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Development of De Novo Chronic Total Occlusion in Native Coronary Arteries of Coronary Artery Bypass Grafting Surgery Patients

Koroner Arter Bypass Greft Cerrahisi Hastalarının Nativ Koroner Arterlerinde Yeni Kronik Total Oklüzyon Gelişimi

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ABSTRACT

Aim: Postoperative de novo chronic total occlusions (CTOs) of preoperatively non-occluded native coronary arteries are commonly seen in coronary artery bypass grafting (CABG) surgery patients in the clinical follow-up; however, data about this course is limited. The aim of this study was to investigate the prevalence of new CTO development in native coronary arteries postoperatively and the clinical factors which may play role in this context.

Materials and methods: A total of 492 CABG patients has been searched from the computer database at Başkent University Hospital Alanya Application and Research Center and patients with a recurrent coronary angiography (CAG) procedure after the first 6 months following surgery were involved in the study population. Recurrent CAG recordings were evaluated for the presence of new CTO development. Logistic regression analysis was used to search the role of demographical and angiographical characteristics in the development of de novo CTOs in native coronary arteries.

Results: Seventy-three CABG patients with recurrent CAG were involved in statistical analysis (Mean age was 65.2 ± 9.8 years; male gender 76.7%). Two hundred eighteen preoperatively non-occluded native coronary arteries were evaluated and 119 new CTOs were detected (54.5% of involved vessels). Preoperative proximal stenosis ≥90% is related to more than 3 times new CTO development (67.8% vs. 22.2%) (p<0.001). Dual antiplatelet therapy (DAPT) is found as a protective factor for the patency of native coronary arteries (HR:-0.259; 95% CI:-0.475 to -0.017; p=0.036).

Conclusion: De novo CTO development in native coronary arteries is commonly seen in CABG patients postoperatively. Significance of preoperative stenosis and absence of DAPT seem to be the essential factors in new CTO occurrence.

Key words: coronary artery bypass grafting; native coronary arteries; chronic total occlusion

ÖZ

Amaç: Koroner arter bypas greftleme (KABG) cerrahisi hastalarının postoperatif klinik takibinde preoperatif olarak tam tıkalı olmayan nativ koroner arterlerin kronik total oklüde (KTO) hale gelmesi sık görülse de, seyriyle ilgili veriler kısıtlıdır. Çalışmamızın amacı postoperatif dönemde nativ koroner arterlerde yeni KTO gelişim sıklığını ve bu konuda rol oynayan faktörleri araştırmaktır.

Yöntem: Başkent Üniversitesi Hastanesi Alanya Uygulama ve Araştırma Merkezi'nde gerçekleştirilen tüm KABG operasyonları bilgisayar sisteminden tarandı ve postoperatif ilk 6 aylık dönemden sonra rekürren koroner anjiyografi (KAG) prosedürü uygulanan hastalar çalışma grubuna alındı. Rekürren KAG görüntüleri yeni KTO gelişimi açısından değerlendirildi ve nativ koroner arterlerde yeni KTO gelişimine yol açan demografik ve anjiyografik özellikler lojistik regresyon analizi kullanılarak test edildi.

Bulgular: Rekürren KAG yapılmış olan 73 KABG hastası istatistiksel analize dahil edildi (Ortalama yaş 65.2 ± 9.8 yıl; erkek cinsiyet %76.7). Preoperatif olarak tam tıkalı olmayan ve greftlenmiş olan 218 nativ koroner arter incelendi ve 119'unda (%54.5) yeni KTO saptandı. Preoperatif proksimal darlığın ≥%90 olması 3 kat daha fazla yeni KTO gelişimi ile ilişkili bulundu (%67.8 vs. %22.2) (p<0.001). İkili antiplatelet tedavisinin nativ koroner arterlerin açıklığını koruyucu rolü olduğu tespit edildi (HR:-0.259; %95 CI:-0.475'den -0.017'ye; p=0.036).

Sonuç: Nativ koroner arterlerde postoperatif yeni KTO gelişimi CABG hastalarında sık görülmektedir. Preoperatif darlığın daha ciddi olması ve ikili antiplatelet tedavinin yokluğu yeni KTO gelişimi için temel faktörler olarak bulundu.

