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Source / Izvornik: *Collegium Antropologicum*, 2013, 37, 833 - 839

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

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# Definition of Acetylsalicylic Acid Resistance Using Whole Blood Impedance Aggregometry in Patients Undergoing Coronary Artery Surgery

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## ABSTRACT

A beneficial effect of acetylsalicylic acid (ASA) on vein graft patency has been described, but some patients experience adverse cardiac events despite appropriate ASA treatment. Study aim was to define ASA resistance using Multiple electrode aggregometry (MEA) preoperatively in group of patients undergoing coronary artery bypass grafting (CABG). Prospective observational trial at University Hospital Center Zagreb enrolled 131 patients scheduled for CABG, and divided them into 4 groups with respect to preoperative antiplatelet therapy (APT). Group 1 received 100 mg ASA per day, Group 2 100 mg ASA + 75 mg clopidogrel per day, Group 3 75 mg clopidogrel per day, and Group 4 did not receive any APT. MEA with ASPI test (sensitive to ASA) and ADP test (sensitive to clopidogrel) was performed prior to surgery. In Group 1, patients were characterized as ASA resistant if their ASPI test value exceeded the 75<sup>th</sup> percentile distribution. Study enrolled 131 patients. Significant differences both in the ASPI ( $p < 0.001$ ) and the ADP test ( $p = 0.038$ ) were observed between patients in different APT groups. In Group (1) ASPI test value of 30 AUC presented 75<sup>th</sup> percentile of distribution, thus indicating ASA resistance. Group 2 patients had slightly lower ADP test values, but no significant difference occurred (mean 60.05 vs. 63.32 AUC,  $p = 0.469$ ). In Group 1 and 2, significant correlations between the ADP test and both, platelet count ( $r = 0.347$ ,  $p < 0.001$ ) and fibrinogen level ( $r = 0.364$ ,  $p < 0.001$ ) were observed. Association between low response to ASA and post-CABG major adverse ischemic events risk increase has been described thus indicating need for ASA resistant patients detection. In patients with preoperative ASPI test exceeding 30 AUC postoperative, ASA dose adjustment or clopidogrel addition according to MEA results should be considered.

**Key words:** 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. Aortocoronary vein graft disease is comprised of three distinct but interrelated pathological processes: thrombosis, intimal hyperplasia and atherosclerosis<sup>1</sup>. Of those, 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<sup>2,3</sup>. A beneficial effect of ASA on vein graft patency has been shown during the first year after CABG<sup>4-6</sup>. However, some pa-

tients experience adverse cardiac events despite treatment with APT. Some of those events could be caused by platelet resistance to administered ASA therapy which inevitably suggests need for antiplatelet drug dose increase, or administration of another antiplatelet agent as a supplement. Platelet resistance to 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<sup>7</sup>. 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 define and evaluate ASA resistance using MEA preoperatively in patients following CABG, and to propose the alternative therapeutic approaches in patients with observed ASA resistance.

## Materials and Methods

The study was conducted in a prospective observational mode at teaching University Hospital Center.

### Patient selection

After institutional review board approval and written informed consent, 131 patients scheduled for elective CABG were enrolled and divided into 4 groups with respect to their preoperative antiplatelet therapy (APT). Daily doses of antiplatelet therapy were as follows: group 1 received 100 mg ASA, group 2 received 100 mg ASA + 75 mg clopidogrel, group 3 received 75 mg clopidogrel and group 4 did not receive any APT prior to surgery procedure. MEA with ASPI test (sensitive to ASA) and ADP test (sensitive to clopidogrel) was performed day before surgery. In Group 1, patients were characterized as ASA resistant if their ASPI test value exceeded the 75<sup>th</sup> percentile distribution.

Criteria for excluding patients from the group of subjects were: patients with cardiac surgical procedures other than isolated CABG, patients with inaccurate APT administration documentation or missing data, an urgent surgery. In our study cohort APT was administered by the referral cardiologist. In patients admitted to our department with daily dose of 100 mg ASA, antiplatelet therapy was continued up to day of surgery. 61/131 (46.56%) of patients received daily dose of 75 mg CLO, either alone or 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. All patients were admitted to our department at least 1 day before surgery.

