Factors influencing graft potency in patients who underwent CABG for treatment of CAD

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Introduction:

Coronary artery bypass graft surgery (CABG) is in use for more than five decades for treatment of patients with coronary artery disease (CAD). Unsolved problem is progression of the disease in bypass grafts and in native coronary arteries. Atherosclerosis is a process which develops in bypass grafts (arterials and veins) as much as in native coronary arteries. Saphenous vein graft disease is composed of three patophysiologically linked processes: thrombosis, intimal hyperplasia, and atherosclerosis. Atherosclerosis and thrombosis are basic processes in coronary artery disease and arterial grafts disease.

Which are the factors that mediate coronary artery graft disease and progression of the disease in native coronary circulation? What is the prognostic meaning of the disease progression and what are the measures that can and have to be done to slow down these processes?

Methods:

We analyzed 102 patients with CAD treated with CABG, who underwent re-coronarography (re-CA) because of AMI, non-stable angina pectoris and/or heart failure. Mean period from CABG to re-CA was 5,97±4,27 years (minimum one, maximum seventeen years). Mean age of the patients was 55,98±8,95 years.

Following data were analyzed:

-pre operative characteristics: risk factors (age, gender, hypertension, hyperlipidemia, diabetes mellitus, obesity, cigarette smoking), clinical and functional status (angina pectoris-CCSC classification and heart failure (HF)-NYHA classification, n-r of ischemic episodes registered by 24-hour ambulatory ECG-Holter monitoring or during exercise stress testing, VT–registered on ECG-

Holter monitoring or during exercise stress testing, METs and MOI calculated from exercise stress testing), left ventricular (LV) morphologic and functional parameters (EF, LV dimensions, segmental kinetics, LV aneurism), and angiographic status (number of diseased vessels, degree of stenosis, calculated Gensini score, EF, LV aneurism);

-per operative characteristics: number and type of conduits, type of revascularization-complete arterial, vein or combined, completeness of revascularization;

-post operative characteristics: risk factors (age, gender, hypertension, hyperlipidemia, diabetes mellitus, obesity, cigarette smoking), clinical and functional status (angina pectoris-CCSC classification and heart failure (HF)-NYHA classification, n-r of ischemic episodes registered by 24-hour ambulatory ECG-Holter monitoring or during exercise stress testing, VT –registered on ECG-Holter monitoring or during exercise stress testing, METs and MOI calculated from exercise stress testing), LV morphologic and functional parameters (EF, LV dimensions, segmental kinetics, LV aneurism) and angiographic status (number of diseased vessels, degree of stenosis in grafts and native coronary arteries (NCA), calculated Gensini score).

Data were gathered threw patients history of disease, physical examination, and consultation of medical reports from clinical investigations: laboratory results, ECG, 24-hour ECG-Hollter monitoring, exercise stress testing, 2-D and Doppler Echocardiography and coronary arteriograpy (CA).

Statistical analysis. Data were analyzed using SPSS software. Continuous variables were reported as mean±SD. Categorical variables were reported as counts (percentages) and compared between groups using a chi-square test.

Continuous variables were examined by a two-tailed t test or by the Mann-Whitney test if not normally distributed. The Spearman rank correlation coefficient was used to estimate the correlation between variables. Freedom from unfavorable coronary events was analyzed by means of Kaplan-Meier curves, with differences between groups tested by long-rank test. The Cox proportional hazard regression models, using a multivariate forward stepping model, were used to examine the time-dependent association between the multiple clinical, functional, echocardiographic, angiographic and per-operative variables and adverse cardiac event occurrence, including cardiac death. For all analyses a p value <0,05 was considered statistically significant.

Results:

Demographic data

Re-coronary arteriography was most frequently performed during the first postoperative year (24,5% of pts), then in seventh (10,8% of pts) and in tenth (10,8% of pts), which is in correlation with the natural history of the disease. Most of re-CA were performed during the first 7 years (68pts-66,6%).