Anahtar kelimeler: koroner arter bypas greftleme; nativ koroner arterler; kronik total oklüzyon

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Introduction

Coronary artery bypass grafting (CABG) is a well-known surgical technique for the management of diffuse coronary artery disease (CAD). For over 50 years, CABG has been recognized as an effective and safe procedure for critical CAD [1] and in recent years, surgical techniques have evolve considerably: shorter cardio-pulmonary bypass times, global usage of arterial conduits and optimal medical treatment (OMT) strategies have increased the effectiveness of CABG in clinical practice. O n the other hand, CABG patients carry unique problems in their follow-up, such as graft failure and the need of recurrent coronary angiographies (CAG) for anginal attacks, and a substantial number of them undergo recurrent CAG procedures, whereas the majority of these cases have been recognized with patent surgical grafts [2].

Acceleration of CAD in preoperatively non-occluded native coronary arteries, was identified as the responsible factor for the development of recurrent anginal attacks in various studies. Progression of native coronary arterial disease from preoperative stenosis to postoperative total occlusion is an important feature, especially in cases of graft failure [3,4]. De novo total occlusion of a priorly non-occluded native coronary artery in the long-term postoperative period is a problematic situation, because total occlusion in CABG patients generally have a more challenging nature than chronic total occlusions (CTO) in native coronary anatomy without CABG operation [5]. The more diffuse, more calcific nature of total occlusions in native coronary arteries make percutaneous revascularization harder, even impossible, in CABG patients [6].

Clinical data about the postoperative progression of stenosis in native coronary arteries in CABG patients is limited. The main aim of the study was to search the prevalence of postoperative developments of de novo CTO in native coronary arteries in the CABG population, and to define the factors related to de novo CTO developments in native coronary arteries.

Material and methods

This study was approved by the Baskent University Institutional Review Board (Project no: 19/442) and supported by the Baskent University Research Fund.

Study population: We enrolled the patients who had undergone isolated CABG surgery for revascularization of CAD at the Başkent University Hospital Alanya Application and Research Center, in Alanya, Turkey. All CABG patients enrolled in the study population were recorded retrospectively and we searched the percentage of the patients who had a clinical indication of recurrent coronary angiography (CAG) in the first 6 months following the surgery for follow-ups. We specifically did not enroll the CABG patients within the first 6 months of the postoperative period, in order to prevent the effect of probable surgical complications on the statistical evaluation. We recorded the baseline characteristics and medical treatments of the patients who needed CAG, as well as how much time had passed from the CABG to the CAG. The study population was evaluated for the development of “malign graft failure”, defined as the occlusion of both of the vascular graft and the grafted native coronary artery. Non-occluded, but severely stenosed native coronary arteries before the surgical procedure, were selected and we aimed to search the prevalence of new chronic total occlusions (CTO) of native coronary arteries, in the CABG patients.

Exclusion criteria from the study population: The consort diagram of the study population is expressed in Figure-1. We searched all CABG procedures from the hospital computer database and we applied some exclusion criteria:

- Presence of additional cardiac surgery such as valvular interventions at the same time as the CABG procedure
- CABG patients without any recurrent CAG procedure in the postoperative period
- Our inability to access preoperative and/or postoperative CAG data
- Patients with recurrent CAG within the postoperative first 6 months
- Grafted native coronary arteries with a preoperative CTO segment

