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Assessment of platelet function by whole blood impedance aggregometry in coronary artery bypass grafting patients on acetylsalicylic acid treatment may advise to switch on dual antiplatelet therapy

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Abstract:

Introduction: Residual platelet reactivity (RPR) following coronary artery bypass grafting (CABG) might be related to thrombotic complications and major ischemic cardiac events. The aim of this study was to evaluate the changes in platelet reactivity, monitored pre- and postoperatively using multiple electrode aggregometry (MEA) and to propose alternative therapeutic approach in subgroup of patients with postoperative RPR.

Methods: 99 patients undergoing elective CABG were enrolled in the study, of those, 41/99 (41.4%) patients were found diabetic. Preoperatively, all patients received 100mg acetylsalicylic acid (ASA), and 47/99 (47.4%) of patients received additionally 75 mg clopidogrel (CLO). The blood samples were drawn day before surgery, first and fourth postoperative day. Platelet count and fibrinogen level were documented, as well as type and daily dose of antiplatelet therapy (APT), received pre- and postoperatively. MEA using ASPI and ADP test was performed day before and 4 days after surgery.

Results: Preoperatively, we detected 31/99 (31.3%) of patients with RPR (ASPI > 30 AUC). Platelet count correlated with both ASPI (p=0.03) and ADP (0.002) test. Fibrinogen correlated with ADP test values (p<0.001) and was found to have a higher level in diabetic subgroup (p=0.01). Comparing to preoperative results, we detected higher values of ASPI test postoperatively (p=0.04) with 46/99 (46.5%) of patients with RPR despite higher dose of 300 mg ASA administered. Postoperatively, diabetic patients had a higher ASPI test values (p=0.01), and higher proportion of patients with RPR comparing to non-diabetic subgroup (58.5% vs. 38%, p=0.04). Subgroup of patients with detected ASPI >30 AUC at fourth postoperative day, received consequently as a part of our clinical routine, additionally 75 mg CLO per day, in terms of platelet inhibition optimization.

Conclusion: MEA can recognize patients with RPR during the both the pre- and post- CABG period. Postoperatively administered 300 mg ASA, did not sufficiently inhibit platelet

aggregation in 46.5% post CABG patients. In this group of patients switch on dual antiplatelet therapy should be considered.

Key words (MeSH Terms): multiple electrode aggregometry, aspirin, coronary artery bypass, platelet aggregation, aspirin resistance

Introduction

The outcome of coronary artery bypass graft surgery (CABG) depends mainly on the patency of the graft vessels. Graft patency is mainly influenced by the type of the graft used, but also by diameter and degree of atherosclerotic changes of the distal vessel into which the graft is placed. Aortocoronary vein graft disease is comprised of three distinct but interrelated pathological processes: thrombosis, intimal hyperplasia and atherosclerosis [1]. Early thrombosis is a major cause of vein graft attrition during the first month after CABG. Bypass patency can be improved with antiplatelet therapy (APT) which is the mainstay of treatment for patients after CABG. Acetylsalicylic acid (ASA) is the best studied, most used and least toxic of the platelet inhibitors [2, 3]. A beneficial effect of ASA on vein graft patency has been shown during the first year after CABG [4-6]. However, some patients experience adverse cardiac events despite treatment with APT. Some of those events could be caused by residual platelet reactivity (RPR) after APT administration which inevitably suggests need for antiplatelet drug dose increase, or administration of another antiplatelet agent as a supplement. RPR after ASA or clopidogrel (CLO) administration, as assessed by platelet function tests, varies widely among patients, and has been reported to range from 1 to 45% for the 2 drugs [7]. RPR following CABG might be related to thrombotic complications and major ischemic cardiac events. This phenomenon has already been described in literature [8, 9]. RPR can postoperatively be presented as a non-reactive state of platelets to APT. Recently, a new point-of-care assay named multiple electrode aggregometry (MEA) using a device called Multiplate analyzer (Dynabyte, Munich, Germany) has become available at our department for rapid and standardized assessment of platelet function parameters. The aim of this study was to evaluate the RPR using MEA, both pre- and postoperatively in patients following CABG, and to propose the alternative therapeutic approach to patients with observed postoperative RPR to ASPI test. APT in diabetes, however, is still a matter of

intense debate due to a high prevalence of RPR, described elsewhere [10]. Additional aim of our study was to clarify whether diabetic patients following CABG showed a higher rate of RPR after ASA administration.

