

SAFEN VEN GREFT RESTENOZLARINA PERKUTANÖZ KORONER GİRİŞİM SONRASI GELİŞEN STABİL ANJİNADA PROGNOZ

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Bu çalışmada, ven greftlerine perkutan transluminal koroner anjioplasti (PTKA) sonrası stabil anjina sıklığının tespiti ve PTKA sonrası stabil anjina gelişen hastalarda restenoz için risk faktörleri sunulmaktadır. Çalışmaya toplam 209 hasta alınmıştır, bunlardan 198'ine başarılı transluminal koroner anjioplasti uygulanmıştır.

36 ay boyunca izlenmiştir (23±10 ay), %25 hasta ven greft restenozuna bağlı stabil anjina semptomları gelişmiştir. Stabil anjina gelişen hastalarda yüksek kolesterol seviyesi daha yüksek bulunmuştur (%82'ye %49), implante edilen stent oldukça sıktır (%47'ye %73, p=0.035), ve rezidüel stenoz kalması daha fazladır (%16±12'ye %8±7, p=0.008). Çalışmada yapılan çok değişkenli regresyon analizinde hiperkolesterolemi (OR: 3.55, 95% CI: 1.64-8.39, p=0.002) ve girişim sonrası art-

mış rezidüel stenoz (OR: 1.04, 95% CI: 1.01-1.07, p=0.04) restenoz nedeni ile oluşan stabil anjina için bağımsız tanımlayıcı faktörlerdir. Hiperkolesterolemili hastalarda subgroup analizi yapıldığında, stabil anjina sıklığı, statin verilmeyenler arasında fazla olmaya eğilimlidir (%52'ye %27, p=0.089).

Sonuç olarak, safen ven greftlerinin balaonla dilatasyonu sonrasında neredeyse çeyreğinde stabil anjina izlenmiştir. Yüksek oranda, restenoz ve stabil anjina tetikleyicisi olarakta hiperkolesterolemi saptanmıştır.

Anahtar kelimeler: Ven grefti, Perkutan koroner girişim, Restenoz, Stabil anjina, Hiperkolesterolemi, Girişimsel kardiyoloji, Hiperlipidemi, PTKA

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INTRODUCTION

Saphenous vein grafts (v. saphena magna) remain the most frequently used conduits in coronary artery bypass graft surgeries (CABG)¹. The usage of these grafts is related to the high risk of the degeneration changes in autografts, therefore the treatment of the patients with atherosclerotic lesion of coronary grafts remains a difficult task in cardiology and cardio-surgery². Nearly 30 % of vein grafts degenerate during 1 year, during the following years the amount of relapses increases considerably^{3,4,5,6,7} and reaches 48% by 5 years⁸. Repeated CABG surgery, as compared to the original surgery, is accompanied by the increased mortality^{9,10,11}. In addition, the risk of the perioperative myocardial infarction (MI) is much higher in case of the repeated surgery whereas the amount of patients without severe cardiovascular complications and events decreases considerably^{12,13}. The success of percutaneous transluminal coronary angioplasty (PTCA)

in vein grafts lesion treatment currently makes up to more than 90%^{3,14} and it is the method of choice¹⁵. The patients who go through vein grafts percutaneous interventions constitute 10%-15% of the total work content of the laboratories carrying out a large number of interventions¹⁶. Under such conditions, hospital mortality in this group of patients does not exceed 1%, MI develops in less than 4% of cases, and the need for the emergency CABG surgery is about 2%. However, restenosis in the treated segment of the vein graft occurs during 6 months in 42%-61% of cases^{14,17}.

Therefore, the aim of the present study is to estimate stable angina (SA) frequency resulted from restenosis after PTCA of the vein graft and to detect the risk factors of SA.