Coronary arteriography findings are presented at Table 1. In average 1,12±0,98 grafts were occluded, and 0,37±0,58 were patent-diseased. In 71 patient native coronary artery progressions disease was found. 41 patients had one occluded graft, 22-two, 7-three and 2 had four occluded grafts. Percentual distribution of patients according to the number of occluded conduits is presented on Figure 1. From 102 patients who underwent re-CA after CABG, 72 (70,6%) patients had graft closure, 33 (32,3%) had non-occlusive graft disease, and in 71 (69,6%) patient progression in native coronary arteries was found.

Although re-CA was most often performed during the first postoperative year, significant difference in disease progression as a function of years after CABG wasn't found (p=ns), which is well documented in Table 2.

Identified prognosticators

We analyzed correlations between graft disease/NCA progression disease from one side, and: risk factors before and after the operation, used medications, data from ambulatory ECG-Hollter monitoring, LV morphologic and functional data, exercise ECG and coronary arteriography data before and after the operation and per-operative characteristics on the other. Variables for which statistically significant correlations were found are presented on Tables 3 and 4. Surprisingly, we found no significant correlations between graft disease and pre/post-operative persistence of risk factors, and pre/post-operative used medications (antiplatelet and lipid lowering therapy). When progression of the disease in native coronary arteries was analyzed, absence of antiplatelet therapy in postoperative period was identified as a significant negative predictor (p=0,026). Graft disease was associated with greater number of diseased vessels before the operation and application of vein grafts. On table 5 we can see that application of vein grafts alone or in combination with left internal mammary artery are significantly associated with graft disease (Pearson Chi-Square p=0.013; Likelihood Ratio p=0.008), which means that more extensive disease before the operation, and greater number of applied conduits leads to earlier graft disease. Progression of the disease in native coronary arteries was associated with more widespread disease preoperatively (greater Gensini score) and more applied conduits.

Multivariate analyze with Cox's regression analyze model identified as independent predictors of graft occlusion (with statistical significance of the model p=0,0001):

-number of diseased vessels before the operation (p=0,010)-more diseased vessels leads to higher probability of early graft occlusion (Graphic 1);

-number of applied conduits (p=0,011)-more applied conduits leads to their earlier closure (Graphic 2);

-antiplatelet therapy (p=0,019)-absence of these agent leads to earlier graft closure (Graphic 3).

Multivariate analyze with Cox's regression analyze model identified as independent predictors of native coronary artery progression disease (with statistical significance of the model p=0,0001):

-Gensini score (p=0,0001)-diffuse distribution of the disease before the operation, leads to its earlier progression;

- antiplatelet therapy (p=0,050)-absence of this agent leads to earlier progression of the disease in native coronary circulation;

-type of applied conduit (p=0,011)-vein conduits are associated with earlier progression of the disease (Graphic 4);

-presence of diabetes mellitus (p=0,020) leads to earlier progression of the disease (Graphic 5).

Prognostic implications:

What are the prognostic implications of graft/NCA progression disease? Is there association between disease progression and cardiac events?

No significant correlation was found between graft occlusion and cardiac events in general. Of 102 patients, 71 have had graft occlusion, 68 of which experienced

some cardiac event, but from 31 patients without graft occlusion, 29 have had cardiac event. Inter-group differences were non-significant (Pearson Chi Square p= 0.898; Pearson's R= 0.899; Odds Ratio=1.052 (0.462-2.365, CI 95%). Statistical significance was found (Pearson Chi Square p=0.253; Spearman Correlation= 0.050) when analyze was performed for different types of cardiac events. Namely, hard events: cardiac death, myocardial infarction and heart failure were significantly more frequent in comparison with soft events or no events (Table 5).

