to a statistically significant improvement in leg pain and swelling compared with a placebo or baseline[23-27]. Taking 300 milligrams of HCSE twice a day for 12 weeks has been found to be as effective as compression therapy in reducing swelling and can be recommended for patients who cannot use compression therapy[27]. It is still uncertain whether HCSE treats CVI compared to placebo since the quality of the evidence is very low. In other words, HCSE treatments do not address underlying venous reflux; rather, they merely address some of the symptoms and manifestations of varicose veins. As a result, they work similarly to compression in that they temporarily relieve pain but do not perform any therapeutic functions[28].

Mg, which is the fourth-most abundant mineral in the body and second-most abundant intracellular cation, modulates endothelial function and vascular smooth muscle tone through participation in vascular calcification, thrombosis, and atherogenesis, the migration, and proliferation of vascular smooth muscle and endothelial cells[29,30]. According to observational prospective studies, both dietary[31,32] and serum Mg levels[9] are inversely related to cardiovascular disease risk. Even though experimental and epidemiological evidence suggests that Mg may be a beneficial therapeutic substance for mitigating cardiovascular risk[33], no interventional research has been conducted to examine how Mg supplementation affects cardiovascular events.

The results of our study indicate MO -attenuated edema in patients with superficial venous reflux disease. Literature includes reports indicating such potential of the agent, especially for cerebral edema, by decreasing the permeability of the blood brain barrier and being useful in patients with headaches[34]. In addition, Orlova et al.[35] revealed that hypomagnesemia was significantly associated with edema in pregnant women. However, such issues regarding Mg supplements is rather neglected.

In this study, we found that additional MO uptake in the symptomatic treatment regime of the patient favored a more efficient relief of symptoms as well as decreased

edema when combined with other anti-varicose vein agents. Even using HCSE-CD combined therapy as the first -line pharmacological treatment is not validated, additional MO support in the treatment was superior to this standard treatment itself, at least in the relief of pain.

Study Limitations

There are 2 major limitations of the study. First cohort size is rather small, comprising 32 patients in totaland 16 patients in each group. The second limitation regards to the duration of the treatment, which was 2 weeks. However, despite a limited number of patients and a short study period, the results were found promising. Further multi-center studies with a longer duration of follow up are warranted.

Conclusion

In conclusion, the results of the current study with a modest number of study cohorts indicated that the addition of MO to the anti-symptomatic treatment of patients with superficial venous reflux disease not only helped in better improvement of subjective symptoms but also relief of edema.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Medipol University Non-Invasive Clinical Research Ethics Committee on November 10, 2022, with a decision number: 948.

Informed Consent: All the patients were informed about the study protocol in detail and researched following their consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Öztaş DM, Bıçakhan B, Erdinç İ, Uğurlucan M, Concept: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Design: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Data Collection and/or Processing: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Analysis and/or Interpretation: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Literature Search: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Writing: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M.

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Research Article

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The Fate of Patent Stents in Patients Undergoing Coronary Artery Bypass Grafting

Serdar Başgöze[1], Onur Şen[2], Yeşim Güner[3], Mert Zihni Duman[4], Mehmet Karacalılar[5], Aylin Demirel[6], Muhammed Bayram[2], Ünal Aydın[2]

[1]Cengiz Gökçek Gynecology and Pediatrics Hospital, Clinic of Pediatric Cardiac Surgery, Gaziantep, Turkey

[2]University of Health Sciences Turkey, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey

[3]Kütahya Health Sciences University, Faculty of Health Sciences, Department of Cardiovascular Surgery, Kütahya, Turkey

[4]Elazığ Fethi Sekin City Hospital, Department of Cardiovascular Surgery, Elazığ, Turkey

[5]Dicle University Faculty of Medicine, Clinic of Cardiovascular Surgery, Diyarbakır, Turkey

[6]University of Health Sciences Turkey, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital, Clinic of Pediatric Cardiac Surgery, İstanbul, Turkey

Abstract

Objectives: Bypassing a patently stented coronary artery has a risk of flow competition, and leaving it ungrafted has a high risk of stent restenosis. This study determines the fate of patently stented coronary arteries bypassed and left ungrafted.

Materials and Methods: Patients undergoing isolated coronary artery bypass grafting (CABG) with previous percutaneous coronary intervention (PCI) were retrospectively scanned between January 1, 2015, and January 1, 2020. Patients undergoing surgery with a patently stented coronary artery were identified. Postoperative coronary angiography was performed in 52 of these patients.

Address for Correspondence: Serdar Başgöze, Cengiz Gökçek Gynecology and Pediatrics Hospital, Clinic of Pediatric Cardiac Surgery, Gaziantep, Turkey

e-mail: basgozeserdar@gmail.com **ORCID:** orcid.org/0000-0002-6146-2095

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Results: There were 24 patients whose patently stented coronary artery was bypassed and 28 whose patently stented coronary artery was not bypassed. The median follow-up time was 49 months in the non-bypass group and 53.5 months in the bypass group. Twenty (71.4%) patently stented coronary arteries remained open in the non-bypass group, and 23 (95.8%) vessels were open in the bypass group (p=0.02). The estimated open rate of vessels was 56% in the non-bypass group and 95% in the bypass group at five years (log-rank p=*0.01*). Major adverse cardiac events were developed in 12 (42.8%) patients in the non-bypass group and 6 (25%) patients in the bypass group.

Conclusion: Patients with an open stented vessel that was not bypassed during CABG have a risk of in-stent restenosis and major adverse cardiac events during the mid-and long-term periods. It may not be safe to leave patently stented coronary arteries ungrafted, particularly those with bare metal stents.

Keywords: Coronary artery bypass grafting, major adverse cardiac events, coronary stent, and percutaneous coronary intervention

Introduction

It is still controversial for patently stented coronary arteries to be bypassed or left ungrafted in patients undergoing coronary artery bypass grafting **(**CABG). There are some concerns about both choices. The first is that bypassing patently stented coronary arteries carries the risk of flow competition between the native vessel and graft; this could lead to thrombosis of one or both of these vessels. The other scenario, which leaves patently stented coronaries ungrafted, has a high risk of in-stent restenosis (ISR). Moussa et al.[1] reported a study in 2020 that included outcomes of 5,100,394 patients in the United States who underwent percutaneous coronary intervention (PCI) for ISR. The researchers concluded that the rate of ISR was 10.6% after coronary stent implantation, with 25% of these patients presenting with acute myocardial infarction[1].

Although PCI and CABG results are similar in the early period, CABG is superior as far as freedom from revascularization, cardiac events, and mortality, especially in patients with diabetes in the long term[2]. Studies have reported that the risk of major adverse cardiac events (MACE) is higher in patients undergoing CABG who previously had PCI than in patients undergoing CABG without previous PCI'[3,4], indicating that leaving patently stented coronary arteries ungrafted may be unsafe. In contrast, Grieshaber et al.[5] reported that the risk of stent stenosis or occlusion in ungrafted patently stented coronary arteries was only 4.7% in the early postoperative period.

In this study, we retrospectively compared patients undergoing CABG with and without graft bypass on a patently stented vessel in terms of mid-and long-term graft and stent patency and incidence of MACE.

Materials and Methods

We retrospectively reviewed the medical records of patients who underwent CABG operations at our institution between January 1, 2015, and January 1, 2020. Patients who underwent concomitant surgery and multiple stents were excluded. Patients who underwent concomitant surgery were excluded because additional procedures needed more retraction and manipulation of the heart. This would be an extra factor influencing the outcome. In addition, we exclude patients with multiple stents in different coronaries. However, patients who had multiple stents in the same coronary artery were included. Patients who had more than 49% ISR were also excluded. There were 106 patients who had open stents in the circumflex artery (Cx) or the right coronary artery (RCA) before CABG. Remaining patients were operated on with two different surgical approaches at our hospital.

While the first approach preferred to bypass the patently stented vessel, the second preferred to leave it ungrafted. Coronary angiography was not performed in 54 patients without angina. Therefore, these patients were excluded from the study. Remaining, 52 patients had postoperative coronary angiography. Invasive coronary angiography (ICA) was performed in 18 patients diagnosed with acute coronary syndrome or likely to have myocardial ischemia and one patient for diagnostic purposes before abdominal aortic surgery. The remaining 33 patients were evaluated with a coronary computed tomographic angiography (CCTA).

There were 24 patients whose patently stented coronary artery was bypassed (bypass group), and 28 patients whose patently stented coronary artery was not bypassed (non-bypass group). Sixteen (66.7%) stents were in the RCA in the bypass group, and eight stents were in the Cx. In the non-bypass group, 22 (78.6%) stents were in the RCA, and six stents were in the Cx. Four out of 24 (16.7%) stents in the bypass group and 16 out of 28 (57.1%) stents in the non-bypass group were drug-eluting stents (DES).

Sixteen bare metal stent (BMS) patients had completed six weeks of Dual antiplatelet therapy (DAPT) from initial stenting, and four DES patients had completed one year. P_2/Y_{12} inhibitors were stopped five days before the surgery, but acetylsalicylate (100 mg per day) and low molecular weight heparin (LMWH) (1 mg/kg twice a day) was continued in these 20 patients. Dual antiplatelet therapy was continued in patients who did not reach one year after DES implantation and six weeks after BMS implantation. After the surgery, LMWH and DAPT were initiated in all patients from the postoperative first day until discharge, and DAPT was continued for at least one year from initial stenting. Demographic information, comorbidities, preoperative and postoperative laboratory findings (cardiac enzyme, bun, creatinine), left ventricle ejection fraction (EF) values with transthoracic echocardiography, hospital and intensive care unit (ICU) stay times, time interval stenting to operation, number of bypasses, the extent of coronary artery disease, intraoperative cardiopulmonary bypass (CPB) and cross-clamping (CC) times, mortality rates, and follow-up angiography images were evaluated. Re-exploration due to bleeding, pericardial tamponade, cerebrovascular events, low cardiac output, acute renal failure, and postoperative intra-aortic balloon pump use were defined as major adverse events (MAE). The amount of drainage was classified according to the definition of the American Association for Thoracic Surgery[6]. Deaths within 30 days of surgery were defined as early mortality. The institutional ethics committee of University of Health Sciences Turkey, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital approved this study (01.10.2018/3-1).

Surgical Procedure

According to the clinical protocol, the on-pump CABG procedure was conducted for all patients. Intraoperative anticoagulation was administered with at least 400 sec of activated clotting time[7,8]. Antegrade tepid blood cardioplegia was administered and repeated every 20 min until releasing the cross-clamp to maintain diastolic cardiac arrest[9]. The left internal mammary artery (LIMA) was used for the left anterior descending artery (LAD), and the great saphenous vein was used for other coronary arteries in all patients.

Follow-up

A transthoracic echocardiography was examined before discharge and one month after surgery for all patients. The patients were called for annual control after the first postoperative examination. Postoperative early follow-up of myocardial ischemia was conducted using electrocardiography (ECG) and transthoracic echocardiography. Depending on the patient's symptoms, it was decided which coronary angiography should be performed or would be followed without imaging.