MATERIALS AND METHODS OF THE STUDY

Criteria of Patients Selection and Elimination: The present study includes 209 patients hospitalized with the native lesion of the vein graft after CABG from 1997 to 2005. All patients demonstrated objective and subjective symptoms of ischemia due to the lesion of the

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Table 1: Baseline characteristics

Parameters	
Age, years	61.5±8.3
Women (%)	24
Age of vein graft, months	121±52
Prior MI (%)	28
Stable angina (%)	78
Diabetes mellitus (%)	22
Hypertension (%)	52
Hyperlipidemia (%)	60
Smoking (%)	22
Obesity (%)	16

grafted segment of the myocardium. SA was the indication for the coronary angiography and bypass angiography in 78% of cases. The written informed consent for PTCA was taken from all patients prior to the start of the invasive treatment.

The present study does not include the patients who either underwent PTCA of the vein graft earlier or had vein autograft occlusion or an arterial graft lesion. Other elimination criteria comprise an acute MI during the first 7 days and allergic reaction to aspirin or clopidogrel.

PTCA

All PTCA of the vein graft were performed through the femoral approach according to the standard technique. Only more than 55% stenosis of vessel diameter were undergone to interventions. Heparin was injected as a bolus of 10,000 unit at the beginning of the intervention and then was added during the procedure to maintain the activated clotting time of more than 300 seconds. Balloon angioplasty was accompanied by stent implantation in case of suboptimal angiographic result or intima dissection. Suboptimal result was regarded as residual stenosis of more than 30% of the vessel lumen. All implanted stents (Ephesos, TAIS, BioDivysio, NIR) were metal matrix balloonexpandable constructions. Stents were deployed under 14 atmosphere balloon pressure. On the day of stenting the patients received 300 mg dose of clopidogrel and continued to receive 75 mg dose per day during the next 2 months. In addition, all patients permanently got 80-125 mg of aspirin per day. In case of the high risk of complications, glycoprotein IIb/IIIa inhibitor tirofiban was administered at the cardiologist discretion. Quantitative angiographic analysis was made initially as well as after PTCA in all cases.

Immediate, Hospital and Remote Outcomes Assessment: The intervention was considered to be successful if residual stenosis was less than 50% of

vessel diameter and there were no apparent complications (death, acute vessel closure with MI development, emergency CABG surgery).

Thrombosis was diagnosed if after contrast agent injection the uncalcined intraluminal filling defect was visualized on the angiogram and proved in several projections¹⁸.

The demographic data, including the angina anamnesis, the existence of prior MI, the existence of atherosclerosis and restenosis risk factors, and also the period from CABG surgery to hemodynamically important degeneration changes, was collected from all patients with vein grafts lesions. Arterial hypertension was considered to be a risk factor if a patient was on the hypotensive therapy and/or showed the increase of blood pressure in anamnesis. Diabetes mellitus was regarded as a risk factor if a patient received insulin or received hypoglycemic preparation perorally. Obesity was accounted as the increase of the body weight index of more than 27 kg/m². SA was diagnosed according to the criteria of ACC/AHA. The onset of SA after PTCA was the end point of the follow-up of a patient. All patients rehospitalized with SA were catheterized. Restenosis was regarded as the repeated luminal narrowing of the vessel of more than 50% in the area of the dilatated lesion developed during 9 months after the intervention. The lesions in other vein grafts or coronary arteries that became hemodynamically important (more than 50% of vessel lumen) during the period of 9 months follow-up were accounted as disease progression with no connection to the conducted endovascular intervention.

Cholesterol level was detected before conducting PTCA. The level of cholesterol of more than 5.2 mmole per liter, high-density lipoprotein of less than 0.9 mmole per liter, low-density lipoprotein of more than 3.4 mmole per liter, triglyceride of more than 2.3 mmole per liter and the cholesterol/high-density lipoprotein ratio of more than 4.7 were attributed to hypercholesterinemia. The cholesterol level of more than 5.2 mmole per liter (0.7±0.2 mmole per liter) was observed in 34 cases, high-density lipoprotein level of less than 0.9 mmole per liter - in 20 cases (0.7±0.2 mmole per liter), low-density lipoprotein level of more than 3.4 mmole per liter - in 23 cases (4.3±0.5 mmole per liter), triglyceride level of more than 2.3 mmole per liter - in 24 cases (3.7±1.1 mmole per liter), and the cholesterol/high-density lipoprotein ratio of more than 4.7 - in 45 cases (6.1±0.9).

