The effect of off-pump coronary artery bypass grafting on platelet activation in patients on aspirin therapy until surgery day

Grzegorz Suwalski a,*, Piotr Suwalski a, Krzysztof J. Filipiak b, Marek Postuła b,c, Franciszek Majstrak a, Grzegorz Opolski b

a Department of Cardiac Surgery, 1st Chair of Cardiology, Medical University of Warsaw, Banacha 1 a Street, 02-097 Warsaw, Poland
b Department of Cardiology, 1st Chair of Cardiology, Medical University of Warsaw, Warsaw, Poland
c Department of Experimental and Clinical Pharmacotherapy, Medical University of Warsaw, Warsaw, Poland

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Abstract

Objective: Antiplatelet therapy is a class I indication in perioperative care after coronary artery bypass grafting to prevent graft occlusion. We sought to determine whether continuation of aspirin until surgery day suppresses platelet activity in the early period after off-pump coronary artery bypass grafting (OPCAB).

Material and methods: Forty-two patients at mean age of 62.5 (±7.9) years were included. Average risk rate (EuroScore logistic) was 2.2 (±1.7) %. In all patients collagen/epinephrine stimulated platelet plug formation (closure time, CT) (CEPI-CT, s) using a platelet function analyzer (PFA-100), troponin I (TnI), creatine kinase-MB (CK-MB), ST segment elevation were evaluated a day before surgery, 4 h after chest closure, 24 and 120 h after surgery.

Results: Preoperative mean CEPI-CT was 224.8 (±79.7) s. In 13 (30%) patients aspirin resistance (CEPI-CT < 163 s.) was observed. In 4, 24 and 120 h time points CEPI-CT was significantly reduced: 164.4 (±79), 168.5 (±83.3) and 167.5 (±80.4), respectively (p < 0.001). TnI and CK-MB (ng/ml) levels raised in respective time points: 4 h (0.26 range 4; 1.9 range 6), 24 h (0.2 range 6; 2.6 range 8), 120 h (0.04 range 2; 0.6 range 5). ST segment elevation (mV) changed in time: 4 h (0.7 range 3.5), 48 h (0.7 range 2.8) and 120 h after surgery (0.2 range 1.5). There were no significant correlations between CEPI-CT and TnI, CK-MB, ST segment elevation found.

Conclusion: Aspirin therapy continued until surgery day does not protect against acute platelet activation in patients after OPCAB.

Keywords: Off-pump revascularization; Platelet function; Aspirin

1. Introduction

Coronary artery bypass grafting (CABG) is a standard treatment for patients with multivessel coronary artery disease (CAD). Early- and long-term results also depend on pharmacological secondary prevention of CAD. Antiplatelet therapy is a class I indication in perioperative care after CABG to prevent graft occlusion [1]. Increased use of off-pump CABG (OPCAB) resulted in an evidence-based consensus that OPCAB technique may effect a decrease in perioperative complications and shorten the length of hospitalization [2]. However, some studies reported lower patency of grafts and procoagulative modulation in comparison to on-pump CABG [3,4]. Surgical intervention with no use of cardiopulmonary bypass may potentially increase the risk of platelet activation and thrombosis. The primary aim of this study was to describe platelet activation profile in the early postoperative days after OPCAB in patients on aspirin (ASA) therapy. The secondary aim was to evaluate the effect of high dose of aspirin on platelet function administered in second postoperative day (POD).

2. Methods

There were 42 patients at mean age of 62.5 (±7.9) years prospectively included. Preoperative characteristics are presented in Table 1. Patients were qualified according to class IA indications for CABG in stable coronary artery disease. Inclusion criteria were: age between 40 and 80 years old, elective CABG, preoperative ASA (75 mg/day), statin, beta-blocker, angiotensin convertase inhibitor therapy or logistic EuroScore below 8%. Patients with a history of hematomal disorders, transfusion less than 4 months before surgery, thrombolysis or platelet glycoprotein IIb/IIIa antagonists treatment in last 4 weeks, acute coronary syndrome in less than 3 weeks, perioperative mechanical
2.1. Operative technique