Materials and methods

Patient selection

The study was conducted in a prospective observational mode. After institutional review board approval and written informed consent, 99 adult men and women scheduled for elective CABG requiring cardiopulmonary bypass (CPB) between August 2009 and March 2010 were prospectively studied. Criteria for excluding patients from the group of subjects were: missing consent, patients with cardiac surgical procedures other than isolated CABG, on APT other than ASA or CLO, patients with inaccurate APT administration documentation or missing data, an urgent surgery, off-pump CABG, redo CABG. In our study cohort APT was administered by the referral cardiologist. All patients were admitted to our department with daily dose of 100 mg ASA which was continued up to day of surgery. 47/99 (47.4%) of patients received daily dose of 75 mg CLO in addition to ASA, and CLO was excluded at our department prior to surgery with individually different time interval from CLO cessation to surgery, from 2 to 8 days, respectively. Time from CLO cessation to surgery varied individually, based on the date of admission to our department and the date of procedure. Patients received APT continuously at least for 10 days prior to admission to our department.

Perioperative management:

All patients had the same anesthetic and perfusion teams, and were admitted at least 1 day before surgery. Surgery was performed in a single unit with standard surgical techniques. Anesthesiologists and surgeons were blinded to the preoperative results of the MEA measurements.

The patients received diazepam and morphine 30 min prior to the induction of anesthesia. Endotracheal tube, urinary catheter, as well as radial artery and pulmonary artery catheters were inserted. The anesthetic regime included induction and maintenance of anesthesia with midazolam, fentanyl and pancuronium bromide. This was coupled with sevoflurane

inhalation. The initial ventilator settings included a tidal volume of 8 ml kg_1, and a respiratory rate of 12 breaths per minute. Typically, the FiO2 was set at 50%. Cardiopulmonary circuit consisted of the Medtronic Affinity Trillium membrane oxygenator, venous reservoir and PVC tubing (Medtronic, Minneapolis, MN, USA) and a Stoeckert III roller pump (Stoeckert, Munich, Germany). It was established via central cannulation, targeting flow at 2.2 l min-1 m-2 and mean blood pressure of 60 mmHg. Heart was arrested with cold blood cardioplegia. Systemic heparinisation aiming at an activated clotting time >480 s was used, followed by full reversal with protamine after decannulation. A dose of 1 g tranexamic acid was given at the induction of anesthesia and after protamine administration. Inotropic support was initiated in order to maintain a cardiac index greater than 2.2 l min-1 m-2. Arterial and venous grafts were used for bypass diseased coronary vessels. The lungs were open to atmosphere during CPB. Weaning from CPB was initiated once the patient's rhythm had stabilized and normothermia had been achieved. Packed red blood cells were added during CPB if the hematocrit level was <20%. Volume replacement in the intensive care unit was administered as deemed necessary by the attending physician using hydroxyethyl starch 6% 130/0.4 and lactated Ringer's solution, Packed red blood cells were transfused if deemed necessary by the consultant anesthesiologist.

Blood Sampling:

Blood samples for MEA measurements were obtained day before surgery and fourth postoperative day using venipuncture, and blood was collected in 4 ml heparin (Lithium Heparin 68 I.U.) coated BD Vacutainer® plastic tubes. Routine laboratory tests were performed each day from day before surgery to fourth postoperative day. The same person, not directly involved in patient care, performed all measurements. Blood samples were at rest for 30 minutes after blood withdrawal and MEA was performed subsequently.

Multiple electrode aggregometry (MEA):

Whole blood aggregation was determined using a new generation impedance aggregometer (Multiplate® analyzer, Dynabyte Medical, Munich). Detailed description of method has already been published [11]. Put briefly, MEA is based on the principle that blood platelets are non-thrombogenic in their resting state, but expose receptors on their surface when they get activated, which allow them to attach on vascular injuries and artificial surfaces. When platelets stick on the Multiplate sensor wires, they enhance the electrical resistance between them, which is continuously recorded. Increase in impedance is expressed in arbitrary area under curve (AUC) units, highlighted as the parameter with the highest diagnostic power [11, 12]. The analysis itself needs 3 min for incubation and 6 min for the measurement after stimulation. Platelet aggregation was determined in response to stimulation with arachidonic acid with a final concentration of 0.5 mM (ASPI test designed to evaluate ASA effect) and adenosine diphosphate (ADP) with a final concentration of 6.4μM (ADP test designed to evaluate thienopyridines, such as CLO, effect). RPR to ASPI aggregation test was defined by an AUC of >30 U (75th percentile of aggregation in ASPI test from 65 control patients with coronary artery disease on chronic 100 mg ASA daily treatment, scheduled for CABG) [13]. This definition is in concordance to literature sources published by our institutional colleagues with the same setting used in cohort of 110 patients with stable coronary artery disease receiving daily dose of 100 mg ASA [14]. Similar results, although with different anticoagulant used for blood sampling for MEA were also described [15, 16].