Statistical Analysis: Quantitative values are presented as mean±standard deviation. The "X²" criterion or Fisher's exact test was used when assessing qualitative values. Portions were correlated by z-cri-

Table 2: Data of patients with and without recurrence of stable angina

Parameters	Group 1, (n=24 patients)	Group 2, (n=76 patients)	P
Age, years	61.2±8.1	62.1±9.2	NS
Women (%)	25	23	NS
Prior MI (%)	32	25	NS
Hyperlipidemia (%)	82	49	0.019
Hypertension (%)	59	48	NS
Diabetes mellitus (%)	24	21	NS
Smoking (%)	25	19	NS
Obesity (%)	17	14	NS
Age of vein graft, months	120±52	125±61	NS
Stents (%)	47	73	0.035
Thrombosis during interventions (%)	16	6	NS
Tirofiban given (%)	14	12	NS
Stenosis before intervention (%)	75±11	78±9	NS
Residual stenosis (%)	16±12	8±7	0.008

NS - not significant

terion to Yate's correction or Fisher's exact test. End points results were compared by Student's t-test. Step-by-step logistic regression model which included variables, was used for searching the indications of SA development resulted from restenosis after PTCA. The results of the regression analysis for every significant variable were presented as odds ratio (OR) and its 95% confidence interval (CI). The level of $p < 0.05$ was considered significant for all methods. In the course of the analysis the statistical package "Statistica 6.0" (StatSoft Inc.) was used.

RESULTS

Immediate and Proximate Results: PTCA was successfully performed in 198 out of 209 cases (94.7%). MI with Q wave in ECG developed in 7 cases (3.5%). Three patients died in the next several hours after PTCA (1.4%). MI without Q-wave developed in 4 cases (2.1%). Thereby, the analysis includes 198 patients after successful PTCA of the vein graft. Their main data is presented in Table 1. Patients' mean age is 61.5 ± 8.3 years old (from 40 to 83 years). The medium period after CABG till PTCA was 121 ± 52 months (from 1 to 262 months, the median is equal to 132 months).

PTCA was successful in 31% of cases. With the suboptimal result, in 69% of cases it was accompanied by the implantation of the balloonexpandable coronary stent. In the course of PTCA 13% of patients needed pharmacological assistance of glycoprotein IIb/IIIa inhibitors (tirofiban).

23% of patients were undergone to PTCA in the vein graft to the left anterior descending coronary artery (LAD), 9% - in the vein graft to the diagonal

branches (DB), 32% - in the vein graft to the obtuse marginal arteries (OMA) from the circumflex artery, and 36% - in the vein graft to the right coronary artery (RCA). Lesions underwent to PTCA were located in 31% of cases in the vein graft ostium or proximally, in 57% of cases - in the middle segment, and in 12% of cases - distally or in the area of anastomosis with the coronary artery.

Hospital Results and Further Follow-up: Hospital outcomes were analyzed prospectively. The follow-up of patients after the discharge from the hospital was conducted during 23 ± 10 months (from 1 to 36 months). During this period 61 patients were rehospitalized with the symptoms of SA. All 61 patients were performed to the control coronary angiography and bypass angiography. Restenosis of more than 50% of the vessel lumen was detected in 49 cases (25% out of all patients with successful PTCA or 80% out of all cases of SA after PTCA). SA was caused in 7 cases by the disease progression in the coronary arteries and in 5 cases by the lesion in other vein grafts. Restenosis developed on average in 7.8 ± 6.2 months and was considered to be early if it occurred during the first month and late if it occurred after 9 months (to 30 months in our follow-up).

Description of Patients with SA and Restenosis: The differences between the patients who had SA resulted from restenosis after PTCA of the vein graft (group 1, 49 patients) and the rest of the patients without restenosis in the dilated vein graft segment (group 2, 149 patients) were analyzed (Table 2). Hypercholesterinemia frequency (82% for group 1 versus 49% for group 2) was significantly higher ($p = 0.019$) in group 1 of the patients with SA.