Anesthesia was induced using propofol 1—2 mg/kg, pancuronium 0.1 mg/kg and fentanyl 10 mg/kg, and was maintained by air/oxygen and propofol 3 mg/kg/h. Normothermia was maintained by using warm intravenous fluids, a heating mattress and with maintaining a warm operating theatre. Medium sternotomy was used to expose the heart. Left internal thoracic artery harvested in the pedicle manner was used in all cases. When grafting on the lateral wall was planned then the right pleural cavity was opened creating a place for heart rotation and vertical positioning with minimized homodynamic compression. One deep pericardial suture was placed at the posterior pericardium. Anticoagulation was achieved using 150 units/kg (not less than 100 mg) of heparin. The activated clotting time (ACT) was maintained above 250 s. The heart was stabilized with tissue stabilisation system (Octopus 3 or Evolution Medtronic Inc., Minneapolis, MN). Coronary shunts were not used. When distal and proximal anastomoses were done protamine was administered in dose of 1:1 heparin—protamine ratio. Skin-to-skin time and intraoperative blood loss were measured as well as adverse events.

2.2. Perioperative procedure

In the morning of surgery day all patients received 75 mg of ASA. After surgery patients were transferred to intensive care unit (ICU) on mechanical ventilation and, if hemodynamically stable with no signs of severe bleeding, anesthetic drugs were off. Mean mechanical ventilation time was 5.5 ± 1.7 h. If chest drainage did not exceed 100 ml per first 3 h heparin infusion was introduced to achieve ACT level between 140 and 160 s. On the second postoperative day (POD) chest drainage was removed, 375 mg of ASA and 60—80 mg/day of enoxaparin were introduced. During the following days 75 mg of ASA per day with enoxaparine were continued. Statin, beta-blocker and angiotensin convertase inhibitor therapy started from 2nd POD.

2.3. Platelet activation and ischemia parameters assessment

A day before surgery, then 4—6, 24 and 120 h (5th POD) post-surgery, blood sampling and ECG parameters were collected. Platelet function was assessed using a platelet function analyzer (PFA-100, Dade Behring, Germany). This analyzer enables quantitative measurement (closure time, CT) of platelet-mediated hemostasis in uncoagulated (citrated) blood. The method simulates platelet activation by mechanical stress (shear stress), and also simulates contact of platelets with the collagen/epinephrine membrane. Detailed methodology used in our laboratory has been described elsewhere [5]. According to company data platelet function block is maintained with ASA when collagen/epinephrine stimulated artificial capillary closure time (CEPI-CT) exceeds 163 s. Aspirin resistance was defined as CEPI-CT less than 163 s on ASA therapy minimum 7 days or lack of CEPI-CT prolongation with ASA high-dose (375 mg) followed by 75 mg per day. From same blood sample troponin I (TnI), creatine kinase-MB (CK-MB), complete coagulation function block is maintained with ASA when collagen/epinephrine stimulated artificial capillary closure time (CEPI-CT) exceeds 163 s. Aspirin resistance was defined as CEPI-CT less than 163 s on ASA therapy minimum 7 days or lack of CEPI-CT prolongation with ASA high-dose (375 mg) followed by 75 mg per day. From same blood sample troponin I (TnI), creatine kinase-MB (CK-MB), complete coagulation parameters were evaluated.

2.4. Statistical analysis

Statistical analysis was performed using Statistica™ (StatSoft™, Inc. 2000). The Shapiro—Wilk W-test was used in testing for normality. If the W-statistic was significant, then the hypothesis that the respective distribution is normal was rejected. Normally distributed continuous variables are expressed as mean ± standard deviation (SD). Non-normally distributed continuous variables are expressed as median and range. Nonparametric and parametric data correlations were evaluated with either Spearman rank-test or Pearson test. Comparison between groups was performed using Student’s t-test for normally distributed continuous variables, and Mann—Whitney test for non-normally distributed continuous variables. Differences of continuous variables within groups in certain time points were analyzed with Wilcoxon signed-rank test (if non-normally distributed) or paired t-test (if

![Fig. 1. Dynamic changes of platelet function (CT-EPI, s) after OPCAB.](https://academic.oup.com/ejcts/article-abstract/34/2/365/412740)
normally distributed). Differences were considered significant at $p < 0.05$.