Postoperative Coronary Scanning

Coronary angiography was performed in 19 patients, and CCTA was performed on 33 patients. Twelve of the patients in the non-bypass group and six in the bypass

group were diagnosed with acute coronary syndrome or stable angina with fatigue, dyspnea on exertion, and echocardiographic changes (new onset of atrioventricular valve regurgitation or contractile disfunction) and underwent ICA. ICA was performed in one patient for diagnostic screening in the non-bypass group before abdominal aortic surgery. Thirty-three patients who presented with non-specific chronic angina without the aforementioned symptoms underwent CCTA. The decision on which coronary angiography will be performed was made according to the latest chest pain guideline[10]. According to the post-operative screening, stenosis was classified for both stents and grafts as follows: 0-49%, 50-69%, 70-90%, and >90%. Those with stenosis below 49% were evaluated as open[11]. MACE were defined as death due to coronary events, myocardial infarction, stroke, hospitalization because of heart failure, and revascularization (both PCI, and CABG)[12]. Figure 1 represents the study's flow chart, including patients' selection criteria and postoperative screening methods.

Statistical Analysis

In the study, the distribution of variables was classified, and descriptive results were obtained using SPSS v. 23. The normality of the data was analyzed using the Kolmogorov-Smirnov test. Because the number of patients in each group was limited, we used non-parametric tests for statistical analyzes. Continuous variables have been given as mean ± SD or median with range and categorical variables as frequencies and percentages of the total. Continuous variables were compared using the Mann-Whitney U test, and categorical variables were compared using the chi-

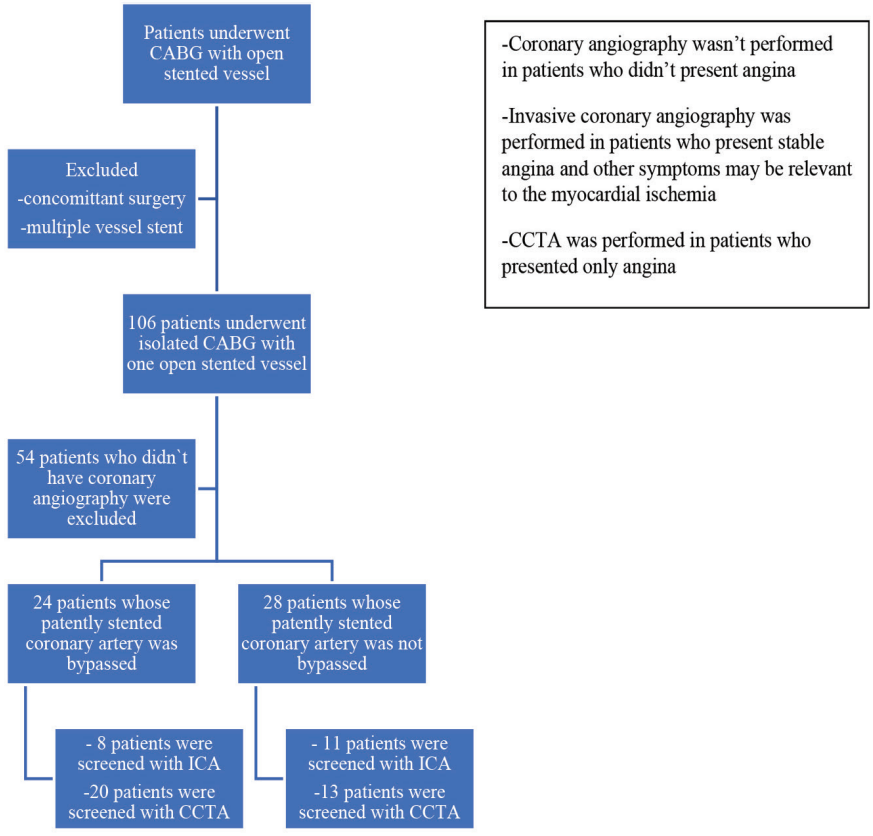

Figure 1. Flow chart of the study
CABG: Coronary artery bypass grafting, ICA: Invasive coronary angiography, CCTA: Coronary computed tomographic angiography

square test. A p-value of <0.05 was considered statistically significant. The effects of covariates on the possibility of vessel occlusion in univariate and multivariate analyses are reported as hazard ratios with a 95% confidence interval using Cox proportional hazards regression. The overall freedom from MACE and open vessel functions of the groups were evaluated with Kaplan-Meier curves, and differences were tested with a log-rank test.

Results

Preoperative and Operative Results

Fifty-two patients underwent surgery; 24 of these had their patently stented coronary artery grafted, and 28 had their patently stented coronary artery left ungrafted. There were 18 (64.3%) patients who had a three-vessel disease and 10 (35.7%) patients who had a two-vessel disease in the non-bypass group. Sixteen (66.6%) patients had a three-vessel disease, and eight (33.3%) patients had a two-vessel disease in the bypass group. There was no statistically significant difference between the patients' preoperative demographic characteristics and accompanying diseases (p>0.05). Preoperative EF was measured at >50% in 10 (41.6%) patients in the bypass group, and in 18 (64.2%) patients in the non-bypass group. The EF was measured at 35-50% in the remaining patients in both groups, and there was no statistically significant difference (p=0.16). The median preoperative PTCA/CABG interval time was 83 days (45751) in the bypass group and 65 days (61-700) in the non-bypass group. Details are shown in Table 1.

As expected, there was a significant difference in the median number of patient bypass vessels (p<0.001). CPB and CC times were longer in the bypass group, and they were statistically significant between the groups (p=0.004 and p=0.015, respectively). There was no statistically significant difference between postoperative EF measurements (p=0.12). There was no statistical difference in ICU and hospital stays between groups (p=0.19 and p=0.13, respectively). No MAE were observed in either group. There was no early mortality in either group. One late mortality in the bypass group was developed due to cerebral malignancy two years after the operation. Details are shown in Table 2.

Table 1. Patients' demographic characteristics and preoperative properties

	Bypass group (n=24)	Non-bypass group (n=28)	p-value
Age (years)	57 (46-72)	60 (46-71)	0.68
Gender (male)	22 (91.6)	20 (71.4)	0.06
BMI>25 (kg/m^2)	12 (50)	18 (64.3)	0.3
HT	22 (91.6)	26 (92.8)	0.87
DM	12 (50)	16 (57.1)	0.61
CPOD	6 (25)	4 (14.3)	0.33
PAD	4 (16.7)	2 (7.1)	0.28
CKD	1 (4.2)	2 (7.1)	0.65
HL	12 (50)	16 (57.1)	0.61
Preoperative EF (%) >50 35-50	 10 (41.6) 14 (58.3)	 18 (64.2) 10 (35.8)	0.1
Extent of coronary artery disease 2 Vessels 3 Vessels	 8 (33) 16 (66)	 10 (35.7) 18 (64.3)	0.86
Preoperative PTCA/CABG interval (days)	83(45-751)	65 (61-700)	0.11

Data are presented as the number of patients with percentages and median with range
BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CPOD: Chronic obstructive lung disease, PAD: Peripheral arterial disease, CKD: Chronic kidney disease, HL: Hyperlipidemia, EF: Ejection fraction, PTCA: Percutaneous transluminal coronary angioplasty, CABG: Coronary artery bypass grafting

Table 2. Patients' operative properties and postoperative results

	Bypass group (n=24)	Non-bypass group (n=28)	p-value
Number of bypasses	2.5 (2-3)	2 (1-2)	*<0.001*
Postoperative EF (%) >50 35-50	 14 (58.3) 10 (41.6)	 22 (78.6) 6 (21.4)	0.12
CPB time (min.)	84.92±20.49	70.32±13.83	*0.004*
CC time (min.)	47.17±13.84	38.5±10.83	*0.015*
Drainage (mL)	833.3±182.17	814.28±150.83	0.68
ICU duration (days)	1 (1-1)	1 (1-2)	0.19
Hospital stays	5 (4-19)	5 (4-6)	0.13
MAE	0	0	-
Early mortality	0	0	-
Late mortality	1 (4.2)	0	0.29

Data are presented as the number of patients with percentages and median with range or mean ± SD
EF: Ejection fraction, CPB: Cardiopulmonary bypass, CC: Cross-clamping, ICU: Intensive care unit, MAE: Major adverse event, SD: Standard deviation

Table 3. Patently stented vessel results according to a type of stent they contain

	RCA stent		RCA stent patent		RCA bypass patent	Cx stent		Cx stent patent		Cx bypass patent	Open vessel	P-value for open vessel
	DES	BMS	DES	BMS		DES	BMS	DES	BMS			
Bypass group (N=24)	2	14	0	10	16 out of 16	2	6	2	4	6 out of 8	23 (95.8)	*0.02*
Non-bypass group (N=28)	12	10	12	4	-	4	2	4	0	-	20 (71.4)	

Data are presented as the number of patients with percentages
DES: Drug-eluting stent, BMS: Bare metal stent, RCA: Right coronary artery, Cx: Circumflex

Follow-up Screening

In the bypass group, postoperative screening showed that 23 (95.8%) patently stented vessels were open; six RCA stents were occluded, but all RCA grafts were open. Two of the Cx stents were occluded, but one of the graft on Cx artery was open. In the non-bypass group, 16 out of 22 (72.7%) RCA stents were open, and four out of six (66.7%) Cx stents were open. A total of 20 (71.4%) stents were open in the non-bypass group. All LIMA-LAD anastomosis was open in both groups. We present the patency of grafts and stents in Table 3. The type of stent is also shown in this table.

The median time from the operation to control screening was 53.5 (18-70) months in the bypass group and 49 (13-67) months in the non-bypass group. The estimated open rate of vessels at three years was 92.8% in the non-bypass group and 95% in the bypass group. The estimated open rate of vessels at five years was 56% in the non-bypass group and 95% in the bypass group (log-rank p=0.01). The Kaplan-Meier results for freedom from vessel occlusion are shown in Figure 2.

A univariate and multivariate Cox regression model was created to determine the effects of four variables (PTCA/CABG interval, stent type, RCA or Cx artery stenting, and bypassing the stented vessel) on vessel occlusion. Univariate and multivariate analyzes showed that grafting the open stented vessel statistically significantly decreased the vessel occlusion (p=*0.047* and p=*0.03*, respectively). The longer PTCA/CABG interval was also favorable for the prevention of vessel occlusion, and it was statistically significant by multivariate analysis (p=*0.049*). Univariate and multivariate Cox regression model results are shown in Table 4.