Figure 1: Patient A., 53 years, with hyperlipidemia. Degenerate changes (90% stenosis) in vein grafts to the obtuse marginal arteries.

Figure 2: Patient A, 53 years. Vein graft with implanted stent. Residual stenosis 10%.

Interestingly, the patients from group 1 had much higher residual stenosis after PTCA if compared to the patients from group 2 ($16\pm 12\%$ versus $8\pm 7\%$, $p=0.008$), but PTCA in group 1 lead to the stent implantation much rarely compared to group 2 (47% versus 73%, $p=0.035$). The tendency of the more frequent thrombosis after PTCA in group 1 (16% in group 1 versus 6% in group 2, $p=0.284$) did not reach significant values. No notable differences between the groups in the frequency of tirofiban application during PTCA were recorded.

The vein graft lesion localization did not have significant intergroup differences. 15 patients in group 1 (31%) and 45 patients in group 2 (30%) had proximal lesions, 26 patients in group 1 (53%) and 88 patients in group 1 (59%) had lesions in the middle segment of the vein graft, and 8 patients in group 1 (16%) and 16 patients in group 2 (11%) had distally located lesions. Coronary basin suffering from the vein graft lesion were also similar between groups 1 and 2. Vein grafts to LAD were undergone to dilatation 6 cases in group 1 (12%) and in 34 cases in group 2 (23%), to DB - in 4 (8%) and 16 (11%), to OMA - in 20 (41%) and 46 (31%), to RCA - in 19 (39%) and 53 (35%) accordingly. The percentage of stenosis in the vein graft before PTCA did not have significant intergroup differences ($75\pm 11\%$ in group 1 versus $78\pm 9\%$ in group 2). Stable angina frequency forced by the native lesion in the vein graft was similar in both groups (36 patients {74%} in group 1 and 113 patients {76%} in group 2).

Restenosis and Stable Angina Risk Factors: During the first stage analysis, all variables which could

have been related to restenosis and SA development according to the results of the previously conducted studies and to our opinion were included in the multi-factor logic regression model. As it turned out, hypercholesterinemia was to the most degree connected with restenosis progress and SA development after PTCA in the vein graft (OR: 3.55, 95% CI: 1.64-8.39, $p=0.002$). Residual stenosis, as it appeared, influenced the development of restenosis and SA rather weakly, though it also appeared to be an important predictor (OR: 1.04, 95% CI: 1.01-1.07, $p=0.04$). Lesion localization (proximal, in the middle of the vein graft, distal), age of the vein graft, stent implantation and tirofiban application in this general model did not affect restenosis and SA prognosis.

Nevertheless, when at the next stage analysis residual stenosis after PTCA was not included in the model, it turned out that stent implantation appears to be a significant predictor of the decrease of restenosis and SA frequency (OR: 0.41, 95% CI: 0.22-0.73, $p=0.01$). Still in this model, obesity, smoking, diabetes mellitus, arterial hypertension as well as patients' gender did not become important predictors of restenosis and unstable clinical course.

In the present study, hypercholesterinemia before PTCA in the vein graft was observed in 118 cases (60%). 91 patients had been on lipid-lowering therapy before PTCA while 27 patients after CABG attained the normalization of the cholesterol level with the help of the diet and life-style modification. 31 patients received pravastatin after CABG, 23 - simvastatin, 30 - lovastatin, 29 - atorvastatin, and 11 - fluvastatin (6 patients received several drugs in dif-

Figure 3: Patient A, 53 years. Restenosis (60%) in stent in vein graft after 5 month

ferent time intervals). After PTCA in the vein graft several patients were prescribed different statins and 1 patient was exposed to lipid-lowering therapy. Thus, after PTCA 33 patients received pravastatin, 24 - simvastatin, 29 - lovastatin, 24 - atorvastatin, and 9- fluvastatin. When comparing SA frequency among the patients with hypercholesterinemia, it turned out that 52% of patients (14 out of 27 patients) who did not receive lipid-lowering therapy appeared to be in group 1 with restenosis and SA, compared to 27% (32 out of 118 patients) who received statins but whose tendency towards the increase in SA frequency among those who received statins nevertheless did not reach significant values.