3. Results

There were no major complications (death, myocardial infarction, stroke, transient ischemic attack, reoperation) observed during procedure and postoperative course. Mean number of distal grafts was 2.9 ($\pm 0.9$) per patient. In 11 (26%) patients total arterial revascularization was performed. Mean skin-to-skin time was 129.4 ($\pm 48.1$) min with median intraoperative blood loss of 420 (range: 1400) ml. Postoperatively, transfusion of blood or plasma was necessary in 14 (33%) patients. In the whole group the average amount of transfusions was 1.3 ($\pm 2.5$) units per patient. Median ICU stay time was 1 (range: 4) day and in-hospital stay 10 (range: 2) days.

3.1. Platelet function

Preoperative mean CEPI-CT was 224.8 ($\pm 79.7$) s. In 13 (30%) patients preoperative aspirin resistance (CEPI-CT < 163 s) was observed. Postoperatively there was significant platelet activation observed (Graph 1), ($p < 0.001$). Activation persisted till 5th POD. After 48 h when all patients received 375 mg of aspirin there was no significant platelet block found, mean CT-EPI 168.5 ($\pm 83.3$) versus 167.5 ($\pm 80.4$) s, after 24 and 120 h, respectively ($p = 0.55$). In aspirin resistant patients no impact of OPCAB on platelet activation (CT-EPI) was observed, respectively: 119.9 ($\pm 17.1$ s, preoperatively), 129.9 ($\pm 68$ s, after 4 h), 120.3 ($\pm 60.8$ s, after 24 h) and 148.2 ($\pm 80.8$ s, after 120 h), ($p > 0.05$). In aspirin responders significant CT-EPI reduction was found in the following time points: preoperatively (277.3 $\pm 30.7$ s), after 4 h (181.7 $\pm 79.8$ s; $p < 0.001$), after 24 h (189.7 $\pm 83.9$ s) and after 120 h (177.1 $\pm 80.2$ s). In aspirin responders higher chest drainage occurred in first 24 h (724.3; $\pm 201$ ml) compared to aspirin resistant patients (583.7 $\pm 83$ ml), ($p = 0.02$). Aspirin resistant patients needed significantly less transfusions (average per patient: 0.3 $\pm 0.9$ units) in comparison to aspirin responders group (average per patient: 1.7 $\pm 2.9$ units), $p = 0.08$.

3.2. Ischemia markers

Dynamic of mean TnI and ST segment elevations are presented in Table 2. There were no significant correlations between CT-EPI changes and ischemia markers found. No significant differences were observed between aspirin resistant and responders groups in terms of TnI, CK-MB, and ST segment elevation dynamics (Table 3). Hemoglobin concentration and hematocrit levels in certain time points did not differ significantly between the groups (Table 4). However, aspirin resistant patients tended to achieve higher hemoglobin concentration 120 h post-surgery: 12.1 $\pm 1.1$ versus 11.6 $\pm 1.2$ g/dl (in aspirin responders group), $p = 0.06$.

4. Discussion

The presented study inspires discussion in three clinical areas: goal and effectiveness of antiplatelet therapy continued until surgery day before OPCAB, review of perioperative antiplatelet strategy in OPCAB patients and clinical implications for early- and long-term secondary prophylaxis of ischemic events after off-pump surgical revascularization.

Current guidelines on surgical treatment of coronary heart disease advise cessation of platelet inhibitors before CABG; 7 days for aspirin and 5 days for clopidogrel [1]. This is mainly based on trials which indicated higher postoperative drainage, more frequent revisions due to bleeding, increased transfusions and a higher incidence of wound healing complications when aspirin therapy was continued [6,7]. However, lately Sun et al. in their meta-analysis have shown that those trials were mainly conducted on patients operated with use of cardiopulmonary bypass and with high aspirin doses administered preoperatively [8]. More recent publications revealed no impact of aspirin on bleeding and transfusions, especially when lower doses were used [9,10]. The predominant goal of platelet blocking before surgical revascularization (both for OPCAB and on-pump CABG) is myocardial perfusion protection during surgery and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Aspirin responders</th>
<th>Aspirin resistance</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative TnI (ng/ml)</td>
<td>0 (0.13)</td>
<td>0 (0.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>TnI after 4 h</td>
<td>0.24 (2)</td>
<td>0.29 (4)</td>
<td>0.9</td>
</tr>
<tr>
<td>TnI after 24 h</td>
<td>0.21 (6)</td>
<td>0.18 (5)</td>
<td>0.8</td>
</tr>
<tr>
<td>TnI after 120 h</td>
<td>0.07 (1)</td>
<td>0.03 (2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Preoperative CK-MB (ng/dl)</td>
<td>0.5 (2)</td>
<td>0.7 (2)</td>
<td>0.8</td>
</tr>
<tr>
<td>CK-MB level after 4 h</td>
<td>2 (5)</td>
<td>1.3 (6)</td>
<td>0.4</td>
</tr>
<tr>
<td>CK-MB level after 24 h</td>
<td>2.6 (8)</td>
<td>2.7 (5.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>CK-MB level after 120 h</td>
<td>0.55 (4)</td>
<td>1.05 (5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Preoperative ST elevation (mm)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>ST elevation after 4 h</td>
<td>0.65 (2.7)</td>
<td>0.8 (3.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>ST elevation after 24 h</td>
<td>0.5 (2.8)</td>
<td>0.9 (2)</td>
<td>0.08</td>
</tr>
<tr>
<td>ST elevation after 120 h</td>
<td>0.3 (1.5)</td>
<td>0.2 (1.4)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Data are expressed as median (range). * p values represent differences between the groups.