No significant correlation was found between non-occlusive graft disease and cardiac events in general, also. 32 of 34 patients with potent-diseased grafts have had cardiac events, but also 65 of 68 patients without graft disease have experienced cardiac event (Pearson Chi Square p= 0.990; Pearson's R = 0.990; Odds Ratio= 0.990 (0.195-5.027, CI 95%). Significant correlations weren't found neither for the type of cardiac event (Pearson Chi Square p=0.661; Spearman Correlation 0.573), although non-stable angina pectoris was somewhat more frequent in these patients (Table 6).

Statistically significant correlation also wasn't found for progression of the disease in native coronary arteries and cardiac events. 69 of 72 patients with native coronary artery disease progression had some type of cardiac event, but also 28 of 30 patients without such progression had experienced cardiac event (Pearson Chi Square p= 0.867; Pearson's R = 0.868; Odds Ratio= 1.067 (0.475-2.399, CI 95%). As for the type of the event, acute myocardial infarction and non-stable angina pectoris were more frequent in these patients but without statistical significance (Pearson Chi Square p=0.563; Spearman Correlation= 0.166) (Table 7).

Percutany coronary interventions were performed in 45 (44,1%) patients, 21 patient went threw PTCA, and in 24 patients endovascular proteses were implanted. In average 1,3 PTCA were performed per patient (from one to three), and 1,6 stents were implanted (from one to five). PCI procedures were significantly more frequently performed on native coronary arteries-in 30/71 patients, than on grafts-in15/105 patients (p<0,000001) (Table 8).

Discussion:

Which are the factors that influence graft potency? Are there differences between factors that determine saphenous vein grafts potency versus arterial grafts?

Saphenous vein graft potency-disease

Endothelial proliferation is a process which starts as soon as the vein graft is connected to the arterial circulation. Peri-procedural trauma may exaggerate this process and start early graft atherosclerosis. Arterial smooth muscles are adapted to pulsatile flow, but smooth muscle in transplanted veins reacts with proliferative response. Veins are also poorly suited to inhibition of platelet-mediated thrombotic events. These elements constitute three patophysiologically linked processes: thrombosis, intimate hyperplasia and atherosclerosis. These elements are responsible for saphenous vein graft disease, especially after the fifth to seventh postoperative year (1-3). Study of Fitzgibbon et al. refers early vein graft potency of 88%, 81% after one year, 75% at five years, and 50% at 10-15 years. He classified aortocoronary vein grafts as: occluded, patent and diseased, patent with high profile lesion (>59% graft stenosis), and non-diseased vein grafts (3). Factors influencing early potency of saphenous vein grafts are: endothelial injury, technical errors and poor arterial runoff. Absence of antiplatelet therapy leads to

distal anastomosis occlusion. Late graft potency is mainly influenced by conduit atherosclerosis, plaque rupture and late thrombosis, and contributors to these situations are hyperlipidemia, inadequate lipid-lowering therapy, cigarette smoking and diabetes mellitus. Tsukamoto et al. find out that HLP and persistence of $\geq$ three risk factors after CABG, leads to earlier vein graft disease (5). Bypassing of right coronary artery, left circumflex artery and non-sequential grafting also leads to graft closure (1,2,3). There are plenty of evidences witnessing importance of risk factors reduction for the benefit of graft potency. In NHLBI (Post Coronary Artery Bypass Graft Clinical Trial), aggressive LDL Cholesterol reduction (1,6-2,2 mmol/L), was significantly associated with better and longer graft potency (4).

