ORIGINAL RESEARCH

Relationship between elevated platelet volume and saphenous vein graft disease

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Manuscript submitted 13th December, 2009

Manuscript accepted 4th April, 2010

Clin Invest Med 2010; 33 (3): E161-E167.

Abstract

Background: Saphenous vein graft (SVG) disease is the major determinant of long term graft viability in patients undergoing coronary artery bypass graft (CABG) surgery. Although, platelets play a major role in this pathogenetic process the nature of this interaction has not been yet been clarified. Mean platelet volume (MPV) reflects platelet production rate and stimulation. This study was designed to investigate MPV in patients with late stage SVG disease.

Methods: The study population composed of 188 patients who underwent elective coronary angiography more than one year after coronary artery bypass surgery. The study population was divided in to two groups according to SVG patency. The first group consisted of 90 patients (75 men, 15 women; mean age, 63.4 ± 9.2 years) with patent SVG's (no-stenosis group). The second group consisted of 98 patients (80 men, 18 women; mean age, 62.1 ± 10.1 years) with SVG stenosis based on the results of coronary angiography (stenosis group). Greater than 50% stenosis within the SVG was accepted as hemodynamically significant.

Results: MPV were significantly higher in patients with SVG disease in comparison with the patients without graft disease group (9.3 ± 1.19 vs. 8.3 ± 1.10 fl, respectively, $p < 0.001$). In a multiple regression model, SVG disease was independently associated with MPV ($\beta = 0.837$, $p = 0.05$) along with LDL-cholesterol ($\beta = 0.159$, $p = 0.008$) and time interval after bypass surgery ($\beta = -0.092$, $p = 0.05$).

Conclusion: Platelet volume, and therefore platelet activation, appears to play a causal role in late SVG disease graft disease; hence, MPV may be useful as a post-operative marker of graft success.

Coronary artery bypass graft (CABG) surgery is effective in relieving the symptoms of angina and prolonging survival in a certain group of patients. Unlike arterial grafts, the saphenous vein graft (SVG) has poorer patency due to more susceptible to early and late atherosclerotic degeneration. SVG disease, therefore, is a major determinant of long term graft viability in patients with CABG.^{1,2} During the first year after bypass surgery up to 15% of venous grafts are occluded and by 10 years 50% of vein grafts are occluded and nearly one-half of the patent grafts show angiographic evidence of atherosclerosis.^{1,3}

On the basis of clinical trials and experimental studies, SVG disease is comprised of three discrete processes: thrombosis (first month after CABG), intimal hyperplasia (between one month and one year), and atherosclerosis (>one year after CABG). All three processes are pathophysiologically interdependent and platelets play a major role in each step.⁴⁻⁶

Mean platelet volume (MPV) reflects the platelet production rate and stimulation. It has been reported that elevated values of MPV are associated with a number of cardiovascular diseases.^{7,8} MPV has also been shown to increase in response to acute myocardial infarction, acute ischaemic stroke, preeclampsia and renal artery stenosis.⁹ In addition, several reports

have demonstrated that there are close relationships between increased MPV and cardiovascular risk factors such as impaired fasting glucose, diabetes mellitus, hypertension, hypercholesterolemia, obesity and metabolic syndrome.¹⁰⁻¹⁶

Thus, increased MPV values may be associated with SVG patency after CABG surgery. The aim of our study was two-fold: first, to determine whether MPV is increased in patients late SVG disease, and secondly, to evaluate the relationship among MPV and other factors associated with SVG.

Methods

Study population

The study population was composed of 188 patients (155 men and 33 women) who underwent elective coronary angiography more than one year after coronary artery bypass surgery. The study population was divided in to two groups according to SVG patency. The first group consisted of 90 patients (75 men, 15 women; mean age, 63.4 ± 9.2 years) with patent SVG's (no stenosis group). The second group consisted of 98 patients (80 men, 18 women; mean age, 62.1 ± 10.1 years) with SVG stenosis based on the results of coronary angiography (stenosis group). Greater than 50% stenosis within the SVG was accepted as hemodynamically significant. All patients had undergone CABG operation involving the use of at least one SVG for bypass. Clinical indications for coronary angiography were (1) recurrent postoperative stable angina pectoris and (2) preoperative evaluation for non-cardiac surgery. Before angiography, a complete medical history, including coronary heart disease risk factors, was obtained for each patient. Exclusion criteria were determined as (1) unstable ischemic conditions (unstable angina pectoris and myocardial infarction), (2) severe valvular heart disease, (3) uncontrolled hypertension, (4) renal or hepatic dysfunction (creatinine >2.5 mg/dl, AST and ALT > 2 times upper limit of normal, respectively),