Table 2

<table>
<thead>
<tr>
<th>Time point</th>
<th>Troponin I (ng/ml)</th>
<th>p-value*</th>
<th>CK-MB (ng/ml)</th>
<th>p-value*</th>
<th>ST-segment elevation (mV)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>0 (0)</td>
<td>--</td>
<td>0.6 (2)</td>
<td>--</td>
<td>0 (0)</td>
<td>--</td>
</tr>
<tr>
<td>After 4 h</td>
<td>0.26 (4)</td>
<td>$&lt;0.001$</td>
<td>1.9 (6)</td>
<td>$&lt;0.001$</td>
<td>0.7 (3.5)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>After 24 h</td>
<td>0.2 (6)</td>
<td>0.7</td>
<td>2.6 (8)</td>
<td>0.08</td>
<td>0.7 (2.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>After 120 h</td>
<td>0.04 (2)</td>
<td>$&lt;0.001$</td>
<td>0.6 (5)</td>
<td>$&lt;0.001$</td>
<td>0.2 (1.5)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Data are expressed as median (range). * p values represent differences between respective time points.
early postoperative period. Gerrah et al. demonstrated that preoperative use of aspirin supported better oxygenation during and after CABG [11,12]. In our cohort there was no significant difference between ASA resistant patients and ASA responders in terms of ischemia markers level during the postoperative observation period. It seems that OPCAB activates platelets in the ASA responders group, so no difference of CT-EPI and ischemia markers occurs between two groups. Few projects revealed a tendency towards better graft function with clinical benefit in mortality when aspirin was continued until surgery day. Increased bleeding was in fact reported but had no impact on hard clinical endpoints [9]. In relation to our results unequivocal conclusions of published projects may result from not taking under consideration preoperative aspirin resistance and acute platelet reaction on surgical interventions. We observed in some patients aspirin protection may be suppressed with OPCAB. Clopidogrel-based pretreatment strategy was considered in latest studies. Data collected in unstable patients (NSTEMI/UA) referred to CABG showed a higher incidence of bleeding and reoperations when clopidogrel therapy was not stopped more than 5 days before surgery [13,14]. On the other hand, a study performed by Karabulut et al. conducted on elective patients did not confirm such results, while 44% of patients received only 75 mg of aspirin showed possible superiority of clopidogrel in terms of event free mid-term survival with the same safety level [24,25]. An important limitation affecting methodology of this and other studies is a lack of general aspirin resistance definition. No single test can definitely demonstrate aspirin resistance. In clinical issues, aspirin resistance is considered when thrombosis occurs on aspirin therapy. In the laboratory, aspirin resistance may be identified as lack of arachidonic acid metabolism block, tromboxane production or present epinephrine stimulated platelet aggregation.

Procoagulative capability after OPCAB may persist for weeks and determine the risk for early graft failure or coronary events [21]. For years early aspirin therapy post-CABG is a class I indication to prevent vein grafts occlusion [1]. However, some studies reported that antiplatelet therapy does not have such impact on internal thoracic artery grafts [22]. As our study showed OPCAB may induce aspirin resistance. Compiling our data with other initial reports showed that aspirin resistance after CABG may persist for weeks and we have to face this oncoming clinical problem. In addition, the number of patients with genetically determined aspirin resistance may reach up to 30%. Larger studies proved a clinical impact of aspirin resistance on worse outcomes in primary prophylaxis in stable ischemic heart disease [23]. Those data support the rationale for looking for better antiplatelet medication than aspirin in patients who underwent OPCAB. First trials comparing clopidogrel with aspirin showed possible superiority of clopidogrel in terms of event free mid-term survival with the same safety level [24,25].