MACE developed in 12 (42.8%) patients in the non-bypass group and 6 (25%) patients in the bypass group. While six patients who developed MACE underwent

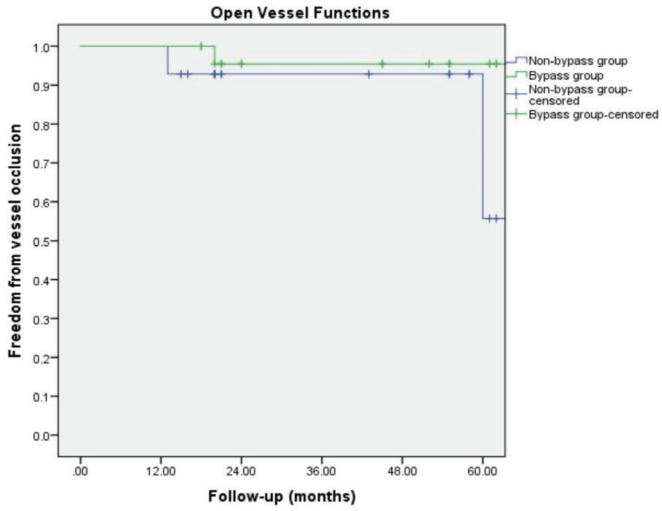

Figure 2. Freedom from vessel occlusion (log-rank p=*0.01*)

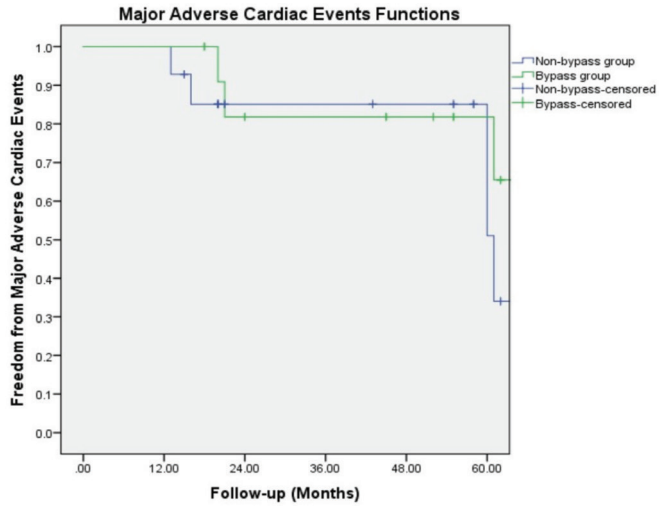

Figure 3. Freedom from major adverse cardiac events (log-rank p=0.077)

Table 4. Predictors of vessel occlusion by univariate and multivariate analysis

	Univariate				Multivariate			
Variable	**B**	**SE**	**HR (%95 QI)**	**p-value**	**B**	**SE**	**HR (%95 QI)**	**p-value**
PTCA/CABG interval (days)	-0.003	0.002	1.003 (0.99-1.008)	0.13	-0.007	0.004	1.007 (1-1.01)	*0.049*
DES	-1.11	1.08	0.33 (0.04-2.74)	0.3	-2.77	1.57	0.06 (0.003-1.35)	0.08
RCA stent	-0.42	0.84	0.66 (0.13-3.43)	0.62	-0.59	0.91	0.55 (0.09-3.3)	0.52
Bypass	-2.12	1.06	0.12 (0.01-0.97)	0.047	-2.35	1.07	0.1 (0.01-0.78)	*0.03*

PTCA: Percutaneous transluminal coronary angioplasty, CABG: Coronary artery bypass grafting, DES: Drug-eluting stent, RCA: Right coronary artery, B: Beta, HR: Hazard ratio, CI: confidence interval, SE: Standard error

target vessel revascularization (TVR) in the non-bypass group, only one patient underwent TVR in the bypass group. Kaplan–Meier results for freedom from MACE are presented in Figure 3.

Discussion

This study compares two different approaches for patients undergoing CABG with a patently stented coronary artery in terms of graft and stent patency. The main finding of this study was that 95.8% of the open stented coronary arteries with bypass grafts were open postoperatively. Only two saphenous vein grafts bypassed to the open stented vessel were occluded (but a stent in these vessels was still open). However, the patency of preoperatively open stented vessels that were not bypassed was 71.4%. MACE developed in 42.8% of the patients in the non-bypass group, with 21.4% requiring TVR.

The main concern in patients undergoing CABG with an open stented vessel is stent thrombosis due to mechanical manipulation when positioning the heart during surgery. Tovar and Borsari[13] conducted an animal study investigating the effect of mechanical manipulation on stents during heart surgery. They concluded that the retraction of the heart resulted in severe deformity of all LAD stents, mild deformity of those in the Cx, and mild or no deformity of those in the RCA[13]. Another issue in this patient population is the discontinuation of DAPT, resulting in in-stent occlusion or thrombosis in patients undergoing both cardiac and non-cardiac surgery. On the other hand, undergoing surgery with DAPT has a risk of bleeding. The current approach suggests that it is necessary to continue DAPT in elective non-cardiac operations with low thrombotic risk for at least six weeks for BMS and at least one year for DES[14]. In patients requiring cardiac

surgery before the completion of DAPT treatment, it is necessary to discontinue P_2Y_{12} inhibitors for 5-7 days before surgery and maintain antiaggregant treatment with glycoprotein IIb/IIIa inhibitors until 4-6 h to surgery[14,15]. The antiplatelet bridging protocol recommended in the latest DAPT guidelines[14,15] was not implemented in this study but, DAPT was continued in patients who did not reach one year after DES implantation and six weeks after BMS implantation. In this context, we hesitated to interrupt DAPT for fear of occlusion of stents that did not complete endothelialization, and we continued DAPT with encouragement we received a report from Karabulut et al.[16]. Similar to Karabulut et al.[16] reported previously, we found that clopidogrel does not increase the risk of bleeding-associated complications in patients undergoing CABG. This showed that P_2Y_{12} inhibitors might be used safely without increasing bleeding complications. Performing CABG with good bleeding control under DAPT might be preferred in patients who did not complete the endothelization interval with the open stented vessel.

Savonitto et al.[17] published a review article and reported that the incidence of perioperative death, myocardial infarction, and stent thrombosis is up to 30% in the first month, 10-15% between 2 and 6 months, and <10% after 6 months. Therefore, cardiac or non-cardiac surgical intervention in the early period after stenting can lead to death and stent thrombosis-related complications. Surgery can lead to inflammatory, hypercoagulable, and hypoxic states associated with plaque instability and perioperative arterial thrombosis. The case fatality rate was 45% in patients after stent thrombosis[18]. The variables that may affect stent-related complications are the discontinuation of DAPT before endothelization, diabetes, kidney disease, bifurcation lesions, and lower EF[18]. Schouten et al.[19] pointed out that, regardless of the type of stent in patients undergoing early surgery, discontinuation of antiplatelet therapy during the perioperative period may be a major cause of the increase in MACE. In addition, many researchers have reported that previous PCI before CABG increases the risk of MACE[4,20]. On the other hand, as we mentioned before, Moussa et al.[1] reported that the rate of ISR was 10.6% after coronary stent implantation, with 25% of these patients presenting with acute myocardial infarction in patients who underwent PCI for ISR. These reports worry surgeons that leaving open stented vessels ungrafted may be unsafe. Our study results support this concern because there was a higher rate of MACE in the mid-and long term in ungrafted open stented vessels compared with bypassed vessels. In our study, 95.8% of the grafted patently stented vessels were open postoperatively, but 71.4% of the vessels were open in the non-bypass group. Additionally, MACE occurred in 42.8% of patients in the non-bypass group.

We found open stent rates of 71.4% in the non-bypass group and 66.7% in the bypass group. Eight out of 12 (75%) BMS were occluded in the non-bypass group, and six out of 20 (30%) BMS were occluded in the bypass group. All 16 DESs were open in the non-bypass group, and two out of four (50%) DESs were open in the bypass group. The type of stents were unequally distributed in the groups, but stent patency was similar. Undesirable results may have occurred in the non-bypass group because of the high rate of BMS occlusion. However, notably while the rate of occluded BMS is 75% in the non-bypass group, it is 30% in the bypass group. Also, another striking point all DES were remained open in the non-bypass group. Although the rate of DES was higher in the non-bypass group, the results were more satisfactory in the bypass group. Most studies have reported that patients treated with BMS are associated with a higher risk of TVR[21-23]. In this way, the results of this study consider that grafting BMS -implanted vessels may reduce the risk of MACE and ISR. However, the stent type was found to be limited statistical significance in our multivariate regression model.

In contrast with mid- and long-term results, no cardiac events were observed in any patients during the early period. No significant ECG changes or cardiac enzyme elevation were observed in any patient in either group. However, even without ECG or cardiac enzyme changes, graft occlusion may occur. Previous studies have reported that early silent graft failure may occur in about 10% of

venous grafts[24]. Stent stenosis or occlusion may also occur without symptoms. Vetrovec et al.[25] reported that about 30% of patients who had undergone CABG suffered from non-specific chronic angina. In our study, 33 out of 106 (31.1%) patients who underwent CABG with patently stented vessels have had CCTA after surgery due to ambiguous symptoms. Eight (24.2%) resulted in coronary artery occlusion or ISR. Grieshaber et al.[5] conducted a study including 107 patients who underwent CABG with an open stented vessel and evaluated graft and stent patency with CCTA and ICA before discharge, reporting that 4.7% of patients had new stent restenosis in the early period. They concluded that perioperative coronary stent stenosis occurs rarely, and it is safe to leave a patently stented coronary artery without grafting. Since we did not perform the imaging in the early period, we do not know our study's early graft and stent failure rate. However, in contrast with Grieshaber et al.[5], the results of the current study suggest that bypassing open stented vessels, especially vessels with BMS, reduce the risk of cardiac complications and repeated TVR in the mid- and long-term periods. In addition, our multivariate regression model showed that performing surgery in the very early period after stenting may provoke vessel occlusion. As we mentioned before, inflammatory, hypercoagulable, and hypoxic conditions related to surgery can cause plaque instability and arterial thrombosis in stents that do not complete endothelialization. It is an important point to keep in mind that hypercoagulopathy and mechanical manipulations brought about by surgery may cause undesirable results, especially in non-endothelialized stents.

Study Limitations

The main restriction of this research is the retrospective study and our limited sample size. Additionally, even though CCTA is less invasive compared to ICA, ICA is the superior method. According to our clinical experience, we have determined that the patients' coronary artery disease severity is similar. However, it would be more accurate to use an objective method such as syntax or calcium score. Since, DES and BMS rates were unevenly distributed among the groups, we built a regression model in an attempt to overcome this limitation. There is a need for prospective studies with the balanced use of DES and BMS in larger patient groups. We have found 106 patients who underwent CABG with an open stented vessel, but 52 of these patients had coronary screening. We do not know the fate of patients who did not undergo coronary angiography because these patients may have developed silent graft or stent failure.

Conclusion

Current data suggest that CABG can be performed with satisfactory medium and long-term results by continuing clopidogrel in patients who have undergone PCI and have not completed DAPT treatment. It may not be safe to leave open stented vessels ungrafted during CABG. In the mid- and long term, the risk of stent thrombosis and MACE are high in cases where open stented vessels (especially with BMS) are left ungrafted. All patients undergoing CABG with patently stented coronaries should be thoroughly discussed by the heart team regarding stent type, time from stent insertion to surgery, and accompanying factors that may relate to stent occlusion.

Ethics

Ethics Committee Approval: The institutional ethics committee of University of Health Sciences Turkey, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital approved this study (01.10.2018/3-1).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Başgöze S, Şen O, Bayram M, Aydın Ü, Design: Başgöze S, Şen O, Karacalılar M, Aydın Ü, Data Collection and/or Processing: Başgöze S, Güner Y, Duman MZ, Demirel A, Analysis and/or Interpretation: Başgöze S, Güner Y, Duman MZ, Demirel A, Literature Search: Başgöze S, Şen O, Karacalılar M, Aydın Ü, Writing: Başgöze S, Bayram M, Aydın Ü.