and (5) acute or chronic infection, abnormal hematocrit and/or abnormal white blood cell count and/or abnormal platelet number. The body-mass index (the weight in kilograms divided by the square of the height in meters) was calculated for each patient. Patients who had smoked within one year of angiography were considered as current smokers. Hypertension was defined as a systolic/diastolic blood pressure of $\geq 140/90$ mmHg on one or more occasions, or if the patient was on antihypertensive medication. Diabetes mellitus was diagnosed by a fasting serum glucose level of >126 mg/dl or an arbitrary serum glucose level of >200 mg/dl or if the patient was treated with insulin or oral hypoglycaemic agents. All patients gave informed consent.

Biochemical Measurements

Blood samples were drawn without stasis at 7-8 o'clock in the morning after 20 min. of supine rest following a fasting period of 12 hours. Glucose, creatinine and lipid profiles were determined by standard methods. MPV was measured in a blood sample collected in tripotassium EDTA (7.2 mg) tubes. Blood samples were analysed within two hours of venipuncture using an automatic blood counter (A Cell-Dyn 3500, Abbot, IL, USA). The control values for MPV in our laboratory ranges from 7.0 to 11.0 fl.

Coronary angiography

Coronary angiograms were performed using the Judkins technique with 6-French right and left heart catheters. Angiograms were recorded on DICOM digital media (Dicom-viewer, MedCom GmbH, Darmstadt, Germany) at 25 squares/sec and were reviewed by two experienced angiographers who had no knowledge of the patients' clinical information. SVGs were visualised from at least two angles by selective injection of contrast material. An aortic root angiography was performed to assess graft patency when needed. Vein graft disease was defined as a stenosis of more than 50% of the vessel diameter in any saphenous

TABLE 1. Characteristics of the patients with stenosis and without stenotic saphenous vein graft disease

	No stenosis group (n=90)	Stenosis group (n=98)	P value
Age (mean $\pm$ SD)	63.4 $\pm$ 9.2	62.1 $\pm$ 10.1	0.71
Sex (male/female)	75 / 15	80 / 18	0.516
Time interval after surgery (years)	4.93 $\pm$ 1.87	6.43 $\pm$ 2.22	< 0.001
Hypertension	58 (64.4 %)	54 (55.1 %)	0.124
Diabetes mellitus	25 (27.8 %)	35 (35.7 %)	0.156
Body mass index (kg/m ²)	25.6 $\pm$ 4.5	26.1 $\pm$ 4.8	0.721
Smoking	5 (5.6 %)	12 (12.2 %)	0.118
Total cholesterol (mg/dL)	186.2 $\pm$ 44.3	209.7 $\pm$ 43.35	< 0.001
LDL-cholesterol (mg/dL)	112.1 $\pm$ 38.9	127.3 $\pm$ 36.8	0.005
HDL-cholesterol (mg/dL)	44.6 $\pm$ 8.6	42.9 $\pm$ 7.8	0.235
Triglyceride (mg/dL)	149.9 $\pm$ 83.4	160.5 $\pm$ 79.7	0.119
History of myocardial infarction	32 (35.6 %)	37 (37.8 %)	0.436
Ejection fraction (%)	54.2 $\pm$ 11.7	52.8 $\pm$ 12.1	0.523
Aspirin	80 (88.8 %)	86 (87.7 %)	0.912
B-blocker	39 (43.2 %)	37 (37.7 %)	0.623
ACE inhibitors	34 (37.8 %)	33 (33.6 %)	0.548
Statins	33 (36.6 %)	36 (36.8 %)	0.854
Internal mammary artery graft	75 (83.3 %)	84 (85.7 %)	0.533
Creatinine (mg/dl)	1.19 $\pm$ 0.9	1.07 $\pm$ 0.4	0.931
Platelets ($\times 10^3$)	245 $\pm$ 61.3	262 $\pm$ 58.3	0.176
Hemoglobin (gr/dl)	14.1 $\pm$ 1.5	15.9 $\pm$ 1.3	0.684
White blood cells ($\times 10^3$)	7.3 $\pm$ 1.4	8.1 $\pm$ 1.5	0.538
Patients with one SVG	25 (28%)	31 (32%)	0.345
Patients with two SVG	32 (35%)	34 (35%)	0.675
Patients with three SVG	33 (37%)	33 (33%)	0.576

LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme; SVG, saphenous vein graft

vein graft and the rest of the patients were classified as no-graft disease. Lesions of anastomosis between SVG and a native artery were excluded from this study.

Statistical Analysis

Continuous variables were given as mean $\pm$ SD; categorical variables were defined as percentage. Differences between groups were tested using Student *t* test for unpaired data, analysis of variance, and χ^2 test when appropriate. The odds ratio and 95% confidence intervals were estimated with a logistic regression model, in which sex, age, diabetes mellitus, smoking, hypertension, hyperlipidemia, low density lipoprotein cholesterol, time interval between bypass surgery and

coronary angiography, and mean platelet volume were included as confounding variables. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (SPSS for Windows 10.0, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

The main characteristics of study population are summarised in Table 1. There were no significant differences between the two groups with respect to age, sex, body mass index, smoking habits, prevalence of diabetes mellitus, previous myocardial infarction history or left ventricular ejection fraction. The time interval between bypass surgery and coronary angiography was significantly longer in the stenotic group. The

FIGURE 1. Comparison of mean platelet volume in both patient groups.

use of salicylates, lipid-lowering drugs, β -blockers and angiotensin-converting enzyme inhibitors were similar in both groups. Creatinine, hemoglobin, white blood cell and platelet counts were also comparable in the both groups.

Although the levels of high density lipoprotein cholesterol and triglyceride were not different, total cholesterol and low-density lipoprotein cholesterol levels were significantly higher in the patients with stenosis than patients without stenosis.

As shown in Figure 1, MPV values were significantly higher in patients with SVG disease compared to patients without graft disease.

Of the 98 patients having diseased saphenous grafts, 33 (32%) had one stenosed vein graft (mean MPV, 9.27 ± 1.17 fl), 39 (40%) of them had two stenosed vein grafts (mean MPV, 9.12 ± 1.17 fl) and 26 (27%) of them had three or more vein grafts disease (mean MPV, 9.94 ± 1.86 fl). MPV values were found to be similar in three subgroups ($p = 0.126$).

Table 2 summarises the reasons for the post-operative coronary angiography. There were no significant differences between two study groups.

In a logistic regression model in which SVG disease was included as a dependent variable together with sex, age, diabetes mellitus, smoking, hyperten-

TABLE 2. Reasons for coronary angiography

	No stenosis group (n=90)	Stenosis group (n=98)	P value
Stable angina	62	60	NS
Unstable angina	18	30	NS
Elective (e.g., non-cardiac surgery)	10	8	NS

NS: non-significant

TABLE 3. Logistic Regression Analysis for predictors of saphenous vein graft disease

	Odds Ratio (Confidence Interval 95%)	p value
Sex	1.983 (0.641-5.860)	0.241
Age	1.012 (0.970-1.056)	0.585
Diabetes mellitus	0.699 (0.298-1.641)	0.411
Hyperlipidemia	0.420 (0.135-1.303)	0.133
Smoking	0.156 (0.017-1.406)	0.098
Hypertension	1.159 (0.486-2.764)	0.740
LDL-Cholesterol	1.013 (1.002-1.024)	0.008
Time interval after bypass surgery	0.938 (0.857-1.002)	0.050
Mean platelet volume	2.066 (1.392-3.067)	<0.001

sion, hyperlipidemia, low density lipoprotein cholesterol, time interval between bypass surgery and coronary angiography, and mean platelet volume; SVG disease was independently associated with MPV ($\beta=0.837$, $p=0.05$), LDL-cholesterol ($\beta=0.159$, $p=0.008$) and time interval after bypass surgery ($\beta=-0.092$, $p=0.05$). Table 3 presents the adjusted odds ratios for risk of development of saphenous vein graft disease in logistic regression analysis.