Arterial graft potency-disease

The left internal thoracic artery bypassed to the left anterior descending coronary artery is the single greatest positive predictor of longevity of graft potency. Internal thoracic artery is biologically better graft compared with vein conduits. It is metabolically active conduit which releases endothelium derived nitric oxide and prostacyclines, which inhibits smooth muscle proliferation, inhibits atherosclerosis and thrombosis, which are the two main determinants of arterial grafts disease (3). Kwang Ree Cho documented better arterial versus vein grafts potency after the first and fifth year. He, and hiss colleges also refer better arterial grafts potency when connected to LAD, and similar potency vs. vein grafts when connected to other coronary arteries. The lowest graft potency is when RCA is bypassed (7). In IMAGE study (8), Berger and al. refers that there isn't significant difference in graft potency during the first postoperative year between arterial and vein grafts, but differences appears after seventh year. This same result was

referred in CABADAS study also (10). Alderman (9) find out that retained graft potency is a result of use of internal thoracic artery, larger size of recipient coronary artery, and better blood flow through the grafts and aspirin therapy. Complete arterial revascularization using BIMA (left and right internal thoracic artery), which can be supplemented by radial or gastroepiploic artery with the method of sceletonisation and T grafts, at this moment is considered as the ultimate treatment of myocardial revascularization despite all disagreements, mostly about technical aspects of the treatment. Survival curves between combined and complete arterial revascularization begins to separate over 10-12 years after CABG (3, 11,12). Importance of risk factors reduction, especially LDL cholesterol and diabetes, is also well documented and for arterial grafts potency (13).

Native coronary artery progression disease

Progression of the disease in native coronary arteries is a combined process of atherosclerosis and thrombosis. Pregowski found no difference in the structure of ruptured atherosclerotic plaque in natural coronary arteries, arterial or vein grafts (14). Factors influencing progression in native coronary arteries are bed control of risk factors, hyperlipidemia, diabetes mellitus, inappropriate lipid-lowering therapy, incomplete revascularization, subtotal occlusions found preoperatively, inappropriate graft insertion (1,3).

What is the clinical significance of graft disease?

Graft disease and progression of the disease in native coronary circulation is associated with worse clinical outcome. The greatest incidence of adverse reactions is registered when grafts to LAD are diseased. Surprising was the fact brought by Zafrir and al., who referred existence of myocardial ischemia in LIMA

to LAD vascular territory bypass grafting even in the absence of significant stenosis of LIMA. They found out that discrepancy and decreased ratio LAD/LIMA is a reason for the ischemia, and occurs when LIMA diameter is smaller than LAD diameter. Such situations can also be present in “steel syndromes” mostly from subclavian artery and powerful intercostals branches, arterial tendency for vasospasm, hypotension, myocardial stunning and bypassing of non-totally occluded arteries (1,3,15). With almost the same incidence of graft disease, women have worse clinical outcome, with greater incidence of cardiac death, myocardial infarction and more frequent need for re-revascularization (16, 17). Angina pectoris is soft event which appears in the first two years after the operation in about 3-4% of patients, and its appearance threw the following years progressively rises. It is a result of progression of the disease, more often is present in patients with uncontrolled risk factors, especially obesity, absence of lipid-lowering therapy, incomplete and/or vein grafts revascularization, and also is dependent from previous anginal status and left ventricular function. Hard events (cardiac death, myocardial infarction and non-stable angina pectoris) are less frequent, but mostly associated with vein grafts, and occlusion of the graft for LAD (1, 2, 3, 9).

Measures to stop the progression of the disease:

Regression of plaque area may be achieved by: depletion of cholesterol esters, which may stabilize the plaque and reduce the stenosis by 10-20%, lyses of occlusive or mural thrombi wound healing that may favorably remodel an acutely disrupted plaque and arterial remodeling through relaxation of arterial vasomotor tone (3). Measures to stop progression of the disease are focused on diminishing of restenosis and thrombosis with pharmacotherapy (mainly with antiplatelet

agents, not with anticoagulants, lipid-lowering therapy, vasodilator therapy (in arterial conduits with long acting nitrates, not with diltiazem), and with percutany coronary interventions (PTCA and/or stenting) (3). For a long period of time interventional cardiologists were not very happy to intervene in grafts. But now there are several reports on this subject. ATLAS Trial reports that PCI procedures performed on SVG are safer with premedication with GP IIb/IIIa inhibitors, but not with the acolysis. Leineweber suggests that stenting of the SVG ruptured plaque has to be performed with distal protection, because of rich with vasoconstricting mediators-debris releasing and worsening of micro vascular perfusion (16,18,19).