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Research Article

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A Novel "Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH)" Score for Blood Viscosity: Predictive Capabilities for Coronary Slow-Flow Phenomenon

Onur Akhan[1], Mehmet Kış[2]

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

Abstract

Objectives: The coronary slow-flow (CSF) phenomenon is a unique clinical angiographic entity defined as delayed coronary opacification without significant occlusive coronary artery disease. Although the etiology has not been clearly revealed, multifactorial causes that affect blood viscosity and thrombus formation are considered in the pathogenesis. We aim to investigate the usability of the novel Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH) score in predicting the CSF phenomenon.

Materials and Methods: A total of 266 patients, 98 diagnosed with CSF and 168 with normal flow, were included in this retrospective cohort study. Coronary angiography images of these patients and blood samples during their hospitalization were retrospectively evaluated by two experienced cardiologists. CSF diagnosis was made according to TIMI-flow and TIMI frame-rate criteria.

Results: In the analysis of the study, there were significant differences regarding age, smoking, hematocrit percentage, mean platelet volume, total protein, and MAPH score parameters (all p-values <0.01). In addition, multivariate analysis revealed that smoking, hematocrit percentage, total protein, and MAPH score parameters were independent predictors of the CSF

Address for Correspondence: Onur Akhan, Bilecik Training and Research Hospital, Clinic of Cardiology, Bilecik, Turkey
Phone: +90 535 594 33 55 **e-mail:** akhanonur@gmail.com **ORCID:** orcid.org/0000-0003-4440-9599
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phenomenon (all p-values <0.05). After the receiver operating characteristic curve analysis to show the discrimination of the MAPH score in the formation of CSF, the area under the curve was found to be 0.719 (95% confidence interval 0.656-0.781, p<0.001). With a cut-off 2.5, the MAPH score sensitivity is 43%, and the specificity is 86% for predicting CSF.

Conclusion: According to the findings of our study, we believe that the novel MAPH score can be used to predict blood viscosity in CSF. There is also a need for multicenter studies involving more patients on the subject. In the current situation, our study will contribute to the literature and can guide future studies.

Keywords: Coronary angiography, coronary slow flow, MAPH score, blood viscosity, microcirculation

Introduction

The coronary slow-flow (CSF) phenomenon was first described as a unique clinical condition in 1972. It was defined as delayed distal opacification of the coronary artery in the absence of significant coronary artery disease (CAD)[1]. Syndrome Y and primary or idiopathic CSF are also used for the nomenclature of this phenomenon[2,3]. CSF phenomenon should be differentiated from slow flow associated with coronary intervention, occlusive CAD, coronary ectasia, and coronary embolism. It is observed in approximately 1-7% of all angiographies[4-6]. Multifactorial causes such as microvascular abnormalities, endothelial dysfunction, increased markers of inflammation, and anatomical factors related to epicardial arteries are suspected for the pathogenesis[4,5,7]. CSF diagnosis can be based on TIMI flow classification and TIMI frame rate criteria[8]. The most common criteria are TIMI-2 current rating (for example, three or more pulses required to opacify the vessel) or a corrected frame count of more than 27[9]. Patients with CSF frequently present with chest pain; some may have acute coronary syndrome features such as ECG changes and troponin increases[5,7,10]. Studies show that CSF is also related to ventricular arrhythmias and ECG changes. It has also been reported that affected patients usually young males[11,12]. Patients with CSF diagnosis presenting with anginal complaints were not classified as having any chronic coronary syndrome in the 2019 ESC guideline, and there is no clear consensus report on prognosis and treatment in CSF[4,5,13].

Increased blood viscosity may be associated with acute coronary syndromes because it can cause thrombus formation[14-16]. It has been shown in studies that many parameters can accompany the increase in blood viscosity, and various scorings have been planned over these parameters to reveal this situation. As an example, the shear rate [includes total protein and hematocrit (Htc)], systemic immune-inflammation index (multiplying the value of platelet and neutrophil/lymphocyte ratio), and PALSE score (includes total protein levels, age, left atrium diameter, systolic pulmonary artery pressure, and left ventricular ejection fraction) can be listed[17-21]. Furthermore, in a recent study in the literature, it was stated that the Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH) score [includes age and blood viscosity biomarkers such as mean platelet volume (MPV), total protein, and Htc] could be used as a new score to reveal the thrombus burden in patients with ST-elevated myocardial infarction[22].

Based on the results of this study, this score could be used as an indicator of blood viscosity. Furthermore, the CSF phenomenon may also be associated with blood viscosity regarding literature and definition. Considering this information, we planned to investigate the usability of the novel MAPH score in predicting CSF.

Materials and Methods

Our study is a retrospective cohort study that included 98 patients who underwent coronary angiography in 2022 and were diagnosed with CSF. Coronary angiography images of these patients and blood samples taken routinely

at the time of the first admission to the hospital were retrospectively evaluated. In addition, hemogram-related parameters (Htc, MPV etc.), total protein, albumin, lipid parameters, and renal function tests were evaluated from blood samples. In addition, age, gender, body mass index, diabetes, hypertension, smoking history, medications used, heart rate and blood pressure values during hospitalization, and left ventricular ejection fraction values were also evaluated from the hospital files of the patients.

In the study, hypertension was defined as a systolic blood pressure of 140 mmHg and diastolic blood pressure of over 90 mmHg (with a mean of repeated measurements), the use of antihypertensive drugs, and diabetes mellitus as a fasting blood glucose of 126 and above, and the use of blood sugar-lowering medication. In addition, smoking was defined as patients who quit or continued to smoke and were included in the study.

Left ventricular ejection fraction values evaluated using Simpson's method were obtained from the hospital information system[23].

Angiography evaluations were performed by two experienced cardiologists based on cineangiography recordings. Absence of occlusive epicardial CAD (no stenosis of 40% or more), delayed distal vessel contrast opacification (TIMI-2 flow or greater than 27 corrected TIMI frame count), and these criteria are valid for at least one coronary vessel were used as the definition of CSF[8].

In addition, 168 control patients without CSF were included in the study as the control group. Exclusion criteria of the study patients who were admitted with acute coronary syndrome, hematologic, oncologic, or inflammatory diseases, cardiac surgery history, moderately advanced valve disease, cardiomyopathies, heart failure, renal failure, liver and thyroid dysfunction, connective tissue diseases, obstructive CAD, coronary angioplasty history, presence of coronary angiography images that are not suitable for evaluation, with insufficient image quality, no-reflow phenomenon, coronary embolism, coronary ectasia, and use of exogenous vasoconstrictor agents.

Receiver operating characteristic (ROC) curve analysis by the Youden index was used for each parameter of the MAPH score to determine a cut-off value. Values at and above the cut-off were scored as 1, values below the cut-off were scored as 0, and the total score was obtained by summing the scores for each parameter. The study was conducted with the approval of the Bilecik Şeyh Edebali University Non-Invasive Clinical Research Ethics Committee (approval no: E-10333602-050.01.04-034066, date: 09.11.2022).

Statistical Analysis

Statistical analysis was performed using SPSS Windows version 24.0. First, the normality of the distribution of continuous variables was checked using the Kolmogorov-Smirnov test. Then, mean ± standard deviation was presented for continuous variables and number and frequency for categorical variables. Student's t-test was used to compare continuous variables. Next, a comparative analysis of categorical variables was performed using Pearson’s chi-square and Fisher’s exact test. In line with the results of the ROC curve analysis, logistic regression analysis was performed to evaluate whether the MAPH score was an independent predictor of slow flow in stable CAD patients. Finally, ROC curve analysis was performed again for sensitivity and specificity and the statistics were completed. P-value <0.05 was considered significant.

Results

A total of 266 patients, 98 diagnosed with CSF, were included in the study. The clinical characteristics, demographic data, and medications used by the patients of the study population are shown in Table 1. The mean age and smoking percentages were higher in the CSF group than in the normal flow group (58.28±6.21 vs. 54.87±11.46, p=0.007; 26% vs. 11%, p=0.001, respectively). There was no significant difference between other clinical features, demographic data, and treatments used.

Considering the clinical laboratory characteristics of the study, Htc, MPV, and total protein values were significantly higher in the slow-flow group compared to the normal-flow group (p<0.001, p=0.005, and p<0.001,

Table 1. Baseline clinical features, demographic data, and medication

Variables	Coronary slow-flow (n=98)	Normal-flow (n=168)	Total (n=266)	p-value
Age (mean±SD)	58.28±6.21	54.87±11.46	56.12±9.98	0.007
Male gender, n (%)	55 (56)	77 (45)	132 (49)	0.105
BMI, kg/m^2 (mean±SD)	28.02±5.13	27.57±5.1	27.73±5.11	0.485
Heart rate, /min (mean±SD)	71.67±8.83	73.89±9.27	73.08±9.16	0.057
Blood pressure, mmHg (mean±SD)				
Systolic	130.24±18.28	127.90±13.97	128.76±15.70	0.241
Diastolic	72.17±11.17	73.23±9.78	72.84±10.31	0.420
Hypertension, n (%)	40 (40)	65 (38)	105 (39)	0.732
Diabetes mellitus, n (%)	10 (10)	22 (13)	32 (12)	0.484
Smoking, n (%)	26 (26)	19 (11)	**45 (16)**	**0.001**
Medication, n (%)				
Beta-blocker	24 (24)	42 (25)	66 (24)	0.926
ACE inhibitor	43 (43)	59 (35)	102 (38)	0.156
ARB	16 (16)	19 (11)	35 (13)	0.243
The Dhp CCB	15 (15)	28 (16)	43 (16)	0.771
Oral nitrate	6 (6)	12 (7)	18 (6)	0.749
Statin	22 (22)	42 (25)	64 (24)	0.639
Acetylsalicylic acid	23 (23)	43 (25)	66 (24)	0.699
Clopidogrel	3 (3)	12 (7)	15 (5)	0.164
Warfarin	13 (13)	16 (9)	29 (10)	0.345
NOAC	6 (6)	8 (4)	14 (5)	0.632

SD: Standard deviation, n: Number of patients, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, Dhp CCB: Dihydropyridine calcium channel blocker, NOAC: Novel oral anticoagulant, Group 1: Slow flow, Group 2: Normal flow

respectively), and no significant difference was observed in the findings other than the MAPH score and linked parameters (Htc, MPV and total protein) in univariate logistic regression (Table 2). Multivariate logistic regression analysis also showed that the MAPH score was an independent predictor of CSF [odds ratio: 0.615, 95% confidence interval (CI): 0.381-0.993, p=0.047]. Table 3 summarizes univariate and multivariate logistic regression analyses in predicting CSF.

After the ROC curve analysis to show the discrimination of the MAPH score in the formation of CSF, the area under the curve was found to be 0.719 (95% CI 0.656-0.781, p<0.001) (Figure 1). With a cut-off level of 2.5, the MAPH score sensitivity is 43%, and the specificity is 86% for the prediction of CSF (Table 4).

Discussion

Our study found statistical differences between the slow-flow and normal-flow groups in the univariate analysis regarding age, smoking, Htc percentage, MPV, total protein, and MAPH score parameters. In addition, multivariate analysis revealed that smoking, Htc percentage, total protein, and MAPH score parameters were independent predictors of the CSF phenomenon. Considering these findings, we can state that the MAPH score can be used to predict CSF, following the purpose of our study.