Statistical analysis:

For statistical analysis we used MedCalc® For Windows software. MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium. The Kolmogorov-Smirnov test was used for evaluating normality of distribution of all continuous variables. Independent t-test was used for two study groups' comparison. Chi square test was used for data comparison between groups. Value of $p \leq 0.05$ was considered statistically significant.

Results

Patients

All patients from the sample were discharged from hospital. Cohort group was divided in the two subgroups regarding preoperative APT. We observed RPR both pre- and postoperatively. No difference occurred among the study group concerning age, sex, and weight. Perioperative laboratory values (hemoglobin, hematocrit, platelet count and fibrinogen level) did not differ among the patients. Descriptive statistics of two groups is presented in Table 1a and 1b.

Platelet count, fibrinogen level, platelet aggregation assessment and residual platelet reactivity prevalence

Considering all CABG patients, we observed 31/99 (31.3%) patients with RPR (ASPI > 30 AUC) preoperatively with no significant difference among the groups regarding APT administered preoperatively (Table 1b). Following the routine clinical protocol, all patients received 300mg ASA postoperatively, starting at first postoperative day. At fourth postoperative day we registered 46/99 (46.5%) CABG patients with RPR despite higher dose of APT, suggesting platelet hyperactivity. Postoperatively registered increase of 15.2% in proportion of patients with RPR was found to be significant, p=0.04. In the group of patients with preoperative registered RPR (n=31), we found in proportion of 18/31 patients (58.1%) with RPR after surgery, while in group with preoperatively adequate platelet inhibition (n=68) we registered proportion of 28/68 patients (41.1%) with RPR postoperatively. Higher amount of patients with preoperative RPR were found to have RPR in postoperative period, but the difference didn't reach statistical significance.

Postoperatively, we detected higher values of both ASPI test, (p= 0.04, shown in Figure 2) and ADP test (p= 0.002, shown in Figure 3) in comparison to preoperative results.

In addition to above mentioned results which suggests postoperative RPR proportion increase, we have found a significant ($p<0.001$) perioperative increase in fibrinogen level (Figure 1). Platelet count and fibrinogen were correlated with ASPI and ADP test both pre- and postoperatively. Preoperatively, we detected significant correlation between platelet count and both ASPI ($p=0.03$) and ADP test ($p=0.002$). Fibrinogen correlated significantly with ADP test values ($p<0.001$). At fourth postoperative day, only platelet count and ADP test correlated significantly ($p=0.01$).

Residual platelet reactivity and diabetes mellitus

We analyzed the difference in the degree of platelet inhibition among patients with respect to the presence of diabetes as a comorbidity, both pre-and postoperatively (Table 2). We found that 41/99 (41.4%) patients were diabetic. In this subgroup of patients, preoperative evaluation of platelet inhibition, revealed 16/41 (39%) of patients with RPR versus 15/58 (25.9%) in non-diabetic subgroup, and the difference was found to be non-significant. We registered higher fibrinogen level in diabetic population preoperatively with respect to non-diabetic patients (4.15 g/L, σ 1.06 vs. 3.66 g/L, σ 0.87, $p=0.01$). Postoperative evaluation of platelet inhibition revealed 24/41 (58.5%) of patients with RPR in diabetic subgroup versus 22/58 (38%) in non-diabetic group, and the difference in proportion of patients with RPR among 2 groups was significant ($p=0.04$). Diabetic patients subgroup had a significant higher postoperative ASPI test values (40.71, σ 27.07), in comparison to non-diabetics (30.28, σ 14.9), $p= 0.01$. Comparing results of preoperative and postoperative measurements, we registered 19.5% increase in the proportion of patients with RPR (from 16/41, 39% preoperatively to 24/41, 58. 5% postoperatively) in diabetic patients compared with 12.1% increase (from 15/58, 25.9% preoperatively to 22/58, 38% postoperatively) in the proportion in non-diabetics subgroup. The difference in patients with RPR proportion increase was not significant.