### Blood sampling

Blood samples for MEA measurements were obtained day before surgery 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 before surgery. The same person, not directly involved in patient care, performed MEA 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® ana-

lyzer, Dynabyte Medical, Munich). Detailed description of method has already been published<sup>8</sup>. 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<sup>8,9</sup>. 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 6.4 μM (ADP test designed to evaluate thienopyridines, such as CLO, effect). In Group 1, patients were characterized as ASA resistant if their ASPI test value exceeded the 75<sup>th</sup> percentile distribution.

### Statistics

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  $p=0.05$  was considered statistically significant.

## Results

### Patients

We prospectively ascertained consecutive sample of 131 patients scheduled for elective CABG. All patients

**TABLE 1.**  
COMPARISON OF ASPI TEST (AUC) AND ADP TEST (AUC) VALUES WITHIN DIFFERENT ANTIPLATELET THERAPY GROUPS REVEALS SIGNIFICANT DIFFERENCES BOTH IN ASPI ( $P<0.001$ ) AND ADP ( $P=0.038$ ) TEST VALUES

		N	Mean	Std. Deviation
ASPI test (AUC)	Group 1*	65	25.14	18.773
	Group 2†	56	22.48	14.315
	Group 3‡	5	79.00	15.700
	Group 4§	5	103.60	27.736
ADP test (AUC)	Group 1*	65	63.32	24.101
	Group 2†	56	60.05	25.344
	Group 3‡	5	68.40	35.133
	Group 4§	5	93.80	19.162

\* monotherapy acetylsalicylic acid group, † dual antiplatelet therapy group (acetylsalicylic acid and clopidogrel), ‡ monotherapy clopidogrel group, § without antiplatelet therapy group.

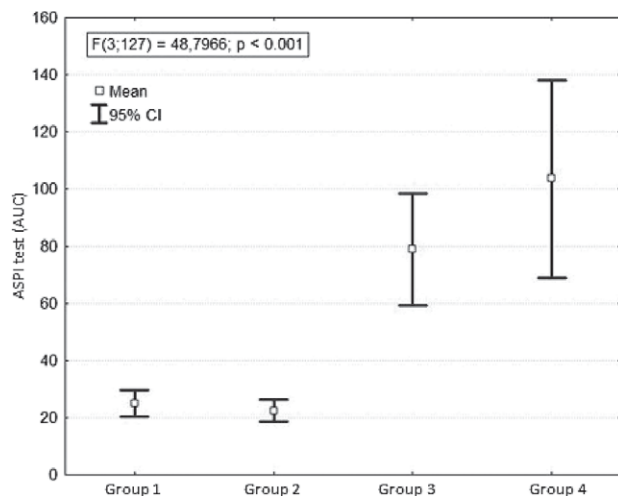


Fig. 1. Differences in ASPI test values (AUC) between groups with respect to preoperative antiplatelet therapy management. (Group 1: 100 mg acetylsalicylic acid daily dose, Group 2: 100 mg acetylsalicylic acid + 75 mg clopidogrel daily dose, Group 3: 75 mg clopidogrel daily dose, Group 4: no antiplatelet therapy administered).

from the sample were discharged from hospital. Cohort group was divided in four subgroups regarding antiplatelet therapy management. Both ASPI and ADP test were compared between groups (Table 1). We found significant difference between groups concerning both ASPI ( $p < 0.001$ ) and ADP ( $p = 0.0385$ ) test as shown in Figure 1 and Figure 2, respectively. In order to assess platelet response to ASA therapy only patients in Group 1 and Group 2 were included in further analysis. No difference occurred between Group 1 and Group 2 concerning demographic, laboratory and operative data (Table 2). Group 2 patients had slightly lower ADP test values, but no significant difference occurred (mean 60.05 vs. 63.32 AUC,  $p = 0.469$ ). In addition to, Group 2 patients had lower ASPI test values (mean 22.48 vs. 25.14 AUC,  $p = 0.38$ ), but the difference did not reach statistical significance.

In order to avoid greater inhibitory effect of dual antiplatelet therapy on platelet aggregation comparing to either agent alone, we decided to define ASA resistance in group of patients receiving daily dose of 100 mg ASA only. In Group 1, ASPI test value of 30 AUC presented 75<sup>th</sup> percentile of distribution, thus indicating cut-off value for ASA resistance definition.