The CSF phenomenon is a clinical condition with specific angiographic diagnostic criteria, and many studies show that this situation is primarily seen in young smoking male patients[8,9-12]. In our study, similar to the

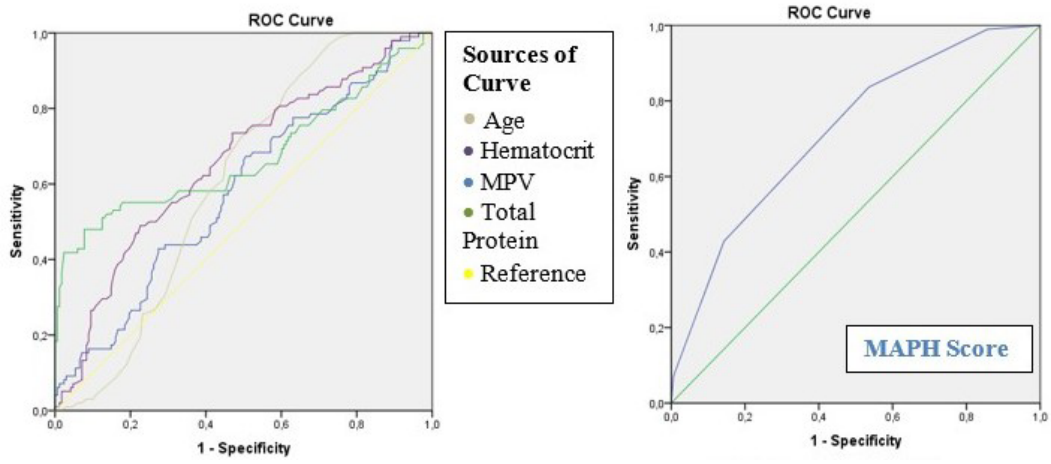

Figure 1. ROC curve analysis to show the discrimination of the MAPH score in the formation of CSF

ROC: Receiver operating characteristic, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, CSF: Coronary slow-flow, MPV: Mean platelet volume

Table 2. Clinical laboratory and left ventricular ejection fraction findings

Laboratory parameters	Coronary slow-flow (n=98)	Normal-flow (n=168)	Total (n=266)	p-value
WBC, x10³/L	9.07±3.54	8.48±2.33	8.70±2.84	0.104
Neutrophil, x10³/L	5.85±3.23	5.25±1.93	5.47±2.50	0.060
Lymphocyte, x10³/L	2.42±0.81	2.55±1.21	2.50±1.08	0.354
Hemoglobin, gr/dL	14.68±1.53	14.32±1.40	14.45±1.45	0.058
Hematocrit, %	44.80±4.15	42.40±4.53	43.29±4.54	<0.001
Platelet, x10³/L	284.91±42.96	279.05±72.41	281.21±63.15	0.467
MPV, fL	9.10±1.23	8.72±0.95	8.86±1.07	0.005
Glucose, mg/dL	105.33±22.34	111.78±32.43	109.40±29.24	0.083
Urea, mg/dL	31.38±9.33	33.26±10.94	32.57±10.40	0.157
Creatinine, mg/dL	0.82±0.16	0.85±0.19	0.84±0.18	0.151
Total protein, mg/dL	7.14±1.03	6.65±0.89	6.83±0.97	<0.001
Albumin, mg/dL	3.30±1.18	3.49±0.91	3.42±1.02	0.160
Total kolesterol, mg/dL	181.23±37.21	187.94±39.54	185.46±38.76	0.174
Triglyceride, mg/dL	178.90±84.72	167.16±90.48	171.46±88.42	0.297
HDL, mg/dL	39.98±8.84	49.56±48.14	46.03±38.87	0.052
LDL, mg/dL	107.06±30.88	110.91±32.87	109.5±32.15	0.347
MAPH score	2.33±0.85	1.54±0.92	1.83±0.97	<0.001
LVEF, % (mean±SD)	59.54±2.59	58.83±5.33	59.09±4.52	0.224

n: Number of patients, WBC: White blood cell, Htc: Hematocrit, MPV: Mean platelet volume, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, LVEF: Left ventricular ejection fraction, Group 1: Slow flow, Group 2: Normal flow

literature, the CSF phenomenon was detected primarily in young men and smokers.

Although the etiology has not been established, microvascular abnormalities, endothelial dysfunction, increased inflammatory markers, and anatomical factors may cause thrombus formation and increased blood viscosity, leading to the CSF phenomenon[4,5,7]. In a study conducted by Akpinar et al.[17] in 2014 investigating the relationship between complete blood count and CSF, it was shown that this might be a subclinical inflammation condition due to the increase in white blood cells and neutrophils. In this study, increases in red cell distribution

Table 3. Uni- and multivariate logistic regression analysis to predict coronary slow-flow

	Univariate logistic regression			Multivariate logistic regression		
Variables	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	0.965	0.940-0.991	0.008	0.987	0.955-1.020	0.432
Hematocrit	0.882	0.829-0.937	<0.001	0.913	0.847-0.985	0.018
MPV	0.715	0.560-0.913	0.007	0.810	0.596-1.102	0.179
Total protein	0.552	0.406-0.750	<0.001	0.665	0.450-0.984	0.041
MAPH score	0.377	0.272-0.521	<0.001	0.615	0.381-0.993	0.047
Smoking	0.353	0.183-0.680	0.002	0.433	0.209-0.899	0.025

MPV: Mean platelet volume, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, CI: Confidence interval, OR: Odds ratio

Table 4. Curve analysis to detect best cut-off values for the MAPH parameters and the MAPH score for differentiating normal and coronary slow-flow

Variable(s)	AUC	95% CI	Std. Error	Cut-off	Sens.	Spec.	Sign.
Age	0.608	0.542-0.675	0.034	57.5	58%	59%	0.003
Hematocrit	0.656	0.588-0.724	0.035	43.65	61%	62%	<0.001
MPV	0.580	0.510-0.651	0.036	8.72	55%	56%	0.029
Total protein	0.671	0.596-0.745	0.038	7.13	58%	57%	<0.001
MAPH Score	0.719	0.656-0.781	0.032	2.5	43%	86%	<0.001

AUC: Area under the curve, CI: Confidence interval, Std: Standart, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, Sens.: Sensitivity, Spec.: Specificity, Sign.: Significance

width and platelet cell distribution width were also shown in CSF, and it was shown that this could lead to an increase in cell deformability and microvascular blood flow resistance (p<0.001 and p=0.028, respectively). In this study, the MPV value was also significantly higher in the CSF group compared to the control group (MPV: 8.63±1.10, 8.22±0.83; respectively, p<0.001). However, no significant difference was found between Htc values (p=0.671)[13-17]. Similarly, our study's MPV values were significantly higher.

Cetin et al.[18], investigating the relationship between blood viscosity and CSF, concluded that blood viscosity calculated using total protein and Htc data is an independent predictor of CSF[19-23]. In our study, Htc and total protein values were significantly higher in the CSF group, similar to the previous study.

Senen et al.[24] showed a correlation between MPV (that is a platelet function marker) values and blood viscosity in CAD. In addition, another study also showed that an MPV value greater than 8 fL may be related to the increased incidence of CAD and stroke[25]. In our study, MPV values were significantly higher in the CSF group, and the laboratory values detected were 8 fL and above.

As mentioned above, blood viscosity may be related to age, Htc percentage, MPV, and total protein parameters. Furthermore, recent studies have stated that the MAPH score created using these parameters can reveal the thrombus burden in myocardial infarction with and without ST elevation[22,26].

We believe that the MAPH score, which is a new score and an indicator of blood viscosity, can be used as a predictor for CSF based on the literature and the results of our study. We can state that future multicenter studies that investigate the possible relationship between the MAPH score and CSF involving more patients and with subgroup analyses of smokers and nonsmokers with CSF to reveal the potential effects of smoking on the study results can be guided by our research.

Study Limitations

The limitations of our study can be listed as the retrospective nature of our research and the possible effects of interobserver variability, although standard diagnostic methods have been used. CSF is more common in smokers, but since smoking in this group is significantly different from the control group, it may affect the parameters in the MAPH score. The low sensitivity of the MAPH score predicting CSF can also be considered among the limitations of our study.

Conclusion

According to the findings of our study, we believe that the novel MAPH score can be used to predict blood viscosity in CSF. There is also a need for multicenter studies involving more patients on the subject.

Ethics

Ethics Committee Approval: The Bilecik Şeyh Edebali University Non-Invasive Clinical Research Ethics Committee approved this study (approval no: E-10333602-050.01.04-034066, date: 09.11.2022).

Informed Consent: Retrospective cohort study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Akhan O, Kış M, Design: Akhan O, Kış M, Data Collection and/or Processing: Akhan O, Kış M, Analysis and/or Interpretation: Akhan O, Kış M, Literature Search: Akhan O, Kış M, Writing: Akhan O.

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Research Article

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Comparison of Thoracotomy and Sternotomy Repair in Neonatal Aortic Coarctation Surgery: A Single Center Experience

Mehmet Çelik

Başkent University, Konya Application and Research Center, Clinic of Pediatric Cardiovascular Surgery, Konya, Turkey

Abstract

Objectives: This study aimed to compare the rates of mortality and development of recoarctation between the thoracotomy and sternotomy methods applied in the repair of aortic coarctation during the neonatal period in our clinic.

Materials and Methods: Thirty-four neonatal patients who underwent aortic coarctation repair at our clinic between June 2017 and January 2023 were included in this study. The demographic data, physical examination findings, and transthoracic echocardiographic and angiographic examination data of all patients were retrospectively obtained from our hospital database. The patients who underwent thoracotomy and sternotomy were divided into groups 1 and 2, respectively. Postoperative recovery and mortality were recorded and compared between the groups.

Results: Thirty-four patients were included in the study, nine (26%) in group 1 and 25 (74%) in group 2. The median age and body weight of the patients in group 1 and group 2 were 14 (interquartile range: 9-22) days, 9 (interquartile range: 4-19) days, p=0.256 and 3.5 (interquartile range: 3.15-3.6) kg, 3 (interquartile range: 2.8-3.25) kg, p=0.057, respectively. Significant differences were found in isthmus diameters, aortic arch, and isthmus Z-scores between the groups (all p<0.05). Significant recoarctation developed in three patients, two (22%) in group 1 and one (4%) in group 2. Early in-hospital

Address for Correspondence: Mehmet Çelik, Başkent University, Konya Application and Research Center, Clinic of Pediatric Cardiovascular Surgery, Konya, Turkey

Phone: +90 332 257 06 06 **e-mail:** mehmert1981@gmail.com **ORCID:** orcid.org/0000-0002-5018-0068

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mortality was observed in nine patients, four (44%) in group 1 and five (20%) in group 2. There was no significant difference in mortality or restenosis between the two groups, p=0.201.

Conclusion: In our study, when sternotomy and descending aorta-ascending aorta end-to-side anastomosis techniques were compared with the thoracotomy repair method in neonatal aortic coarctation repair, no difference was found in terms of mortality and development of recoarctation. We believe that coarctation repair with sternotomy has a similar mortality and recoarctation frequency as coarctation repair with thoracotomy.