Residual platelet reactivity and gender

We assessed RPR prevalence with respect to gender both pre- and postoperatively. In female group, preoperative assessment revealed 11/25 (44%) patients with RPR. In male group, 20/74 (27%) patients showed RPR at same time. Postoperatively, RPR occurred in 12/25 (48%) within female, and in 34/74 (45.9%) within male population. Although the differences in RPR prevalence with respect to gender were not significant both pre- and postoperatively it is worth mentioning that male population had postoperative RPR prevalence increase of 18.9% versus 4% in female population.

Of note, we noticed a non-significant difference in prevalence of diabetes mellitus among genders.

Discussion

Our study presumably identified a group of patients with RPR to ASPI aggregation test, sensitive to ASA effect, both pre- and postoperatively. Platelet aggregation, assessed with MEA ASPI test, was not sufficiently inhibited in 46.5% post CABG patients despite 300 mg ASA administered postoperatively. Proportion of patients with RPR was higher postoperatively, despite higher daily dose of 300 mg ASA ($p=0.04$).

Coronary artery disease is a leading cause of death in developing and developed countries [2, 17]. No uniform guidelines exist for the postoperative prevention of thrombotic complications after CABG [18]. It is widely accepted that platelets play a pivotal role in the development of thrombosis [19, 20]. Early graft failure is hypothesized to be related to thrombus development, of which RPR may be an important component [21].

Several laboratory assays are commonly used to assess response to APT. The fact that aggregation in MEA takes place on surfaces is a major difference compared to other methods such as Born aggregometry and single platelet counting. MEA uses anticoagulated whole blood for analysis. Whole blood is the physiological environment where platelet function takes place in vivo, and the use of whole blood for in vitro testing eliminates the need for time-consuming centrifugation steps required for Born aggregation measurements. The ideal anticoagulant for accurate platelet aggregometry remains controversial. Citrate is still now used as the anticoagulant of choice for platelet testing. At our department only citrate and heparin are available as blood sample anticoagulants. Heparin may be used as an anticoagulant for platelet aggregation studies [22, 23] although early literature refers heparin to affect aggregation results [24]. Therefore, different reference interval of test values should be considered. We obtained blood samples by performing anticoagulation with heparin. Truss et al [22] has compared aggregation data obtained performing MEA using either citrate or

heparin as an anticoagulant. MEA responses to arachidonic acid, ADP and collagen, obtained with heparin as anticoagulant resulted in lower values than data obtained with citrated blood. Taking into consideration the fact we regularly use unfractioned heparin as an anticoagulant for MEA we made our own definition of RPR. RPR to ASPI aggregation test was defined by an AUC of >30 U (75th percentile of aggregation in ASPI test from 65 control patients with coronary artery disease on chronic 100 mg ASA daily treatment, scheduled for CABG) [13].

Antiplatelet therapy management:

Based on our data supporting that patients after CABG have hyperactive platelets, the use of low molecular weight heparin as additional thromboprophylaxis may not be the optimal strategy, because low molecular weight heparin does not inhibit platelet function per se. Currently, there is no established therapeutic approach for managing low response to ASA that has been shown in large trials to have clinical benefit. Our data presumably identified a subgroup of patients with RPR following CABG who may be at increased risk for developing thromboembolic complications. In this subgroup of patients higher doses of ASA would not be prudent in terms of worsening endothelial – mediated arterial dilatation [25]. These patients could benefit from a more aggressive antithrombotic treatment regimen such as dual antiplatelet therapy with CLO addition to ASA therapy. CLO is very useful, especially taking into consideration the fact that our study cohort had a higher postoperative ADP aggregation test values ($p=0.002$) which can be specifically inhibited by CLO. However, this therapeutically approach needs randomized control trial with large study group to evaluate the benefit of such treatment. The benefit of such a treatment regimen has been investigated in CASCADE trial [26]. The authors investigated on the impact of dual antiplatelet therapy on venous graft disease in CABG patients. The primary outcome was saphenous vein graft intimal hyperplasia, determined by intravascular ultrasound. Secondary outcomes were graft