In Group 1 and Group 2, demographic, laboratory and operative data were correlated to both ASPI and ADP test values (Table 3). Significant correlations between the ADP and both, platelet count ( $r = 0.347$ ,  $p < 0.001$ ) and fibrinogen level ( $r = 0.364$ ,  $p < 0.001$ ) were described taking into consideration both groups together. ASPI test values did not correlate to platelet count and fibrinogen ( $p = ns$ ).

Given the presence on ASA resistance, demographic, laboratory and operative data among the groups receiving ASA therapy were compared. Only difference occur-

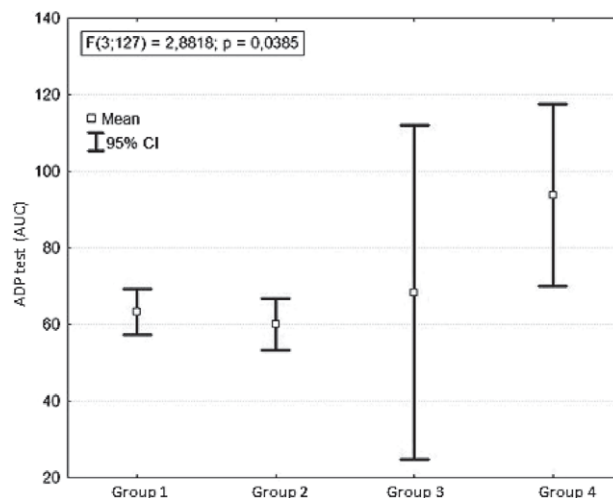


Fig. 2. Differences in ADP test values (AUC) between groups with respect to preoperative antiplatelet therapy management. (Group 1: 100 mg acetylsalicylic acid daily dose, Group 2: 100 mg acetylsalicylic acid + 75 mg clopidogrel daily dose, Group 3: 75 mg clopidogrel daily dose, Group 4: no antiplatelet therapy administered).

red among red blood cells count. ASA resistant patients had higher values (4.77 vs. 4.52,  $p = 0.017$ ). Although statistically significant, we found it of no clinical relevance. In Group 2 with dual antiplatelet therapy administration, ADP test value was correlated to number of days after CLO withdrawal. There was no significant correlation ( $r = 0.01$ ,  $p = 0.99$ ).

## Discussion and Conclusion

This study defined ASA resistance using MEA in patients undergoing CABG. To our knowledge this is first study with definition of ASA resistance using MEA in group of patients undergoing CABG. In our opinion, the lack of objective quantification of the antiplatelet effect of both ASA and CLO constitutes a major drawback of antiplatelet therapy management in coronary artery disease patients. The incidence of ASA resistance varies widely in the literature<sup>1</sup> and independently raises the incidence of adverse cardiovascular events and venous graft occlusions<sup>1</sup>. Therefore it would be critical to detect ASA resistance preoperatively and adjust for this variable in postoperative phase.

Our study presumably identified a group of patients with preoperative ASA resistance. No uniform guidelines exist for the postoperative prevention of thrombotic complications after CABG<sup>10</sup>. It is widely accepted that platelets play a pivotal role in the development of thrombosis<sup>11,12</sup>. Early graft failure is hypothesized to be related to thrombus development, of which ASA resistance may be an important component<sup>13</sup>.

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

**TABLE 2.**  
BASIC DEMOGRAPHIC, LABORATORY AND OPERATIVE DATA

	Group	N	Mean	SD	P
EuroScore (%)	Group 1*	65	3.57	3.59	0.334
	Group 2†	56	3.00	2.69	
Body mass index (kg/m <sup>2</sup> )	Group 1	65	28.20	4.01	0.843
	Group 2	56	28.33	3.48	
Body surface area (m <sup>2</sup> )	Group 1	65	1.97	0.21	0.817
	Group 2	56	1.98	0.19	
Age (years)	Group 1	65	64.65	8.01	0.438
	Group 2	56	63.52	7.87	
Red blood cell count (cells/mL)	Group 1	65	4.54	0.53	0.312
	Group 2	56	4.63	0.44	
Hemoglobin (g/L)	Group 1	65	135.82	16.41	0.553
	Group 2	56	137.52	14.83	
Hematocrit (x100%)	Group 1	65	0.40	0.05	0.363
	Group 2	56	0.41	0.04	
Platelet count (x10 <sup>9</sup> /L)	Group 1	65	211.48	61.18	0.169
	Group 2	56	227.96	69.76	
Fibrinogen (g/L)	Group 1	65	3.80	0.89	0.387
	Group 2	56	3.95	1.08	
ASPI (AUC)	Group 1	65	25.14	18.77	0.389
	Group 2	56	22.48	14.31	
ADP (AUC)	Group 1	65	63.32	24.10	0.469
	Group 2	56	60.05	25.34	
Cross clamp time (min)	Group 1	65	63.54	23.01	0.381
	Group 2	56	59.93	21.96	
Cardiopulmonary bypass time (min)	Group 1	65	91.42	27.06	0.130
	Group 2	56	83.95	26.61	