Keywords: Aortic coarctation, congenital heart disease, neonatal cardiac surgery

Introduction

Coarctation of the aorta is observed in 4/10,000 live births, constituting 5-8% of all congenital heart diseases[1,2]. If left untreated, systemic hypertension, congestive heart failure, cerebral hemorrhage, infective endocarditis, and dissection may develop, causing death[3]. In addition to isolated aortic coarctation, this pathology may be accompanied by aortic arch or isthmus hypoplasia, or both. It can also be observed together with intracardiac defects such as ventricular septal defects and transposition of the great arteries. The primary surgical approach for isolated aortic coarctation is a left thoracotomy with resection of the coarctation segment and end-to-end anastomosis of the aorta. In the presence of concomitant arcus aorta or isthmus hypoplasia and intracardiac defects, complete correction can be performed in one step with the classical median sternotomy and cardiopulmonary bypass support[4]. In this study, we aimed to compare the rates of mortality and development of recoarctation between the thoracotomy and sternotomy methods applied in the repair of aortic coarctation during the neonatal period in our clinic.

Materials and Methods

This study included 34 neonates who underwent aortic coarctation repair between June 2017 and January 2023. The study design was approved by the appropriate Başkent University Institutional Review Board (project number: KA22/315). Data were collected retrospectively from the hospital has database. Detailed physical examinations, laboratory tests, and echocardiographic evaluations were performed on all patients. Additional cardiac anomalies, genetic anomalies, preoperative prostaglandin E1 use, and the need for mechanical respiratory support were also noted. In the pre-operative echocardiographic evaluation, the diameter of the ascending aorta at the level of the right pulmonary artery, the largest systolic diameters of the proximal and distal transverse aortic arches, and the largest systolic diameters of the aortic isthmus and descending aorta were measured in millimeters. The aortic arch and isthmus diameters were measured, and Z scores were calculated. Echocardiography is a reliable diagnostic tool for evaluating cardiac function. In our study, we primarily used echocardiography to obtain measurements. In cases requiring more detailed information, computed tomography or magnetic resonance angiography can be used. However, these methods were not necessary for the patient in our study.

The patients were divided into two groups according to the surgical method applied: group 1 underwent thoracotomy and group 2 underwent sternotomy. Resection and end-to-end anastomosis and extended end-to-end anastomosis and subclavian flap aortoplasty were performed in patients in group 1. In group 2 patients, the descending aorta-ascending aorta end-to-side anastomosis technique was applied. Postoperative echocardiographic evaluations were performed on all patients. Recoarctation was defined as a gradient measurement of >20 mmHg in the presence of a diastolic-extending flow pattern in the descending aorta on continuous wave Doppler. Patients

in whom balloon angioplasty failed underwent a surgical correction.

Operative Technique

In patients treated with thoracotomy under general anesthesia, a left posterolateral thoracotomy was performed, and the thorax entered through the fourth intercostal space. The distal aortic arch descending aorta, left carotid artery, and left subclavian artery were dissected and removed from the surrounding tissue. The ductus arteriosus was then divided. Before placing the cross-clamps, 100 IU/kg heparin was administered. Resection and end-to-end anastomosis, resection, and extended end-to-end anastomosis or subclavian flap aortoplasty techniques were applied depending on the surgeon's preference and anatomical variations. In cases approached with sternotomy, median sternotomy was performed using cautery under general anesthesia. The thymus was removed, and cardiopulmonary bypass was initiated after aortobicaval cannulation. The ductus arteriosus was then divided. The ascending, arch, and descending aortas were dissected along with their branches and freed from the surrounding tissues. Cardioplegic arrests were also observed. In the presence of deep hypothermic circulatory arrest or antegrade selective cerebral perfusion, the isthmus was ligated from the distal left subclavian artery and transected. The distal aorta was the left stump. The descending aorta was cut from the distal part of the coarctation tissue and prepared for anastomosis, and an end-to-side anastomosis was made to the aortotomy extending from the distal ascending aorta to the proximal aortic arch (Figures 1 and 2). Whole-body perfusion was initiated after the de-airing procedure. Intracardiac repair was performed after the arch repair.

Statistical Analysis

Statistical analyses were performed using IBM SPSS statistical software (version 25.0; IBM Corp. 25.0, Armonk, NY, USA). Continuous variables were not normally distributed; therefore, the Mann-Whitney U test was used to compare variables between independent groups. The Fisher's exact test was used to compare dichotomous variables. Statistical significance was set at p-value <0.05. Continuous variables were expressed as medians

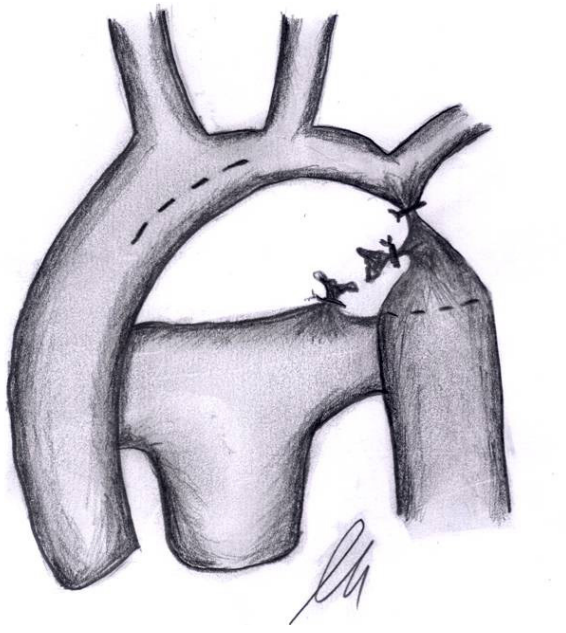

Figure 1. Ductus arteriosus division and anastomosis lines

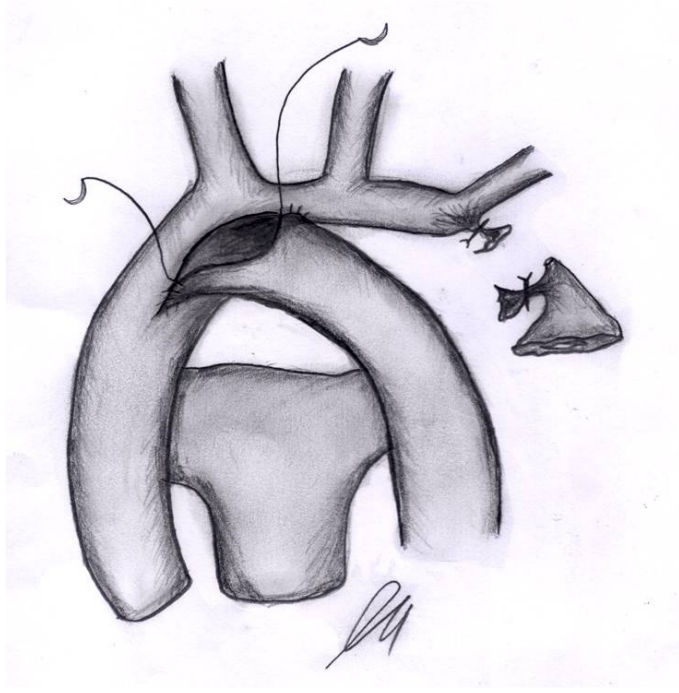

Figure 2. Descending aorta-ascending aorta end-to-side anastomosis

[interquartile range (IQR): 25th-75th], and categorical variables were expressed as numbers (percentages).

Results

The median age and body weight of 34 patients (18 male) included in the study were 12 (IQR: 4-20) days and 3.1 (IQR: 2.8-3.4) kg, respectively (Table 1). There were 9 (26%) patients in group 1 and 25 (74%) in group 2. In group 1, four patients underwent resection and end-to-end anastomosis, four underwent resection and extended end-to-end anastomosis, and one underwent subclavian flap aortoplasty. The descending aorta-ascending aorta end-to-side anastomosis technique was applied to all patients in group 2.

Biventricular cardiac physiology was observed in 30 patients (88%). A bicuspid aortic valve was detected in 10 (29%) patients: seven (78%) in group 1 and three (12%) in group 2. Simultaneous cardiac surgery was performed in 19 patients: two (22%) in group 1 and 17 (68%) in group 2. Genetic anomalies were detected in six (18%) patients: two in group 1 and four in group 2. Seventeen (50%) patients, 5 in group 1 and 12 in group 2, required preoperative mechanical ventilation. Seventeen (50%) patients, six (67%) in group 1 and 11 (44%) in group 2, received preoperative prostaglandin E1 infusion. The median preoperative aortic arch diameters of the patients in group 1 and group 2 were 3.5 (IQR: 3.1-4.4) mm and 3.3 (IQR: 3.6-3.9) mm, and isthmus diameters were 3.5

Table 1. Data of the patients

	All patient (n=34)	Group 1 (n=9)	Group 2 (n=25)	p-value
Age (day)	12.5 (4-20.2)	14 (9-22)	9 (4-19)	0.256
Wieght (kg)	3.1 (2.8-3.4)	3.5 (3.1-3.6)	3 (2.8-3.2)	0.05
Gender (male/female)	18/16	4/5	14/11	0.703
Genetic syndrome, n (%)	6 (17.6)	2 (22.2)	4 (16)	0.644
Cardiac physiology (biventricular/ univentricular)	30/4	8/1	22/3	1
BAV, n (%)	10 (29.4)	7 (77.8)	3 (12)	0.001
PMV, n (%)	17 (50)	5 (55.6)	12 (48)	1
PGE1, n (%)	17 (50)	6 (66.7)	11 (44)	0.438
Aortic arch diameter (mm)	3.4 (3-4)	3.5 (3.1-4.4)	3.3 (2.6-3.9)	0.143
Aortic arch Z-score	-4.4 (-5.71/-3.28)	-3.18 (-3.47/-2.32)	-4.85 (-6.26/-4.19)	<0.001
Isthmus diameter (mm)	2.1 (1.7-3.5)	3.5 (3-3.5)	2 (1.5-2.5)	<0.001
Isthmus Z-score	-5.21 (-6.78/-2.81)	-2.84 (-3.54/-2.30)	-5.63 (-8.14/-4.46)	0.002
Pulmonary banding, n (%)	8 (23.5)	2 (22.2)	6 (24)	1
Simultaneous cardiac surgery, n (%)	19 (55.9)	2 (22.2)	17 (68)	0.025
CPB time (min)	-	-	86 (69-106)	-
X clamp time (min)	-	17 (12.5-31)	29 (22-66)	-
ASCP time, (n=15) (min)	-	-	20 (20-25)	-
DHCA time, (n=12) (min)	-	-	21 (16-29)	-
Peritoneal dialysis, n (%)	6 (17.6)	1 (11.1)	5 (20)	1
Chylothorax, n (%)	3 (8.8)	2 (22.2)	1 (4)	0.164
Tracheostomy, n (%)	2 (5.9)	1 (11.1)	1 (4)	0.465
Left main bronchus obstruction, n (%)	1 (3)	-	1 (4)	-
Recoarctation, n (%)	3 (8.8)	2 (22.2)	1 (4)	0.164
Exitus	9 (26.5)	4 (44.4)	5 (20)	0.201

ACCP: Antegrade selective cerebral perfusion, BAV: Bicuspid aortic valve, CPB: Cardiopulmonary bypass, DHCA: Deep hypothermic circulatory arrest, PGE1: Prostoglandin E1, PMV: Preoperative mechanical ventilation

(IQR: 3-3.9) mm and 2 (IQR: 1.5-2.5) mm respectively. The median aortic arch Z scores of the patients in group 1 and group 2 were -3.18 (IQR: -3.47/-2.32) and -4.85 (IQR: -6.26/-4.19), respectively. The median isthmus Z scores of the patients in group 1 and group 2 were -2.84 (IQR: -3.54/-2.30) and -5.63 (IQR: -8.14/-4.46), respectively. Preoperative isthmus diameter ($p<0.001$), arcus ($p<0.001$), and isthmus ($p=0.002$) Z scores were significantly lower in group 2 patients.