patency, major adverse cardiovascular events, and major bleeding. No significant difference occurred regarding both the primary and secondary outcomes between ASA-CLO and ASA-placebo postoperative APT regimen group. The lack of objective quantification of the antiplatelet effect of both ASA and CLO constitutes a major drawback of the study [27]. Nevertheless, since RPR raises the incidence of adverse cardiovascular events and venous graft occlusions, it would seem critical to adjust for this variable [1]. This problem was further amplified by ignoring the variability to CLO response. Therefore, randomization of patients with MEA assessed inappropriate response to ASA on CLO or placebo addition could reveal different results. Further, MEA evaluation of response to CLO in group receiving dual antiplatelet therapy could be useful. Another alternative therapeutic approach is mono antiplatelet therapy with CLO. The Aspirin Non-Responsiveness and Clopidogrel End point Trial (ASCET) is currently evaluating whether switching to CLO will be superior to continuing ASA therapy in improving clinical outcomes in ASA low responders [28]. Our study showed that diabetics are prone to have RPR after ASA administration, especially after CABG. Increased baseline platelet reactivity may be more commonly observed in specific clinical scenario such as diabetes mellitus, as described in literature [10]. APT in diabetes, is still a major issue due to a high prevalence of RPR after APT administration [10]. Higher prevalence of RPR described in our diabetic patients' subgroup might be a major contributor to poorer outcomes among diabetic patients. It has been recently reported that platelet reactivity is tightly associated with glycemic control in diabetics [29]. Elevated glycosylated hemoglobin levels are common among diabetic patients scheduled for coronary surgery, particularly in patients receiving insulin, and are associated with more frequent occurrence of perioperative myocardial infarction [30]. These data suggest that diabetic patients with poor metabolic control and the high degree of platelet reactivity may benefit from aggressive APT strategies [31]. Using MEA to guide APT allowed us individual tailoring therapy after MEA

assessment at fourth postoperative day. Individual tailored therapeutic approach significantly improves clinical outcomes. Awidi et al found that the combination of ASA and CLO had greater inhibitory effects on platelet function than either agent alone [2]. However, we found no significant difference in the proportion of low-responders to ASA between groups with respect to preoperative APT regime strategy. The reasons for such a difference may be the fact that CABG undergoing patients are those who may be considered 'treatment failures' following percutaneous coronary interventions, as described by Preisman et al [32]. Prospective, outcome evaluating randomized trials, with platelet function assessment are needed to clarify the benefits of dual antiplatelet therapy.

Using thromboelastography for assessment of platelet function Bochsen et al suggested that CABG patients are prone to platelet hyperactivity at fourth postoperative day [8]. Although revealed with different assay, study described the same phenomenon as we did. Using modified TEG with arachidonic acid as platelet agonist Preisman S et al showed 44% rate of non-responsiveness to aspirin [32]. Using the turbidimetric method for platelet aggregation measuring, Kempfert et al reported 28.8% patients with RPR before CABG. Postoperatively almost half of patients (49%) developed RPR [33]. These results are similar to the results of our study, although it is worth mentioning that the patients had different postoperative ASA dosing regimens compared with patients in our study. Standard definition to assess antiplatelet drug response has not been fully established and differences in assays, agonist concentrations and cut-off values have contributed to the existing variability [7]. Antiplatelet response to ASA, as assessed by platelet function tests, varies widely among the patients, and that could possibly explain early graft occlusion within the first month after surgery despite appropriate ASA treatment [4]. These results suggest that a more aggressive antithrombotic treatment might be warranted for patients undergoing CABG in postoperative period.

Limitations of study

We have not performed an in house reference interval of normal values of platelet aggregation assessed by MEA with arachidonic acid and ADP as agonists by using heparin as anticoagulant. In addition to, in house studies of imprecision of the method have not been performed. Hemostatic studies are usually performed on citrated blood samples. Due to fact that heparin has been used as anticoagulant in our study, differently by the other authors, we obtained cut off value for RPR, by using the same setting in the 65 consecutive patients requiring CABG.

The study was conducted as prospective observational, and we did not analyze the outcome with respect to MEA results and subsequent APT adjustment. The purpose of study was to evaluate RPR prevalence both pre- and postoperatively, with APT adjustment proposal in RPR appearance. Our study contained no randomization, and the scope of this study was not to identify the event rate of thromboembolic complication with regards to MEA results.

The impact of dual antiplatelet therapy on cardiovascular ischemic events reduction was not evaluated. We did not repeat MEA measurements after APT adjustment so did not distinguish whether the RPR was permanent or temporary. Although we assessed ADP test both pre- and postoperatively we did not assessed preoperatively RPR to ADP test with respect to CLO administration. The reason is in the fact that measurements were performed the day before surgery, and CLO was excluded from therapy in different time intervals from measurements, so technically it would be impossible to mark someone to be CLO resistant, i.e. 5 days after CLO withdrawal.

However, the use of MEA ADP test, sensitive to CLO effect, was useful because it showed a significant increase ($p=0.002$) in values in the postoperative period, which inevitably suggests the use of CLO in patients with detected postoperatively RPR to ASPI test.