The example of the changes in the vein graft to the OMA of Patient A. aged 53 with hyperlipidemia, the results of PTCA with stent implantation and the posterior restenosis in 5 months period are presented in Figure 1-3.

DISCUSSION

The results of the present study demonstrate that only one quarter of patients exposed to PTCA on the occasion of vein graft degeneration subsequently sustain SA that develops in the dilatation area because of restenosis. According to our data, the disbalance of cholesterol metabolism and residual stenosis appeared to be significant factors that influenced the development of restenosis and SA.

Unlike the restenoses in segments of coronary arteries, restenosis areas in vein grafts contain more cell elements and are less fibrin saturated. During the histologic study of restenosis after PTCA in vein grafts, it turned out that the vein segment with

restenosis contains a lot of necrotic mass, cholesterol inclusions, foamy cells and thrombuses compared to arterial coronary restenosis¹⁹. Abundant foamy cells content and cholesterol inclusions were also observed in degenerated vein segments after the stent implantation²⁰. The study of the stented vein grafts showed that in addition to the fibromuscle hyperplasia, atherosclerosis progression contributes considerably to the restenosis process. The formation of thrombuses was also found in the half of the examined vein grafts²¹. Thereby, SA provocation resulted from vein graft restenosis may be related to the defined pathologic processes.

Risk Factors: In the present analysis hypercholesterinemia appeared to be the most important risk factor of the development of SA after PTCA. The previous studies suggested that atherosclerosis progression after CABG surgery is directly related to the increase of the cholesterol level in blood^{22,23}. Insufficient and conflicting data about the role of residual stenosis after PTCA of the vein graft in the disease progression and SA development was previously known. Initially Foley et al detected the feedback between residual stenosis and restenosis declaring itself in the form of angina²⁴. Afterwards, other researchers established that greater residual stenosis after PTCA is an important predictor of the further adverse clinical events²⁵. In the present study residual stenosis appeared to be a feeble predictor of SA resulted from restenosis.

It is worth mentioning that in the course of the multivariant analysis in the present study, stents application did not appear to be the independent predictor of the favorable outcome without restenosis and SA. Indirect influence of stents on the outcome may be related to the attainment of lesser residual stenosis after PTCA. Since, in spite of the best indirect result, medium-term and long-term outcomes of the stenting but appeared to be comparable to the results of ordinary balloon angioplasty^{26,27}, it is worth paying attention to lesser residual stenosis after stenting in all the previously indicated studies. The tendency to the greater thrombosis frequency before PTCA was observed in group 1, since the angiography compared to the angioscopy or intravascular ultrasound (IVUS) often undervalues the existence of thrombuses²⁸, the application of the angioscopy or IVUS was likely to more accurately divide the groups according to the initial thrombosis frequency. Likewise, not significantly higher hypertension frequency in group 1 could have played its role in the onset of SA. Since the number of patients

who were received glycoprotein IIb/IIIa inhibitors was not relatively big, their infusion did not greatly affect the group results. In the previously conducted researches, glycoprotein IIb/IIIa inhibitors also did not change the late outcomes of PTCA during the angioplasty of the patients with stenoses in vein grafts^{29,30}. The lesion localization as well as the vein graft age were related to the adverse outcomes of PTCA, but they did not become significant predictors of SA resulted from restenosis^{31,32}.

Dislipoproteinemias and Vein Grafts Degeneration: The role of dislipoproteinemia in vein autografts degeneration deserves being discussed further. The progression of intima proliferation as well as the development of atherosclerosis in the vein graft is more often diagnosed with the patients with the cholesterol metabolism disbalance. In the course of the autopsy material examination of the patients with normal and elevated cholesterol levels who had CABG surgery, it turned out that intima thickening and atherosclerotic changes prevailed among the patients with the high cholesterol level³³. Dislipoproteinemia reinforces the production of superoxide anion that, in its turn, stimulates the atherosclerotic process³⁴. The atherosclerosis process in vein autografts increases the risk of the remote insufficiency of the vein graft³⁵ and it is an independent factor provoking vein graft thrombosis and occlusion in the remote period³⁶.