\* monotherapy acetylsalicylic acid group, † dual antiplatelet therapy group (acetylsalicylic acid and clopidogrel)

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<sup>14,15</sup> although early literature refers heparin to affect aggregation results<sup>16</sup>. Therefore, different reference interval of test values should be considered. We obtained blood samples by performing anticoagulation with heparin. Our 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<sup>17</sup>. Similar results were also described, although with different anticoagulant used for blood sampling for

MEA<sup>18,19</sup>. Truss et al.<sup>14</sup> 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 unfractionated heparin as an anticoagulant for MEA we made our own definition of ASA resistance which is applicable for use in the setting of heparin as an anticoagulant for blood sample.

Currently, there is no established therapeutic approach for managing ASA resistance that has been shown in large trials to have clinical benefit. Our data presumably identified a subgroup of patients with ASA resistance who may be at increased risk for developing thromboembolic complications. In this subgroup of patients higher doses of ASA should be considered in postoperative phase. At our Department of Cardiac Surgery 300 mg ASA is routinely administered in postoperative phase starting on first postoperative day. If ASA resistance occurs in postoperative phase despite 300 mg ASA adminis-

**TABLE 3.**  
CORRELATION BETWEEN DEMOGRAPHIC, LABORATORY AND OPERATIVE DATA TO BOTH ASPI AND ADP TEST VALUES  
IN GROUP 1 AND GROUP 2.

		Group 1*		Group 2†	
		ASPI test (AUC)	ADP test (AUC)	ASPI test (AUC)	ADP test (AUC)
Body mass index (kg/m <sup>2</sup> )	Pearson Correlation	0.001	-0.082	-0.130	-0.052
	p	0.996	0.516	0.339	0.702
	N	65	65	56	56
Body surface area (m <sup>2</sup> )	Pearson Correlation	0.033	-0.234	-0.165	-0.101
	p	0.794	0.061	0.223	0.458
	N	65	65	56	56
Age (years)	Pearson Correlation	0.063	-0.082	-0.091	0.126
	p	0.620	0.517	0.503	0.356
	N	65	65	56	56
Red blood cell count (cells/mcL)	Pearson Correlation	0.273	0.059	0.118	-0.126
	p	0.029	0.645	0.387	0.354
	N	65	65	56	56
Hemoglobin (g/L)	Pearson Correlation	0.198	-0.005	0.087	-0.240
	p	0.113	0.970	0.523	0.074
	N	65	65	56	56
Hematocrit (x100%)	Pearson Correlation	0.223	-0.011	0.100	-0.198
	p	0.075	0.928	0.463	0.144
	N	65	65	56	56
Platelet count (x10 <sup>9</sup> /L)	Pearson Correlation	0.150	0.429	0.154	0.292
	p	0.233	<0.001	0.257	0.029
	N	65	65	56	56
Fibrinogen (g/L)	Pearson Correlation	0.090	0.424	0.078	0.326
	p	0.482	0.001	0.567	0.014
	N	65	65	56	56
Cross clamp time (min)	Pearson Correlation	-0.080	-0.113	-0.255	0.194
	p	0.526	0.370	0.057	0.152
	N	65	65	56	56
Cardiopulmonary bypass time (min)	Pearson Correlation	-0.121	-0.144	-0.280	0.194
	p	0.338	0.252	0.037	0.152
	N	65	65	56	56