Distribution of re-coronary arteriographies during years after CABG in our patients was typical for the natural evolution of the disease. The most frequent were during the first postoperative year, which correlates with the period of early graft disease, in vein, but also in the arterial conduits (especially when radial artery was applied). Second critical period was between fifth and seventh year, which is the period of occurrence of vein graft disease, and the third critical period was tenth year-period when arterial grafts disease is expected.

There weren't significant differences in factors influencing graft disease and progression of the disease in native coronary arteries. In our patients, usage of vein grafts as conduits, more conduits (which means less sequentional grafting), bypassing of obstructed but not-occluded coronary arteries ("steal" threw native artery), absence of aspirin and lipid-lowering therapy and diabetes were identified as factors that accelerate and aggravate grafts and native coronary arteries disease. Graft occlusion was associated with cardiac death, acute myocardial infarction and heart failure, while non-occlusive graft disease and native coronary artery

progression disease was associated with angina pectoris. But surprisingly, we failed to find statistically significant differences in occurrence of cardiac events in our patients as a function of presence/absence of graft disease. The number of registered cardiac events in our study was very high. Reasonable explanation lies in the study design. This was opservational study which analyzed patients who underwent re-CA after CABG because of some event: AMI, APNS or heart failure, so at the time of performing the re-CA, patients were already experiencing some type of cardiac event. If patient selection was done from stable patients (relatively asymptomatic), results about the prognostic implication of graft disease probably would be much different. We feel that this is a great limitation of our study.

In our patients PCI procedures were conducted significantly more often on native coronary arteries in comparison with vein grafts, which can be explained with suitability of the diseased vessels for PCI procedure.

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Structured abstract

Objectives: to identify factors that influence graft disease and native coronary arteries progression disease and prognostic implication of this process.

Background: Unsolved problem in CABG patients is progression of the disease in bypass grafts and native coronary arteries.

Methods: Data from 102 patients with CABG, who underwent re-coronarography, were analyzed:

-Pre and post-operative variables: risk factors, clinical status, functional capacity, left ventricular parameters and angiographic status (before and after CABG);

-Per-operative characteristics: number and type of conduits, type of revascularization, number of applied conduits;

Statistical analysis. Two-tailed t test, chi-square test, Spearman rank correlation coefficient, Kaplan-Meier curves, Cox proportional hazard regression model, were used, $p<0,05$ was considered statistically significant.

Results: Coronary arteriography was most often performed during the first, seventh and tenth post-operative year. There wasn't any significant difference in disease progression as a function of years after CABG. Diabetes, antiplatelet and lipid-lowering therapy, n-r of diseased vessels, disease widespreadnes before the operation, vein grafts and number of applied grafts were identified as predictors of graft disease/native coronary arteries progression disease. Significant correlation with the type of cardiac event was found. Cardiac death, myocardial infarction and heart failure were more frequent in patients with graft occlusion, non-stable angina pectoris in non-occlusive graft disease, which together with acute myocardial infarction was more often in patients with native coronary arteries progression disease. PCI was significantly more often performed on native coronary arteries.

Conclusion:

Graft disease and native coronary artery progression disease is a continuous process which can be slowed by aggressive risk factors reduction, medications, and PCI procedures. In contrary, it leads to unfavorable clinical outcome.

Kay words: graft disease, risk factors, cardiac events

Condensed abstract

Graft disease/native coronary artery progression disease is a continuous process that leads to unfavorable clinical outcome. Diabetes, antiplatelet and lipid-lowering therapy, number of diseased vessels before the operation, vein grafts, number of applied grafts were identified as predictors of this process, which can be slowed by risk factors reduction, medications, and PCI procedures, that can be safely performed on grafts as on native coronary arteries.