Peritoneal dialysis was needed in six (18%) patients, one (11%) in group 1, and five (20%) in group 2. Chylothorax developed in three (9%) patients: two (22%) in group 1 and one (4%) in group 2. Tracheostomy was performed in two (6%) patients due to chronic lung failure, one (11%) in group 1 and one (4%) in group 2. Left main bronchial compression occurred in one (3%) patient in group 2. Recoarctation developed in three (9%) patients, with development times of 5, 4 and 10 months, respectively. Two patients in group 1 who developed recoarctation were treated with balloon angioplasty, and one patient in group 2 was treated surgically. Nine (26.5%) hospital mortality were observed in four (44%) patients in group 1 and five (20%) patients in group 2. Five patients died due to low cardiac output, two died due to sepsis, one died due to chronic lung disease, and one died due to multiorgan failure. There was no significant difference in mortality between the two groups ($p=0.201$). The mean follow-up period was 34±21 months.

Discussion

Thoracotomy is the generally accepted approach for isolated aortic coarctation. However, in the presence of aortic arch or isthmus hypoplasia and intracardiac pathologies, repair is possible in a single sternotomy[5-8]. Different methods have been used to define aortic arch and isthmus hypoplasia. It can be concluded that the transverse aortic arch, distal aortic arch, and isthmus are <60%, 50%, and 40% of the ascending aortic diameter, respectively[9]. Similarly, if the hypoplastic aortic arch, the smallest aortic arch dimension, is less than the weight of the patient plus 1 (in mm) it can be considered hypoplasia[10]. In addition, values lower than -2 Z score can be defined as hypoplasia. We used all three methods depending on the patient's condition[11].

Aortic coarctation should be evaluated not only as a localized disease of the aorta but also as an anatomical and physiological developmental defect of the left ventricle[11]. In our study, ten patients had bicuspid aortic valves. In such cases, which can cause significant stenosis in the outflow tract, the diameter of the ascending aorta may remain below normal limits or enlarge due to post-stenotic dilatation. Therefore, comparing the diameters of the transverse arch, distal arch, and isthmus with those of the ascending aorta may lead to incorrect evaluations. Similarly, in severe coarctation with ductus-dependent systemic circulation, circulatory dynamics may be affected and edema may develop. In such cases, it may be impossible to determine the patient's actual weight, which may lead to an incorrect evaluation of the arcus according to the kilogram + 1 formula.

Limited surgical vision and small vessel diameters in newborns can cause difficulties in applying thoracotomy techniques. Tension and suboptimal sutures in the anastomosis may cause residual stenosis[12-14].

Ramachandran et al.[15] reported that preoperative transverse arch and isthmus diameters and Z scores were not related to postoperative residual stenosis in patients who underwent coarctation repair by thoracotomy and that residual stenosis was not observed even in hypoplastic isthmuses with a Z score below -2. They also stated that because cardiopulmonary bypass and deep hypothermia are not required, it provides a neurological advantage to the patient and the recovery period is shorter. Developments in cardiopulmonary bypass techniques have minimized these risks. Distal body perfusion may be insufficient during thoracotomy repair, particularly in patients with insufficient collateral circulation during the neonatal period. Moreover, it is possible to repair mild- tomoderate hypothermia accompanied by selective antegrade cerebral perfusion without deep hypothermic

circulatory arrest during sternotomy. Although there were no age restrictions in the authors' study, only neonatal patients were included. We also adopted the opinions of these authors for older patients with adequate collateral circulation, appropriate body weight and no excessive isthmus or arcus hypoplasia.

Although some studies have reported that the transverse aortic arch diameter does not cause recoarctation, leaving a hypoplastic segment during repair causes residual stenosis and postoperative hypertension[16-19]. Weismann et al.[18] determined that there was a significant correlation between the diameters of the transverse arch of the aorta and isthmus and Z scores before discharge and the development of recoarctation. Additionally, the presence of an untreated hypoplastic aortic arch may be responsible for the development of long-term recurrent aortic stenosis and hypertension[20]. The descending aorta-ascending aorta end-to-side anastomosis is a technique that allows physiological repair without residual stenosis with completely native tissues, provides an anastomosis with growth potential, can be performed with low mortality and morbidity, and allows simultaneous cardiac repairs[5].

Two of the patients who died had genetic anomalies and immunodeficiency, and four had concomitant pulmonary banding. Concomitant pulmonary banding during arch repair is a risk factor for mortality[9]. The rates of recurrent stenosis and mortality in our study were consistent with those reported in the literature[9,15,16,18].

Study Limitations

This was a retrospective study involving a single center. Therefore, a longer follow-up period is required. The small number of patients and inhomogeneity of additional cardiac anomalies complicate the evaluation.

Conclusion

In our study, we found that the mortality and recovery rates after sternotomy and coarctation repair were consistent with those reported in the literature. There was no significant difference between the two methods in terms of mortality and development of recoarctation. We believe that the sternotomy method, which is generally preferred when additional cardiac surgery is required, can also be used for isolated coarctation surgery during the neonatal period. Multicenter studies with larger patient series are required. We believe that our results will encourage further studies in this area and will support our findings. This study broadens our current knowledge of cardiology by comparing the methods of thoracotomy and sternotomy. Our findings would help inform clinicians and patients considering aortic coarctation surgery and facilitate the improvement of current practices and patient outcomes.

Ethics

Ethics Committee Approval: The study design was approved by the appropriate Başkent University Institutional Review Board (project number: KA22/315).

Informed Consent: This was a retrospective study.

Peer-review: Externally peer-reviewed.

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Ischemic Stroke after CABG and Embolic Stroke of Undetermined Source: A Case Report

Mehmet Işık[1], Hasan Hüseyin Kozak[2], Serkan Yıldırım[1], Ömer Tanyeli[1]

[1]Necmettin Erbakan University Meram Faculty of Medicine, Department of Cardiovascular Surgery, Konya, Turkey
[2]Necmettin Erbakan University Meram Faculty of Medicine, Department of Neurology, Konya, Turkey

Abstract

One of the complications seen after coronary artery bypass graft operation (CABG) is ischemic stroke. In recent years, "embolic stroke of undetermined source" (ESUS) has been defined as a subtype of ischemic stroke. In this study, a 49-year-old patient with a history of preoperative ischemic stroke and recurrent ischemic stroke after CABG is presented. The necessity of a detailed evaluation of preoperative stroke risk factors and the importance of determining stroke etiologies are discussed in the context of ESUS, which is a new subtype.

Keywords: CABG, acute ischemic stroke, stroke, ESUS, ischemic heart disease

Introduction

Acute ischemic stroke (AIS) that develops after coronary artery bypass graft operation (CABG) can cause serious clinical consequences that can lead to death. Symptomatic stroke after CABG has been reported at a rate of 2-3%[(1)]. Ischemic stroke is caused by reduced blood flow to the brain due to a thrombotic or embolic process. In embolic processes, embolic residues originate from any part of the body (especially cardiac origin) prevent blood flow in the vascular area where they are located. The etiology of stroke affects both prognosis and results[(2)].

In this article, a 49-year-old male patient with diabetes mellitus (DM), hypertension (HT), smoking, ischemic

Address for Correspondence: Mehmet Işık, Necmettin Erbakan University Meram Faculty of Medicine, Department of Cardiovascular Surgery, Konya, Turkey
Phone: +90 533 550 75 49 **e-mail:** drmisik@hotmail.com **ORCID:** orcid.org/0000-0002-2154-7473
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heart disease (IHD), and a history of previous stroke (HPS) developed AIS on the fourth postoperative day after CABG. The necessity of detailed assessment of stroke risk factors before cardiac surgery and the importance of identifying stroke etiologies are discussed in the context of a new stroke etiological subgroup, embolic stroke of undetermined source (ESUS).

Case Report

The 49-year-old male patient had DM for 15 years, HT for 10 years, has been smoking for 25 years/pack, had neovascular glaucoma for 5 years, and HPS (partial anterior circulation infarction) 3 months ago. Body mass index was calculated as 25.2. While investigating the etiology of stroke, IHD was detected and coronary angiography was performed. A stent was placed in the left anterior descending (LAD) after determining chronic occlusion in the LAD and right coronary artery (RCA). It was observed that the stent in the LAD was obstructed, the circumflex artery had plaque, and the RCA was totally occluded in the angiography performed upon the presence of effort dyspnea while being monitored under medical treatment (Figure 1). The transthoracic echocardiography report showed an ejection fraction of 35%, wall motion defects in the apical, mid, and basal regions, 1st degree mitral regurgitation, 1st degree tricuspid regurgitation, and pulmonary artery pressure of 30 mmHg. In myocardial perfusion scintigraphy performed for living tissue research, areas with perfusion defects and metabolic activity (viable tissue) were observed in the areas with defects. It was decided to perform CABG with the decision of Cardiology and Cardiovascular Surgery Council.

In preoperative analyses, hemoglobin was 12.7 g/dL, creatinine 1.4 mg/dL, eGFR53 mL/min, HDL 26 mg/dL, LDL 44 mg/dL, cholesterol 115 mg/dL, and HbA1c 7%. During the 72-h Holter monitoring, basic rhythm was sinus and atrial fibrillation (AF) was not observed. Preoperative cranial magnetic resonance imaging (MRI) and carotid computed tomography (CT) angiography was reported as chronic infarction in the left Perisylvian region, the extra and intracranial arteries were open, and no calcification images were seen in the traced segments of the aortic wall (Figure 2).

On neurological examination, he had right-sided frieze paresis and mild dysarthria, and a modified Rankin score of 3. The patient was taking acetylsalicylic acid 100 mg/day, clopidogrel 75 mg/day, valsartan hydrochlorothiazide 160/12.5 mg/day, bisoprolol 5 mg/day, atorvastatin 40 mg/day, insulin aspart 10 units in the morning and 16 units in the evening, insulin glargine 24 units, and empagliflozin 10 mg/day.