\* monotherapy acetylsalicylic acid group, †dual antiplatelet therapy group (acetylsalicylic acid and clopidogrel)

tration, further increase in ASA dosage would not be prudent in terms of worsening endothelial – mediated arterial dilatation<sup>20</sup>. These patients could benefit from a more aggressive antithrombotic treatment regimen such as dual antiplatelet therapy with CLO addition to ASA therapy. ASA resistance is a transient phenomenon present in the majority of the patients undergoing coronary artery bypass grafting<sup>21</sup>. Without quantitative preoperative platelet function assessment, and subsequent ASA resistant patients detection it is quite hard to distinguish permanent from transient platelet hyperactivity following CABG. We propose alternative APT management in patients with ASA resistance. CLO therapy could affect the graft patency in patients with ASA resistance. Preoperatively detected ASA resistant patients are more likely

to be ASA resistant in postoperative period. However, some patients with adequate platelet inhibition prior to surgery can develop transient ASA resistance in the postoperative period. Assessment of platelet function prior to CABG with ASA resistant patient detection may advise to ASA dose increase or switch to dual antiplatelet therapy in postoperative phase. Postoperative assessment of platelet function can detect platelet function changes and propose APT adjustment according to both ASPI and ADP test values. 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<sup>22</sup>. 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<sup>23</sup>. Nevertheless, since ASA resistance raises the incidence of adverse cardiovascular events and venous graft occlusions, it would seem critical to adjust for this variable<sup>1</sup>. 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 to ASA resistant patients 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<sup>24</sup>.

Using MEA to guide APT may allow individual tailoring therapy after MEA assessment in postoperative phase. Individual tailored therapeutic approach could significantly improve clinical outcomes. Awidi et al found that the combination of ASA and CLO had greater inhibitory effects on platelet function than either agent alone<sup>3</sup>. In our study, although slightly lower, ASPI test values did not differ significantly between group receiving ASA monotherapy and dual antiplatelet therapy ( $p=ns$ ). Prospective, outcome evaluating randomized trials, with platelet function assessment are needed to clarify the benefits of dual antiplatelet therapy. Bochsén et al suggested that CABG patients are prone to platelet hyperactivity at fourth postoperative day<sup>25</sup>. In addition to Kempfert et al reported 28.8% patients with ASA resistance before CABG. Postoperatively almost half of patients (49%) developed ASA resistance<sup>21</sup>. Comprehensive platelet function assessment both pre- and postoperatively can distinguish patients who need temporary or permanent increase of ASA dose or CLO addition. Routine platelet function

assessment in patients on APT can provide optimal APT safety profile concerning both ischemic and bleeding events. 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<sup>7</sup>. 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<sup>6</sup>. Therefore, a more aggressive antithrombotic treatment might be warranted for patients with ASA resistance in postoperative period.

### Limitations of study

The study was conducted as prospective observational, and we did not analyze the outcome with respect to MEA results and the scope of this study was not to identify the event rate of thromboembolic complication with regards to ASA resistance. The purpose of study was to define ASA resistance in bedside laboratory setting in group of patients undergoing CABG. Although we assessed ADP test preoperatively we did not assess CLO resistance in group of patients with recent 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 with different time intervals from CLO withdrawal to time of platelet function assessment. As we already described, there was no correlation of ADP test and number of days after CLO withdrawal. The degree of platelet inhibition after CLO treatment varies from patient to patient, and 4 to 30% of patients treated with CLO do not have adequate antiplatelet response<sup>26</sup>. In addition to, the great variability in ADP test values could be result of different inherent platelet ADP receptor activity with different proportion of newborn platelets ADP receptors activity after CLO withdrawal. However, in absence of MEA in routine clinical practice, strong correlations of ADP test (sensitive to CLO effect) and both platelet count ( $p<0.001$ ) and fibrinogen level ( $p<0.001$ ) may advise administration of CLO in patients with high fibrinogen and platelet count values.

## REFERENCES

- ZIMMERMANN N, GAMS E, HOHLFELD T, Eur J Cardiothorac Surg, 34 (1) (2008) 93. DOI: 10.1016/j.ejcts.2008.03.023. — 2. MATSURA K, IMAMAKI M, ISHIDA A, SHIMURA H, MIYAZAKI M, Heart Vessels, 24 (3) (2009) 169. DOI: 10.1007/s00380-008-1105-2. — 3. AWIDI A, SALEH A, DWEIK M, KAILANI B, ABU-FARA M, NABULSI R, BENER A, Heart Vessels, 26 (2011) 516. DOI: 10.1007/s00380-010-0086-0. — 4. GOLDMAN S, COPELAND J, MORITZ T, HENDERSON W, ZADINA K, OVITT T, KERN KB, SETHI G, SHARMA GV, KHURI S, Circulation, 89 (3) (1994) 1138. DOI: 10.1161/01.CIR.89.3.1138. — 5. GOLDMAN S, COPELAND J, MORITZ T, HENDERSON W, ZADINA K, OVITT T, DOHERTY J, READ R, CHESLER E, SAKO Y, Circulation, 80(5) (1989) 1190. DOI: 10.1161/01.CIR.80.5.1190. — 6. GOLDMAN S, COPELAND J, MORITZ T, HENDERSON W, ZADINA K, OVITT T, DO-