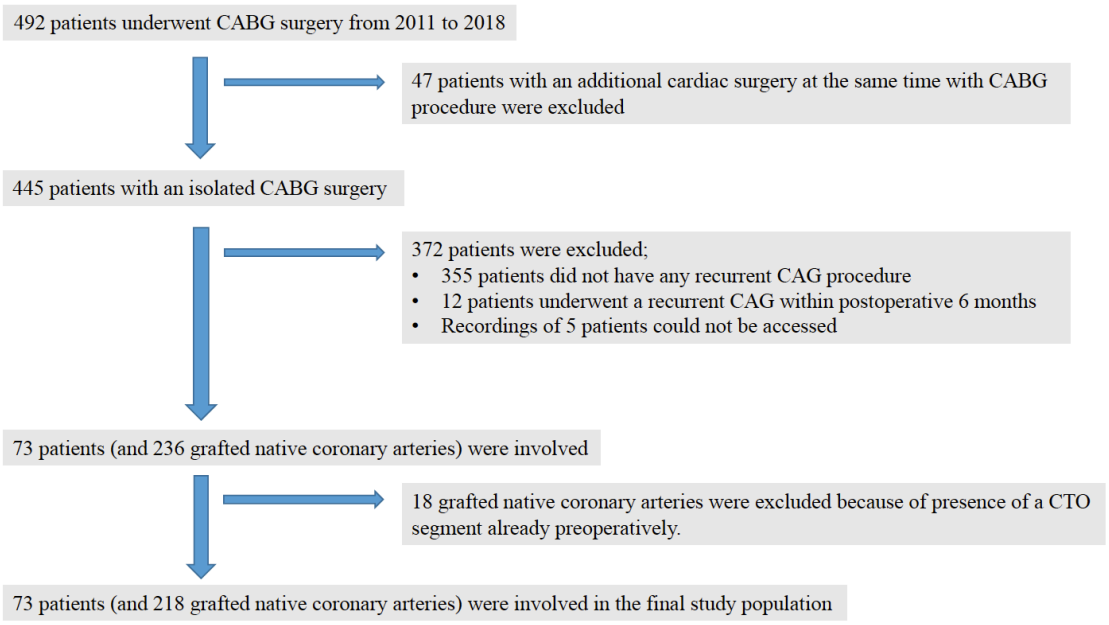

Figure-1: Derivation of the study cohort. CABG, coronary artery bypass grafting; CAG, coronary angiography; CTO, chronic total occlusion

Evaluation of coronary angiographies: All coronary angiography views were selected from the hospital's computer database and two independent cardiology specialists evaluated the views for patency of vascular grafts and native coronary arterial system. CTO were defined (preexisting or newly-developed) as the presumed occlusion of the native coronary artery, at least for 3 months prior to either preoperative or postoperative diagnostic CAGs. Severity of luminal narrowing has been classified as ≥90% or <90% in non-CTO native coronary arteries.

Statistical analysis: Continuous variables were expressed as mean ± SD and median (25th to 75th percentile) and categorical variables as percentages (%). Normal distribution was tested with the Kolmogorov-Smirnov test. Differences between the two groups were tested with the Student-t test and the Mann Whitney-U test for continuous variables, as well as the Chi-square test, for categorical variables. We evaluated the effects of demographical characteristics of the study population on clinical end points, via the multivariable logistic regression analysis. Intraclass correlation coefficient was used to test intraobserver and interobserver differences and their coefficients of variations were calculated as 2.8% and 3.3%, respectively. A p value<0.05 was accepted as significant for all statistical analysis.

Results

A total of 492 patients were found to have undergone a CABG procedure from 2011 to 2018. After the exclusion of patients whose status was in violation of the study protocol, 73 CABG patients were included in the final study population (14.8% of total CABG patients), with a mean age of 65.2 ± 9.8 years and a range of 43 to 87 years, with 56 males and 17 females (a male percentage of 76.7%). We found that a total of 236 native coronary arteries had been bypassed in these 73 patients (3.2 grafts per patient in average). Preoperative CTO of at least one native coronary artery were detected in 24.7% of patients (18 CTOs in 18 patients: there were 218 preoperatively non-CTO native coronary arteries). The time from CABG to recurrent CAG was determined to be a median of 20 months, with a minimum of 6 and a maximum of 85 months. Over 70% of study population had presented as an ACS clinic prior to CABG procedure (52 patients, 71.2% of study population). Most of the patients had undergone an urgent CABG (during the index hospitalization) performed following the basal coronary angiography (75.3%).

We evaluated 218 preoperatively non-CTO native coronary arteries for the development of new

CTO, in the postoperative follow-up. New onset CTO was found in 119 native coronary arteries (119 of 218 vessels: 54.5% of preoperatively patent native coronary bed). New onset CTO in at least one coronary artery was been seen in 72.6% of study population (53 patients). Graft failure were detected in 31 grafts (30 saphenous vein grafts, 1 radial artery graft) from a total of 236 grafts (13.1%). Malign graft failure was seen in 9 grafts from 9 patients (1 graft for each patient); its prevalence was 12.3% of patients (9/73) and 3.8% of total grafts used (9/236).

Approximately one fourth of all grafted coronary arteries revealed a preoperative stenosis of ≥90% (56 of 218 vessels, 25.6% of total non-occluded vessels included). In our study, preoperative severity of native coronary artery disease was found to be related to the development of new CTO. Coronary arteries which were narrowed ≥90% ended with a new CTO more commonly than the arterial stenosis by <90% (67.8% vs. 22.2%) (p<0.001) (Table-1).

Table-1: Effect of severity of preoperative native coronary artery stenosis on the development of new CTO (p<0.001).