The patient underwent of-pump CABGO surgery between LIMA - LAD and aorta - RCA (with saphenous vein). Endarterectomy was performed on both distal

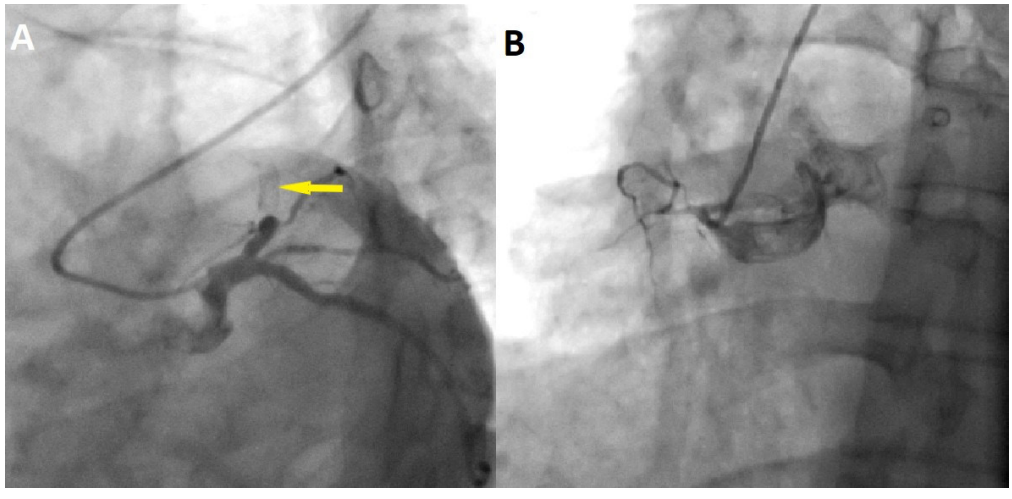

Figure 1. Coronary angiography image (occluded LAD stent)
LAD: Left anterior descending

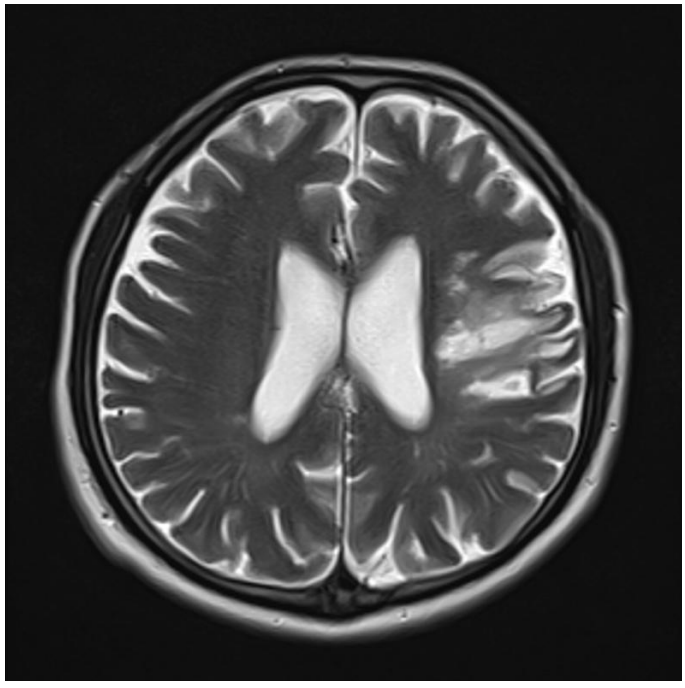

Figure 2. Preoperative cranial MRI image
MRI: Magnetic resonance imaging

anastomosis sites. At the end of the surgery, 0.08 micrograms/kg/min noradrenaline infusion was available as an inotropic support. The patient was extubated on postoperative day 0, the inotropic support was terminated by reducing on the postoperative 1st day, and his hemodynamics remained stable on the 2nd and 3rd postoperative days. On the 4th postoperative day, endotracheal intubation was performed upon detecting confusion, respiration superficialization, and hypoxia when the patient was in the sitting position. During the postoperative period, the patient was monitored and no blood pressure or rhythm problems that could impair hemodynamics were observed. In the brain diffusion MRI taken after the neurology consultation, a wide diffusion restriction at the vertex level in the right middle cerebral artery area was detected (Figure 3). The patient died on the 6th postoperative day of to multiorgan failure.

Discussion

According to the Trial of Org 10172 in Acute Stroke Treatment classification, ischemic stroke can be divided

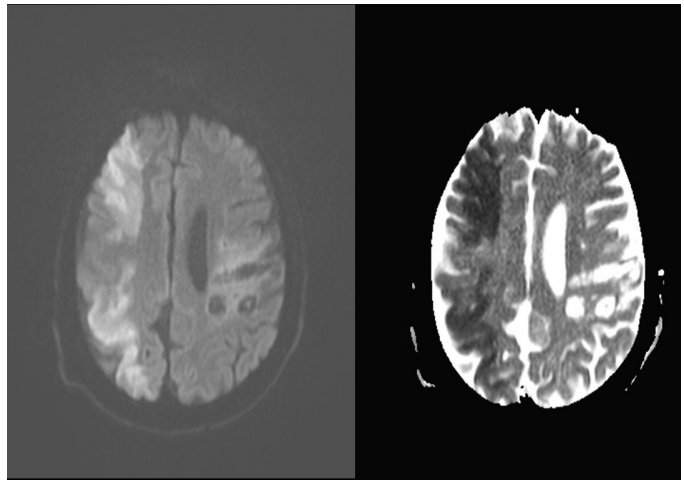

Figure 3. Postoperative cranial MRI image
MRI: Magnetic resonance imaging

into five subtypes: large-artery atherosclerosis, small-artery disease, cardioembolism, stroke of other determined etiologies, and stroke of undetermined etiology. The ischemic stroke of undetermined etiology, often referred to as cryptogenic stroke, accounts for 20-30% of all ischemic strokes. Cryptogenic stroke is a heterogeneous classification that consists of (1) true cryptogenic stroke with sufficient survey of etiology, (2) stroke within complete investigation, and (3) stroke with multiple causes[3,4]. The heterogeneous nature of cryptogenic stroke always has prevented the determination of the clinical features and optimal treatment of this type of stroke. Strategy determination studies have been conducted to determine the characteristics of this problematic clinical condition and secondary preventive treatments. In addition, most cryptogenic strokes show the clinical and radiographic appearance of embolism-like stroke from unknown sources. In 2014, Hart et al.[5] proposed a new clinical entity, which they defined as ESUS, to determine this problematic clinical situation. Therefore, the ESUS definition was designed to refine the cryptogenic stroke category by excluding patients with incomplete evaluation or multiple causes that could lead to stroke. A diagnostic definition of ESUS includes (1) non-lacunar infarction (small vessel occlusion, subcortical infarct ≤1.5 cm on CT

or ≤2.0 cm on MRI), (2) no 50% large artery atherosclerotic stenosis supplying the ischemic area, (3) no major-risk cardioembolic sources permanent or paroxysmal AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, myocardial infarction within the past 4 weeks, left ventricular (LV) ejection fraction <30%, valvular vegetation's or infective endocarditis, and (4) no other specific causes of stroke (such as vasculitis, dissection, migraine/vasospasm, drug misuse, etc.)[5].

Initially, the definition of ESUS was based on the hypothesis that AF would be the main cause of stroke in this subpopulation of cryptogenic stroke. Studies have shown that the results of in-depth examinations performed to establish a diagnosis of ESUS also revealed etiologies that were previously thought not to be related to ESUS. Cardiac abnormalities such as atrial cardiomyopathy, cardiac thrombus, patent foramen ovale, coagulation disorders, and underlying malignancies were cited among these. Currently, the relevance and causal effect of these etiologies for ESUS is unclear. Interestingly, recent studies suggest multiple or overlapping etiological causes for this stroke subtype[6].

Our case, who was evaluated by the neurology clinic before the operation in relation to a previous stroke, was evaluated as stroke associated with the ESUS subtype considering the etiological screening, clinical status, and radiological appearance. Stroke detected within the first 7 days after CABG is considered early postoperative stroke. Early postoperative strokes, although predicted to be primarily associated with arrhythmias and hemodynamic imbalances, are associated with embolic materials resulting from perioperative aortic manipulation, postoperative low cardiac output syndrome, and postoperative surgical bleeding[7].

In this study, the absence of any hemodynamic distress or any condition that could lead to hemodynamic distress for four days after surgery, the complete end of the need for inotropes in the early postoperative period, and the absence of any calcification image in the aortic wall in preoperative vascular imaging led us to the conclusion that the newly developed ischemic stroke was not associated with the surgical procedure.

In recent studies, it has been established that one-third of ESUS patients aged >45 years have coronary artery disease. In addition, LV wall motion abnormalities and LV diastolic dysfunctions have been associated with ESUS in patients with ESUS[8]. Also, DM and HT are independently associated with impaired LV function, and their coexistence creates a negative synergistic effect on LV mechanics[9].

The first stroke in our present case was evaluated in the context of ESUS, and the deterioration associated with ventricular dynamics was clearly detected in preoperative laboratory evaluations. All these data suggest that AIS, which develops postoperatively and resembles embolism-like stroke clinically and radiologically, is far from the causes of stroke that may arise due to perioperative and postoperative reasons. The fact that the patient experienced a new AIS episode after a peri- and postoperative period without any problems revealed our opinion that the processes related to ventricular dynamics would be a new area that should be discussed in the context of the ESUS subtype when the above literature information and the dynamics of the case were re-evaluated.

In the context of the case, the detection of coronary disease with the previous stroke followed by stent placement and subsequent surgical process suggest that ventricular dynamics in both the previous and postoperative periods may negatively contribute to all these processes.

Based on meta-analyses, the frequency of ESUS is estimated to be 17% (9 to 25%) of ischemic strokes. While most ESUS patients (86%) are treated with antiplatelet therapy during monitoring, the average annual stroke recurrence rate is 4.5% (2.3 to 6.8%)[5,10]. Although the long-term mortality risk is lower than cardioembolic strokes for ESUS patients despite similar composite cardiovascular endpoints and recurrence rates, it is associated with a higher risk of stroke recurrence than

the probable recurrence risk for other non-cardioembolic strokes[11]. Some clinical features such as previous ischemic stroke or transient ischemic attack, advanced age, current tobacco use, multiple acute infarctions in neuroimaging, and diabetes are independent predictors of recurrent ischemic stroke in ESUS patients[12]. All these data reveal the importance of recognizing and evaluating the ESUS subtype. Consequently, knowing the etiology of stroke in patients with a preoperative history of stroke may shed light on the prediction and/or prevention of a new stroke that may develop postoperatively. There are no data revealing the relationship between stroke that develops after cardiac surgery, especially the history of preoperative stroke in the ESUS subtype and pre-operative stroke subtypes.

In conclusion, preoperative ESUS definition and treatment planning for neurologists and postoperative embolism-like stroke patterns and determination of goal and treatment toward the cause in terms of ESUS for cardiac surgeons are emerging as a new area of discussion. All in all, the necessity of cardiovascular and neurological physicians to work together in this field and to solve this mystery together is revealed once again.

Ethics

Informed Consent: Written consent of the patient was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Işık M, Kozak HH, Yıldırım S, Tanyeli Ö, Concept: Işık M, Tanyeli Ö, Design: Işık M, Kozak HH, Yıldırım S, Data Collection and/or Processing: Işık M, Kozak HH, Analysis and/or Interpretation: Işık M, Kozak HH, Yıldırım S, Tanyeli Ö, Literature Search: Işık M, Kozak HH, Writing: Işık M, Kozak HH.

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