- HERTY J, READ R, CHESLER E, SAKO Y, Circulation, 77(6) (1988) 1324. DOI: 10.1161/01.CIR.77.6.1324. — 7. BEN-DOR I, KLEIMAN NS, LEV E, Am J Cardiol, 104(2) (2009) 227. DOI: 10.1016/j.amjcard.2009.03.022. — 8. TOTH O, CALATZIS A, PENZ S, LOSONCZY H, SISS W, Thromb Haemost, 96(6) (2006) 781. — 9. CALATZIS A, WITWER B, KRUEGER, Platelets, 15 (2004) 479. DOI: 10.1080/0953710041233122587. — 10. HANSEN KH, HUGHES P, STEINBRUCHEL DA, Scand Cardiovasc J, 39(6) (2005) 369. DOI: 10.1080/14017430500199428. — 11. PAPARELLA D, GALEONE A, VENNERI MT, COVIELLO M, SCRASCIA G, MARRAUDINO N, QUARANTA M, DE LUCA TUPPUTI SCHINOSA L, BRISTER SJ, J Thorac Cardiovasc Surg, 131(2) (2006) 290. DOI: 10.1016/j.jtcvs.2005.10.018. — 12. MOOR E, BLOMBACK M, SILVEIRA A, WIMAN B, CEDERLUND K, BERGSTRAND L, IVERT T, RY-

- DEN L, HAMSTEN A, Thromb Res, 98(1) (2000) 39. DOI: 10.1016/S0049-3848(99)00221-2. — 13. ROCCA B, PATRONO C, J Thromb Haemost, 3(8) (2005) 1597. DOI: 10.1111/j.1538-7836.2005.01380.x. — 14. TRUSS NJ, ARMSTRONG PC, LIVERANI E, VOJNOVIC I, WARNER TD, J Thromb Haemost, 7(11) (2009) 1897. DOI: 10.1111/j.1538-7836.2009.03589.x. — 15. KALB ML, POTURA L, SCHARBERT G, KOZEK-LANGENECKER SA, Platelets, 20(1) (2009) 7. DOI: 10.1080/09537100.802364076. — 16. O'BRIEN JR, SHOOBRIDGE SM, FINCH WJ, J Clin Pathol, 22(1) (1969) 28. DOI: 10.1136/jcp.22.1.28. — 17. SKORIC B, MILICIC D, LOVRIC D, GORNIK I, SKORIC KN, SERTIC J, Int J Cardiol, 140(3) (2010) 356. DOI: 10.1016/j.ijcard.2008.11.031. — 18. VON PAPE KW, DZIJAN-HORN M, BOHNER J, SPANNAGL M, WEISSER H, CALATZIS A, Hamostaseologie, 27(3) (2007) 155. — 19. JAMBOR C, WEBER CF, GERHARDT K, DIETRICH W, SPANNAGL M, HEINDL B, ZWISSLER B, Anesth Analg, 109(1) (2009) 25. DOI: 10.1213/ane.0b013e3181a27d10. — 20. FURUNO T, YAMASAKI F, YOKOYAMA T, SATO K, SATO T, DOI Y, SUGIURA T, Heart Vessels, 26(3) (2011) 267. DOI: 10.1007/s00380-010-0054-8. — 21. KEMPFERT J, ANGER K, RASTAN A, KRABBES S, LEHMANN S, GARBADE J, SAUER M, WALTHER T, DHEIN S, MOHR FW, Eur J Clin Invest, 39(9) (2009) 769. DOI: 10.1111/j.1365-2362.2009.02175.x. — 22. KULIK A, LE MAY MR, VOISINE P, TARDIF JC, DELAROCHELIERE R, NAIDOO S, WELLS GA, MESA-NA TG, RUEL M, Circulation, 122(25) (2010) 2680. DOI: 10.1161/CIRCULATIONAHA.110.978007. — 23. GASPAROVIC H, PETRICEVIC M, BIOCINA B, Circulation, 124(6) (2011) e193. DOI: 10.1161/CIRCULATIONAHA.111.019174. — 24. PETTERSEN AA, SELJEFLOT I, ABDELNOOR M, ARNESEN H, Scand Cardiovasc J, 38(6) (2004) 353. DOI: 10.1080/14017430410024324. — 25. BOCHSEN L, ROSENGAARD LB, NIELSEN AB, STEINBRUCHEL DA, JOHANSSON PI, J Extra Corpor Technol, 41(1) (2009) 15. — 26. NGUYEN TA, DIODATI JG, PHARAND C, J Am Coll Cardiol, 45(8) (2005) 1157. DOI: 10.1016/j.jacc.2005.01.034.