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Tables

Table 1.

a) Descriptive statistics of patient groups according to preoperative antiplatelet therapy administered

b) Basic demographic and operative data

*monotherapy group (acetylsalicylic acid), †dual antiplatelet therapy group (acetylsalicylic acid and clopidogrel), ‡ fourth postoperative day, § residual platelet reactivity to ASPI aggregation test

a)

	Groups	N	Mean	σ	P (Mann-Whitney U test)
Platelet count preoperative ($x10^9$/L)	ASA*	52	209.8	58.2	0.166
	DAT†	47	224.7	61.8	
Fibrinogen (g/L) preoperative	ASA	51	3.8	0.9	0.508
	DAT	47	3.9	1.0	
Cardiopulmonary bypass time (min)	ASA	52	95.5	27.4	0.009
	DAT	47	82.5	32.6	
ASPI test preoperative (AUC)	ASA	52	29.4	26.2	0.674
	DAT	47	28.9	20.1	
ADP test preoperative (AUC)	ASA	52	60.0	24.7	0.188
	DAT	47	54.4	24.4	
ASPI test POD 4‡ (AUC)	ASA	52	33.9	19.2	0.972
	DAT	46	35.5	23.8	
ADP test POD 4‡ (AUC)	ASA	52	69.9	30.8	0.524
	DAT	46	68.9	39.8	
Platelet count POD 4‡ ($x10^9$/L)	ASA	52	188.9.	75.5.	0.408.
	DAT	47	198.5	73.1	
Fibrinogen (g/L) POD 4‡	ASA	52	7.1	1.1	0.254
	DAT	47	7.3.	1.2.	
Age (years)	ASA	52	64.8	8.0	0.416
	DAT	47	63.4	7.8	
Body mass index (kg/m^2)	ASA	52	28.3	4.1	0.494
	DAT	47	28.9	3.9	
Euro SCORE (%)	ASA	52	3.2	3.2	0.628
	DAT	47	2.8	2.5	

b)

		Groups				P (Chi-square test with Yates correction)
		ASA*		DAT†		
		Count	%	Count	%	
Gender	Male	40	76.9%	34	72.3%	0.770
	Female	12	23.1%	13	27.7%	
Diabetes mellitus	No	29	55.8%	29	61.7%	0.693
	Yes	23	44.2%	18	38.3%	
Preoperative RPR§	No	37	71.2%	31	66.0%	0.734
	Yes	15	28.8%	16	34.0%	
Postoperative RPR§	No	26	50.0%	27	57.4%	0.589
	Yes	26	50.0%	20	42.6%	
Smoking	No	32	61.5%	27	57.4%	0.834
	Yes	20	38.5%	20	42.6%	
Hypertension	No	6	11.5%	4	8.5%	0.869
	Yes	46	88.5%	43	91.5%	
Hyperlipidemia	No	10	19.2%	2	4.3%	0.028
	Yes	41	78.8%	45	95.7%	
No Grafts	1	0	.0%	3	6.4%	0.052
	2	21	40.4%	23	48.9%	
	3	31	59.6%	19	40.4%	
	4	0	.0%	2	4.3%	

Table 2.

Differences in proportion of patients with residual platelet reactivity in ASPI test both preoperatively and postoperatively with respect to diabetes mellitus as comorbidity. Preoperative phase p=0.16, Postoperative phase p= 0.04. *residual platelet reactivity to ASPI aggregation test

			Preoperative RPR*		Postoperative RPR*	
			Without RPR	With RPR	Without RPR	With RPR
Diabetes mellitus	Without Diabetes	Count	43	15	36	22
		% within Diabetes mellitus	74.1%	25.9%	62.0%	38.0%
	With Diabetes	Count	25	16	17	24
		% within Diabetes mellitus	61.0%	39.0%	41.5%	58.5%
Total		Count	68	31	53	46
		% within Diabetes mellitus	68.7%	31.3%	53.5%	46.5%