5. Conclusions

Aspirin therapy continued until surgery day does not protect against acute platelet activation in patients after OPCAB. Platelet activation persists for a minimum of 5 days after OPCAB. OPCAB may induce aspirin resistance. Since acute platelet activation occurs in aspirin responders preoperative aspirin therapy may have no impact on the perioperative ischemia markers level.

References


Table 4

Hematocrit (Htc) and hemoglobin (Hb) levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Aspirin responders</th>
<th>Aspirin resistance</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative Htc (%)</td>
<td>40.1 ± 4.6</td>
<td>40.5 ± 4.9</td>
<td>40.5 ± 4.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Htc after 4 h</td>
<td>33.2 ± 3.5</td>
<td>33.1 ± 3.7</td>
<td>33.4 ± 3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Htc after 24 h</td>
<td>32.1 ± 3.3</td>
<td>31.8 ± 3.6</td>
<td>32.7 ± 2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Htc after 120 h</td>
<td>34.1 ± 3.8</td>
<td>33.6 ± 3.5</td>
<td>34.9 ± 4.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Preoperative Hb level (g/dl)</td>
<td>13.6 ± 1.5</td>
<td>13.6 ± 1.5</td>
<td>13.6 ± 1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Hb level after 4 h</td>
<td>11.3 ± 1.2</td>
<td>11.3 ± 1.2</td>
<td>11.2 ± 1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Hb level after 24 h</td>
<td>10.8 ± 0.9</td>
<td>10.7 ± 0.9</td>
<td>11.1 ± 0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Hb level after 120 h</td>
<td>11.6 ± 1.2</td>
<td>11.2 ± 1.1</td>
<td>12.1 ± 1.1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* p values represent difference between ASA-responders and ASA-resistance.


Appendix A. Conference discussion

Dr P. Sergeant (Leuven, Belgium): I think the subject of your presentation is a very important one. You have partially failed to give us the anticoagulation protocol during the procedure itself. It is well known that insufficient levels of anticoagulation during the procedure will create an activation process. Can you inform us about your ACT levels, and what are your targets and how frequently are they controlled?

Dr Suwalski: They are controlled. In those group of patients, we perform half a dose of heparin. We’re trying to reach more than 250, even higher, ACT levels. And then we’re coming back with protamine. But, no, sorry, I was wrong. It was much higher.

Dr Sergeant: There is no scientific proof that half-anticoagulation does give sufficient protection. Your study could have been destabilized through insufficient anticoagulation. Your point is also very well taken that your aspirin is not giving you the protection. This means that immediately after surgery — first of all, during surgery, you need to have sufficient levels of ACT which you need to check every 15, 20 min. And, in addition, immediately after surgery for the last 2500 patients in OPCAB we have given low molecular weight in therapeutic doses. It is insufficient to give 60 mg once a day.

Dr Suwalski: Yes, of course, but first of all, we wanted to see how the platelets function.

Dr Sergeant: Yes. But if you activate the whole clotting cascade during your procedure, and you cannot put your patients at risk by giving insufficient anticoagulation in the days after surgery, you have definitely put your patients at risk.

Dr Suwalski: But if it’s enough to give just heparin or if we should give heparin with platelet blocking. As we can see, we may give platelet blocking but, in fact, we do not block them.

Dr R. Poston (Baltimore, Maryland): I’d like to contribute to this debate about heparinization during surgery. Two years ago I presented a paper here at EACTS, and you actually commented to me about the same question. I actually presented a paper about aspirin resistance after off-pump CABG, and I went back and looked at it, about whether or not a peak ACT above 400 or less than 400 had any influence on aspirin resistance or coagulation.

I’ll actually be presenting those results in an hour, and I will say it does defend the presenter’s position that an ACT of 250 is probably adequate according to the assays that I used. And that may not necessarily be the end result.

Dr Sergeant: Our anesthesiologists have analyzed this very extensively, a whole cascade of tests, and they have identified that a minimum ACT level of 400 was needed. But we’re willing to listen to whatever.