Cholesterol level changes appear to be very important during the atherosclerotic progress of the patients with vein autografts as these effects yield to the modification under the action of lipid-lowering drugs and have the dose-dependent character. In the randomized study of the effect of lipid-lowering therapy to the patients after CABG surgery, it was shown that the increase of the dose led to the lesser frequency of the vein graft occlusions or new lesions³⁷. Compared to moderate lipid-lowering effect, the aggressive influence decreased the occlusions frequency by 31%. Not long ago the researchers found out that the inhibition of the atherosclerotic process in vein grafts can be attained by aggressive lipid-lowering therapy irrespective of the gender, age and other atherosclerotic risk factors such as diabetes mellitus, hypertension, smoking, etc³⁸. In the present study the cholesterol metabolism disbalances appeared to be more powerful predictors of the onset of angina resulted from restenosis. According to the previous observations, the connection between the cholesterol metabolism and vein grafts degeneration as well as the advantages of aggressive lipid-lowering therapy have an important

clinical value. Aggressive lipid-lowering therapy after PTCA in the vein graft can inhibit the degeneration process and lessen restenosis and SA frequency. In spite of the lack of control of the cholesterol level in the course of treatment, we detected the tendency of the decrease in SA frequency in the group of patients receiving statins. The increase in the number of patients of the present study would have made it possible to attain significant differences in the frequency of the adverse clinical events. The limitations of the organization of the present study did not make it possible to determine in dynamics how lipid-lowering therapy influenced restenosis. In this respect it is worth mentioning that the processes of atherosclerosis and restenosis progress differently in coronary arteries and in vein autografts^{19,20,21} and thus, the results of lipid-lowering therapy in the coronary pools should not be projected on vein grafts without an adjustment^{39,40,41}.

Since the present study was planned without randomization, it is possible that the cardiologist's individual preferences during PTCA affected the results of the procedure. But the analysis was conducted prospectively on the consecutively formed patients sampling. The criteria of patients including and elimination were much closer to the real clinical practice than in most specially set up multicentred randomized trials. Angioscopy and intravascular ultrasound were not used in the present study in spite of their greater sensitivity compared to the ordinary digital angiography in the diagnostics of coronary thrombosis⁴². Although angioscopy and intravascular ultrasound excel the ordinary digital angiography in the lesion estimate, they are not available for the wide application in clinics. Therefore, the frequency of the thrombosis detection was most likely underestimated but based on the widely used visual radiomorphological analysis⁴². The importance of this limitation should be really estimated with the subject to 100% specificity of the digital angiography in thrombosis detection²⁸ and also with the subject to the costs of angioscopy and IVUS⁴³. The frequency of the usage of glycoprotein IIb/IIIa inhibitors in the present study was not extensive; they were prescribed at the discretion of the PTCA cardiologist. Thereby, it is difficult to eliminate the influence of the antithrombotic therapy on the outcome, though in the previous studies glycoprotein IIb/IIIa inhibitors did not substantially influence the frequency of the cardiovascular complications and events after PTCA in vein grafts^{29,30}. In spite of the heterogeneity of the group without SA and the lack of the angiographic control of most of the patients of this group, we believe that the

probability of restenosis among these patients is rather low. The previously conducted studies showed that significant restenosis in the vast majority of cases is exhibited clinically⁴⁴. Thus, the performance of the routine control angiography of all patients would not likely have changed the findings.

CONCLUSION

Stable angina resulted from restenosis develops with the quarter of the patients after PTCA of the vein graft. The cholesterol metabolism disbalance causes to the most degree the onset of restenosis and SA. Residual stenosis after PTCA prognosticates the onset of restenosis and SA to a lesser degree. The value of stents implantation lies in the first place in the decrease of residual restenosis after PTCA. Hypercholesterinemia as well as residual stenosis are the modified factors that yield to invasive and medicinal correction. Aggressive lipid-lowering therapy can substantially decrease restenosis and SA frequency after PTCA in the vein graft.

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