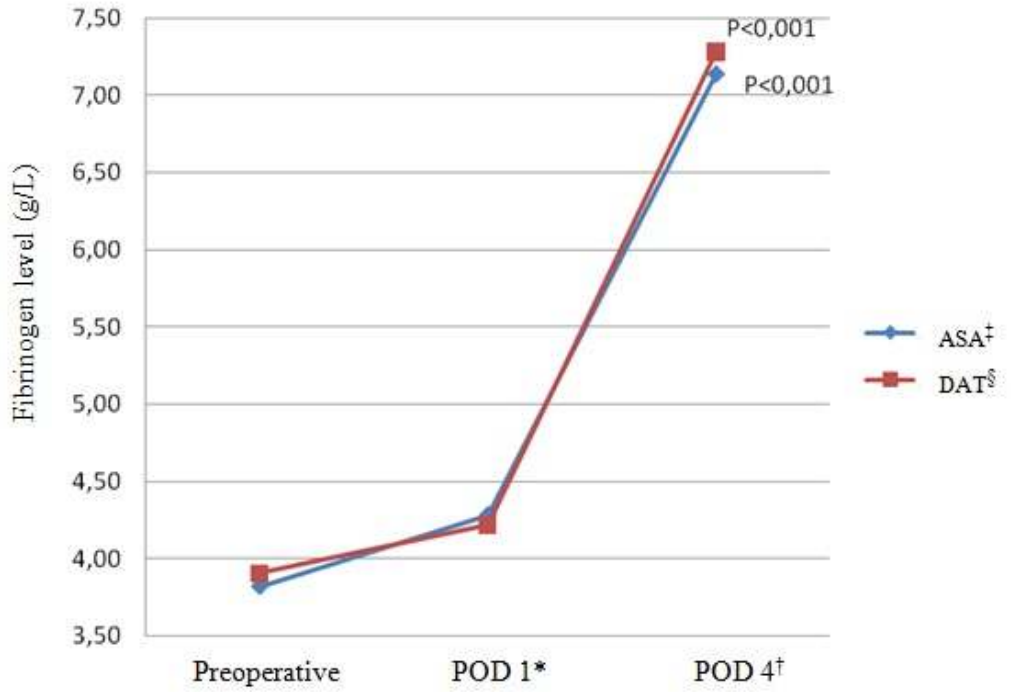

Figure 1. A significant increase in fibrinogen levels in the perioperative period suggests postoperative hypercoagulable state. *first postoperative day, †fourth postoperative day, ‡ monotherapy with acetilsalycylic acid, §dual antiplatelet therapy