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## DEFINICIJA REZISTENCIJE NA ACETILSALICILNU KISELINU UPOTREBOM IMPEDANCIJSKE AGREGOMETRIJE KOD BOLESNIKA KOJI SE PODVRGAVAJU OPERACIJI KORONARNOG PREMOŠTENJA

### SAŽETAK

Povoljan učinak acetilsalicilne kiseline na prohodnost venskih graftova već je opisana, ali određeni broj bolesnika poslijeoperacijski doživi nepovoljna ishemijska zbivanja unatoč adekvatnom liječenju acetilsalicilnom kiselinom. Cilj studije je prijeoperacijski definirati rezistenciju na acetilsalicilnu kiselinu upotrebom impedancijske agregometrije (MEA) u skupini bolesnika koji se podvrgavaju operaciji koronarnog premoštenja (CABG). Prospektivna opservacijska studija u Kliničkom bolničkom centru Zagreb uključila je 131 bolesnika kod kojih je planiran CABG. Bolesnici su podijeljeni u 4 skupine obzirom na prijeoperacijski ordiniranu antiagregacijsku terapiju. Skupina 1 je primala acetilsalicilnu kiselinu 100 mg/dnevno, skupina 2 100 mg acetilsalicilne kiseline te 75 mg klopidoogrel dnevno, skupina 3 je primala klopidoogrel 75 mg dnevno dok skupina 4 nije primala antiagregacijsku terapiju prije operacije. MEA s ASPI testom (koji je senzitivn na učinak acetilsalicilne kiseline) i ADP testom (senzitivn na učinak klopidoogrela) je izvedena prije operacije. U skupini 1, bolesnici kojima je vrijednost ASPI testa iznosila više od 75. percentile distribucije vrijednosti ASPI testa su okarakterizirani kao rezistentni na acetilsalicilnu kiselinu. Značajne razlike u vrijednostima ASPI ( $p < 0.001$ ) i ADP testa ( $p = 0.038$ ) uočene su između skupina bolesnika definiranih prema režimu prijeoperacijskog antiagregacijskog liječenja. U skupini 1, vrijednost ASPI testa od 30 AUC (engl. area under curve) je predstavljala vrijednost 75-te percentile, označavajući graničnu vrijednost za definiciju rezistencije na acetilsalicilnu kiselinu. U skupini 2 (izloženi klopidoogrelu) izmjerene su niže vrijednosti ADP testa, međutim bez statistički značajne razlike (srednja vrijednost 60.05 vs. 63.32 AUC,  $p = 0.469$ ). U skupini 1 i 2, uočene su značajne korelacije između vrijednosti ADP testa i broja trombocita ( $r = 0.347$ ,  $p < 0.001$ ) te razine fibrinogena ( $r = 0.364$ ,  $p < 0.001$ ). Povezanost između izostanka odgovora na acetilsalicilnu kiselinu i povećanog rizika za neželjena poslijeoperacijska ishemijska zbivanja je već opisana što naglašava potrebu za brzim i lakoizvedivim definiranjem bolesnika s rezistencijom na acetilsalicilnu kiselinu. Kod bolesnika s prijeoperacijskim vrijednostima ASPI testa većim od 30 AUC, trebalo bi razmotriti prilagodbu doze acetilsalicilne kiseline ili dodavanje klopidoogrela (tzv. dvojna antiagregacijska terapija) na osnovi MEA monitoriranja.