Discussion

CABG has become widely accepted and established as an effective therapy for coronary artery disease; however, its long-term efficacy is limited by SVG disease.^{1,2} Many risk factors for SVG disease, including smoking, elevated levels of cholesterol, diabetes and longer intervals after CABG, have been identified.^{17,18} In the present study, we have found that patients with SVG disease have significantly higher MPV values compared to patients without SVG

disease, indicating that elevated levels of MPV and serum LDL-cholesterol are independent risk factors for SVG disease. There were no differences in MPV values in patients with SVG disease with respect to the number of stenotic saphenous grafts.

On the basis of cumulative evidence, several predisposing factors have been associated with reduced vein graft patency: hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, native vessel diameter, effect of gender, grafted vessel, age of graft, severity of bypassed proximal stenosis and plasma levels of lipoprotein(a), homocysteine and fibrinogen.⁶ These risk factors are broadly similar to those recognized for native coronary artery disease. In addition, harvesting of venous conduits is associated with focal endothelial disruption during and after surgery and may also contribute to SVG. Unlike arterial grafts, vein grafts are more susceptible to intimal hyperplasia, arteriosclerosis, progressive stenosis and occlusion. All of these stages of the pathogenetic process are closely associated with platelets and platelet function. Although the potential role of platelets has been evaluated during the development of vein graft disease, their relationship is yet to be clarified. Steele and colleagues have established a relationship between decreased platelet survival and saphenous vein graft occlusion.¹⁹ Similarly, Latour and colleagues have demonstrated that platelet regeneration time was reduced in patients with late occlusion of aortocoronary saphenous vein bypass grafts.²⁰ In a previous study, Aras and colleagues have reported that serum sP-selectin level, which is accepted as an indicator of increased platelet reactivity, was found to be increased in patients with late SVG disease.²¹ These reports, together with and numerous studies demonstrating that antiplatelet therapies improve SVG patency after coronary artery bypass grafting, suggest that platelets play an important role in the development of SVG disease.²² This study was designed to evaluate the relationship between SVG disease and MPV, which has been introduced as a new method for assessment of platelet function, as MPV reflects the

platelet production rate and stimulation. MPV appears to correlate more closely with platelet function than the platelet count alone, since several factors in addition to the platelet count have been shown to influence platelet function, including platelet size, density, age and previous haemostatic interactions.²³ Hemostatically reactive platelets, which are larger platelets, have more granules and adhesion receptors that result in decreased bleeding time showing increased activation.²⁴ An increase in MPV may also be due to the consumption of small platelets during ischemia.²⁵ Thus, MPV reflects both platelet number and activity and has become a prognostic factor in atherosclerotic coronary disease.²⁶ It is known that increased platelet activation and aggregation are closely related to cardiovascular complications.¹⁸ In previous reports, there are different methods that were used for the analyses of platelet activation: optical aggregometry, platelet function analyzer (PFA-100), platelet reactivity test or platelet aggregate ratio, flow cytometry and thromboxane B(2) generation.²⁷ All tests have limitations in their use due to complex preanalytic factors, reduced specificity and poor reproducibility; however, MPV is a simple marker, not requiring advanced or expensive technology

The main limitation of this study is that patients were referred for elective angiography for a variety of reasons. Our findings do not include outcomes of the patients who had acute coronary syndrome or died following CABG surgery. In addition, our study did not include initial or follow-up MPV values. Further prospective studies investigating this relationship - from the beginning of CABG surgery - are needed to elucidate the role of MPV in patients presenting with SVG disease.

Conclusion

Our study is the first to show a significant increase in MPV in patients with SVG disease. This result indicates that platelet activation may play a causal role in late SVG disease graft disease; thus, MPV has the po-

tential to be used as a follow up marker during post-surgical patient management.

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