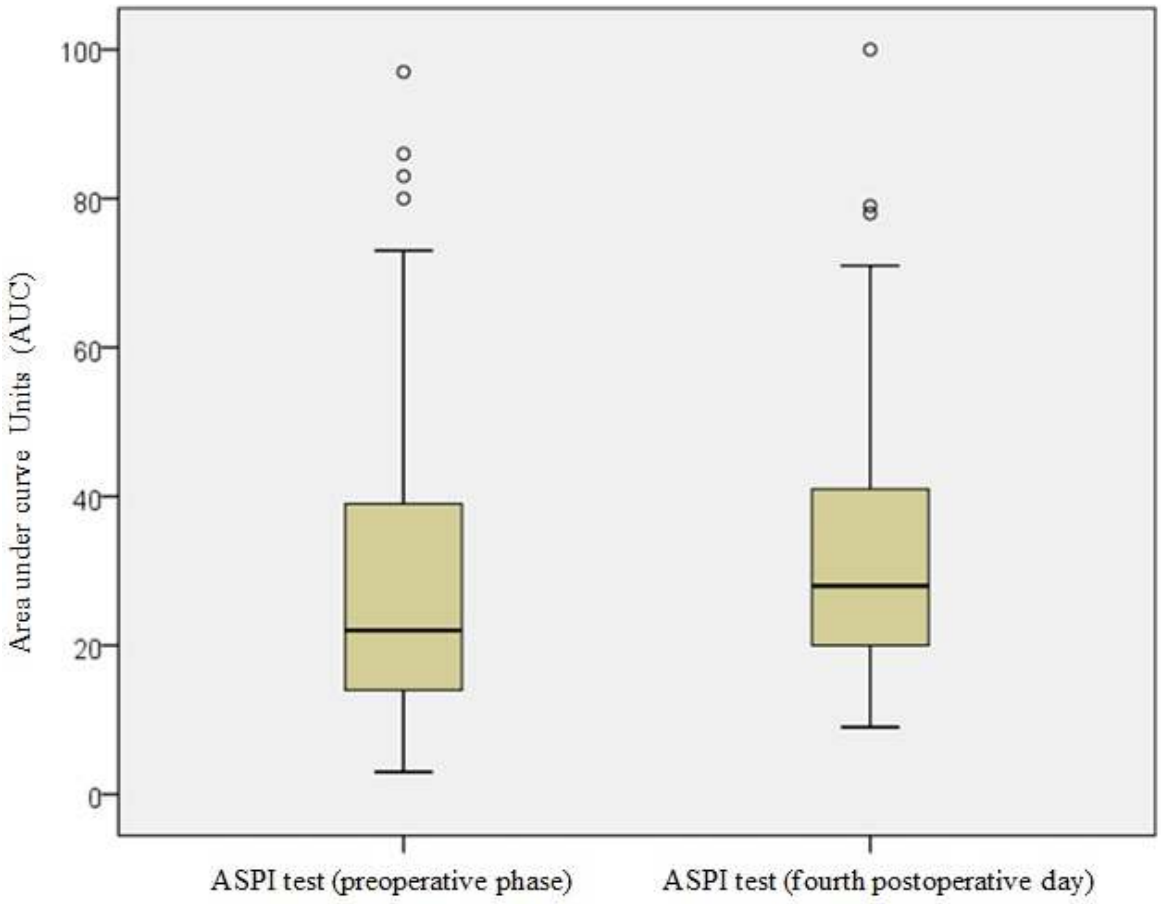

Figure 2. Increase in ASPI aggregation test values at fourth postoperative day (p=0.04).

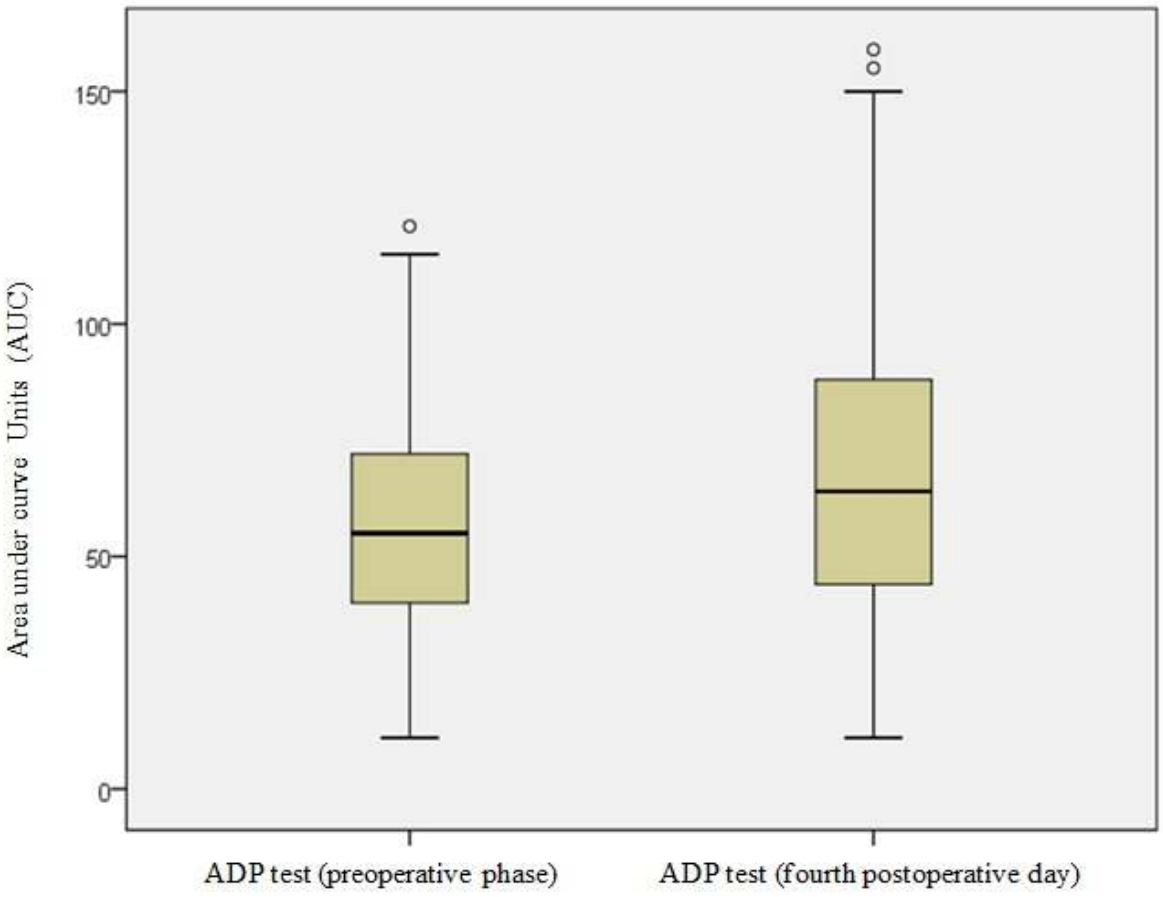

Figure 3. Increase in ADP aggregation test values at fourth postoperative day (p=0.002).