		CTO development		
		New CTO (+) (# of vessels)	New CTO (-) (# of vessels)	Total # of vessels
Coronary stenosis (%)	≥90	38	18	56
	<90	36	126	162
	Total # of vessels	74	144	218

Abbreviations: CTO, chronic total occlusion

DAPT (acetylsalicylic acid plus either clopidogrel or ticagrelor) at least in the first year postoperatively was detected in 24 patients (32.9% of study population). DAPT therapy was more common in patients with ACS presentation prior to CABG (91.6% vs. 4.0%) (p<0.001). New onset CTO in native coronary arteries were lower in DAPT group (54.1% vs. 75.4%) (p=0.024). Saphenous vein graft failure was present in 27 patients (36.9%) and DAPT had a tendency to protect from saphenous vein graft failure, though this difference did not reach a statistical significance (45.8% vs. 32.6%) (p=0.310). Comparison of demographical characteristics and laboratory results regarding the presence or absence of new onset CTO, have been outlined in Table-2.

Table-2: Comparison of the demographical and laboratory characteristics of the study population regarding the development of new onset CTO in native coronary arteries.

Parameter	New CTO (+) 53 patients	New CTO (-) 20 patients	"
Age (mean±SD)	64.9±9.9	66.0±9.5	0.679
Male gender (%, N)	69.8 (37)	95.0 (19)	0.029
Time from CABG to control CAG (months) (median, 25th-75th percentile)	21.0 (11.5-42.5)	13.5 (7.0-37.5)	0.175
Diabetes mellitus (%, N)	50.9 (27)	40.0 (8)	0.404
Insulin needed diabetes mellitus (%, N)	22.6 (12)	20.0 (4)	0.808
Hypertension (%, N)	75.4 (40)	60.0 (12)	0.193
Hyperlipidemia (%, N)	35.8 (19)	50.0 (10)	0.270
İliofemoral atherosclerosis (%, N)	9.4 (5)	25.0 (5)	0.085
Carotid artery disease (%, N)	43.3 (23)	55.0 (11)	0.375
Prominent aortic calcification (%, N)	11.3 (6)	10.0 (2)	0.872
Cigarette smoking (%, N)	39.6 (21)	45.0 (9)	0.677
Preoperative glucose (mg/dL) (median, 25th-75th percentile)	111.0 (96.0-181.0)	101.5 (92.2-160.7)	0.390
Preoperative LDL-C (mg/dL) (median, 25th-75th percentile)	126.0 (103.5-156.0)	97.5 (92.0-117.5)	0.003
Preoperative HDL-C (mg/dL) (mean±SD)	39.3±11.5	38.3±9.3	0.733
Preoperative Hemoglobin (gr/dL) (mean±SD)	13.5±1.4	13.3±2.1	0.555
Preoperative Hematocrit (%) (median, 25th-75th percentile)	41.0 (38.3-44.7)	41.9 (38.0-43.4)	0.951
Preoperative Creatinine (mg/dL) (median, 25th-75th percen-tile)	0.9 (0.8-1.0)	0.9 (0.7-1.2)	0.975
Glomerular filtration rate (mL/min) (median, 25th-75th per-centile)	80.0 (65.0-93.5)	91.5 (58.7-95.0)	0.692
LV ejection fraction (%) (mean±SD)	52.0±11.8	54.8±11.8	0.372

Abbreviations: CABG, coronary artery bypass grafting; CAG, coronary angiography; LV, left ventricle

Factors which might have a role in the development of new CTO has been evaluated via a regression analysis. Age, gender, DM, smoking, LVEF, beta blocker or statin therapy were found to be unrelated to the development of new CTO. Only DAPT has shown to have a protective role from the development of new CTO in native coronary

arteries (HR: -0.259; 95% CI: -0.475 to -0.017; p= 0.036) (Table-3).

Table-3: Multivariate regression analysis of clinical factors for the prediction of the development of new CTO of native coronary arteries.

	B	Standardized Coefficients (Beta)	95 % C.I. for EXP (B)		P
			Lower	Upper	
Age (years)	-0.007	-0.147	-0.018	0.004	0.230
Gender (male)	-0.247	-0.234	-0.533	0.039	0.089
Diabetes mellitus	0.015	0.017	-0.200	0.230	0.890
Smoking	0.057	0.063	-0.180	0.294	0.634
Preoperative LVEF	-0.003	-0.081	-0.012	0.006	0.499
Beta blocker usage	-0.097	-0.128	-0.056	0.009	0.241
Statin usage	-0.028	-0.048	-0.165	0.110	0.687
DAPT usage	-0.246	-0.259	-0.475	-0.017	0.036
Constant	1.592		0.588	2.596	0.002

Abbreviations: LVEF, left ventricle ejection fraction; DAPT, dual antiplatelet therapy

Discussion

We found the prevalence of de novo CTO in native coronary arteries in 54.5% of the total grafted vessels. This prevalence is higher than the previous results reported in the literature [7,8]. A delayed latent period between CABG and recurrent CAG may be the reason for a higher de novo CTO percentage in native coronary arteries in our study: indeed, median time intervals between the surgery and the postoperative CAG was approximately 2 years in our CABG population. Additionally, the significance of proximal stenosis in native coronary arteries was found as an important predictor for the development of de novo CTO [8]. Similar to this finding, we found that a proximal stenosis ≥90% is related to more common development of new occlusion in native coronary arteries (67.8% vs. 22.2%) (p<0.001). Independent from the type of conduit used, the presence of a low resistant competitive flow seems to be the main cause of the acceleration of preexisting stenosis in native coronary arteries, in CABG patients [9]. In previous clinical studies, the competitive flow between non-occluded native coronary artery and conduit graft was thought of as the most probable mechanism of either graft failure, or new native coronary occlusion [10-12].

In the PREVENT-IV clinical trial, SVG failure was determined to be 43% at the end of first year postoperatively [13]; our result for SVG failure (13.1% of total SVGs) was therefore lower. Higher percentages of preoperative stenosis ≥90% than previous studies [14] may play a role for increased SVG patency in our CABG cohort. Cataldo et al. found that the SVG patency at the end of postoperative first year was related to several angiographic factors, such as target vessel diameter and coronary territory of right coronary artery, rather than demographical characteristics of the patients [14]. SVG failure with the possible acceleration of atherosclerosis in native coronary arteries, ends up as “malign graft failure”, an essential problem in the follow-up of CABG patients [4]. In our study, the presence of malign graft failures was low (3.8% of total grafted vessels). Otherwise, our population revealed a relatively high prevalence for native coronary arteries stenosed as ≥90% preoperatively (25.6% of total grafted vessels) and this might play a protective role from the development of malign graft failure, because of the absence of an important competitive native coronary artery blood flow.

Recent studies demonstrated the possible advantages of DAPT therapy in CABG patients, such as lower SVG failure at the end of first year postoperatively [15]. A meta-analysis of 22 clinical trials showed that DAPT therapy within the postoperative first year, has a protective role for the patency of SVGs [16]. We did not reach the same result (45.8% vs.32.6%) (p=0.310) but this might be related to our delayed median time interval between CABG and postoperative CAG procedure. Additionally, type II error could not be ignored in the failure of DAPT from protection of SVG disease. The effect of DAPT therapy on the de novo CTO development in native coronary arteries had not been studied before, and we found that DAPT may have a protective role for the patency of native coronary arteries. The new CTO percentage was lower in the DAPT group in our study (54.1% vs. 75.4%) (p=0.024). DAPT may protect the patency of native coronary artery by preventing coronary thrombosis, which can be triggered through decreased blood flow as a result of competition with anastomosed conduit graft. Decrement of blood flow rate in distal coronary bed

can be the main responsible factor in development of coronary thrombosis [15,16]. Beside DAPT therapy, beta blockage and statin treatments were also found in a tendency to prevent de novo CTO in native coronary arteries in CABG patients, but these findings did not reach statistical significance for both of these medications. In the previous randomized studies, optimal medical treatment (OMT) [17-19] was linked to better outcomes in revascularized patients, both in percutaneous coronary intervention and CABG patients. We did not find the similar effect of OMT, but insufficient patient compliance in Turkey to prescribed medical treatments such as beta blockers or statins, because of their possible side effect; this may be the most probable cause for statistical analysis not reaching significance.

In conclusion, de novo CTO development in native coronary arteries is commonly seen in the follow-up of CABG patients. Preoperative significance of proximal stenosis and absence of postoperative DAPT treatment, are the prominent factors related to the development of new total occlusion in native coronary arteries. We should define a sweet spot point for DAPT usage, somewhere between protectiveness from de novo CTO development and increased risk of bleeding. DAPT should be considered in the first year postoperatively, in particular in patients with low bleeding risk. Additionally, we need prospective, randomized clinical trials to search the compliance to medical treatment in CABG patients in Turkey.

Study limitations

Our study has some limitations, namely the fact that it was a single center evaluation with a retrospective design, and we need prospective studies in this context. Small population size is another limitation and may have a possible effects, such as type II error. Additionally, all of the surgeries were performed by the same surgeon, the atherosclerotic progression in the non-grafted native coronary arteries were not evaluated and were not compared with the grafted ones, and we did not examine the effect of vascular conduit type or grafted coronary territory on the development of endpoints. Finally, complications related to medical treatment such as bleeding were not examined in our clinical evaluation.

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