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ORIGINAL ARTICLE

Mean platelet volume-to-platelet count ratio after elective cardiac surgical procedures is superior in reflecting platelets metabolic hyperactivity compared to other routine morphological platelet indices: A preliminary report

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Abstract

Background: *Excessive metabolic excitation of platelets after cardiac procedures may be related to some adverse events but assessment of their metabolic activity is not routine. The purpose of this study was to evaluate which of the basic platelet morphological parameters best reflects their metabolic status.*

Methods: *The blood samples of 22 cardiac surgical patients (mean age of 62.3 ± 10.3 years) were taken before surgery (BS), and 1, 24 and 48 hours after the operation. Correlations between morphological platelet parameters (platelet count [PLT], mean platelet volume [MPV], platelet distribution width [PDW] and MPV/PLT) and their metabolic activity (total concentration of malondialdehyde [MDA] and MDA/PLT) were estimated.*

Results: *Significant decline in PLT after operation (from 223 ± 44 × 10^{12}/L to 166 ± 57 × 10^{12}/L) was accompanied by marked increase in MPV (from 8.4 ± 0.9 fL to 9.1 ± 1.2 fL) and no change of PDW. Consequently, MPV/PLT index increased significantly after procedures from (median with IQR) 0.038 (0.030–0.043) to 0.053 (0.043–0.078). Simultaneously, a significant increase in total platelet MDA content and MDA/PLT was noted reaching peak levels soon after operation. The strongest correlation was observed between MPV/PLT and MDA/PLT ($r = 0.56$; $p < 0.001$), although the others were also found to be significant (MDA/PLT vs. MPV; $r = 0.35$; MDA/PLT vs. PDW; $r = 0.34$).*

Conclusions: *Among basic morphological parameters and indices, the MPV-to-PLT ratio reflects the best metabolic status of platelets in cardiac surgical patients.* (Cardiol J 2023; 30, 6: 995–1002)

Key words: cardiac operation, platelet, mean platelet volume, malondialdehyde

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Introduction

Cardiac surgical operations carried out in the cardio-pulmonary bypass (CBP) are invasive procedures with activation of various cell types and production of numerous biologically active molecules [1, 2]. Among other blood cells, platelets are involved in developing postoperative systematic inflammatory response syndrome (SIRS) [3]. It was shown previously that SIRS with clinical symptoms was noted in 30% of all individuals undergoing heart surgeries [4, 5]. Moreover, SIRS occurrence had an adverse effect on the postoperative course and led to higher postoperative morbidity, including organ failure [4, 6]. On the other hand, the postoperative activation, adherence and aggregation of platelets is mandatory to prevent blood loss at sites of vascular injury and to simultaneously initiate the healing process (a fibrin clot provides a scaffold for attracted inflammatory cells) [7, 8]. Contrary to hyperactivation of platelets, their impaired recruitment on damaged vessels is due to inherited or acquired defects that may promote excessive postoperative bleeding that is usually difficult to counteract by means of surgical maneuvers [9].

So far, many laboratory methods have been developed to test platelet function and metabolic activity that might have potentially applicability after surgical or intravascular procedures [10, 11]. Some of them, such as flow cytometry or light transmission platelet aggregation, are performed predominantly for basic research because they are time-consuming and require sophisticated analytic equipment [10]. Among rapid tests, a whole blood aggregometer (e.g., Multiplate Analyzer) based on impedance platelet aggregometry enables on-site evaluation of platelet function, but appropriate management with blood samples and analysis of its findings needs experienced laboratory personnel that usually are not available 24 hours a day. Moreover, interpretation of results when platelet count (PLT) is below 120×10^{12}/L may be biased [12]. Of note, not uncommonly, PLT is relatively low after cardiac surgical interventions. Additionally, serum thromboxane B_2, a stable metabolite of thromboxane A_2 (TXA_2) produced by activated platelets, has also been shown as a good marker of platelet's reactivity. However, its measurement is laborious and time-consuming, also when using commercially available colorimetric assays. On the other hand, malondialdehyde (MDA), a broadly and easily assayed marker of lipid peroxidation and oxidative stress [13], is also known to be produced by the platelet's thromboxane synthase in amounts that are equimolar to TXA_2 [14]. Therefore, the aforementioned methods may not be considered as routine studies done in all patients in the early postoperative period. In particular, in view of a critical clinical setting that some of them can be related to the abnormal (hyper- or hypo-) activity of platelets, intensivists together with cardiac surgeons must undertake immediate actions to rescue patients. Thus, we need cost-effective and easy-to-perform tests/methods to define platelet metabolic status. It was previously showed that some information withdrawn from basic blood morphology analysis could be clinically relevant [15]. Mean platelet volume (MPV) and platelet distribution width (PDW) were observed to be increased during platelet activation [15]. The others, MPV-to-PLT ratio even better than MPV alone predicted long-term adverse outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary interventions (PCIs) [16].

The purpose of this study was to estimate which of the routinely examined basic morphological parameters or their derivatives correlate best with platelet MDA content, a marker of platelet metabolic activity and oxidative stress, after elective standard cardiac surgical procedures carried out from median sternotomy.

Methods

Patients

The study involved 22 consecutive patients with a mean age of 62.3 ± 10.3 years who underwent elective cardiac surgical procedures from full median sternotomy and in CPB during 1 month period in a single center. The patients who were operated out on a beating heart (off-pump coronary artery bypass grafting [OPCAB]), urgently or emergently, who had any previous cardiac surgical procedures or had to be treated surgically without cessation of antiplatelet (other than acetylsalicylic acid [ASA]) agents as well as on any anticoagulants (including low-molecular-weight heparin [LMWH]) irrespective of the indications, with proven inherited or acquired platelet dysfunction and/or other coagulopathy, PLT less than 120×10^{12}/L on admission and those who had excessive postoperative bleeding followed by chest re-exploration and/or blood products transfusions (n = 2) were excluded from the study (Fig. 1). The selected demographic and preoperative clinical data are outlined in Table 1.

All patients expressed written informed consent to participate in this trial. The study protocol

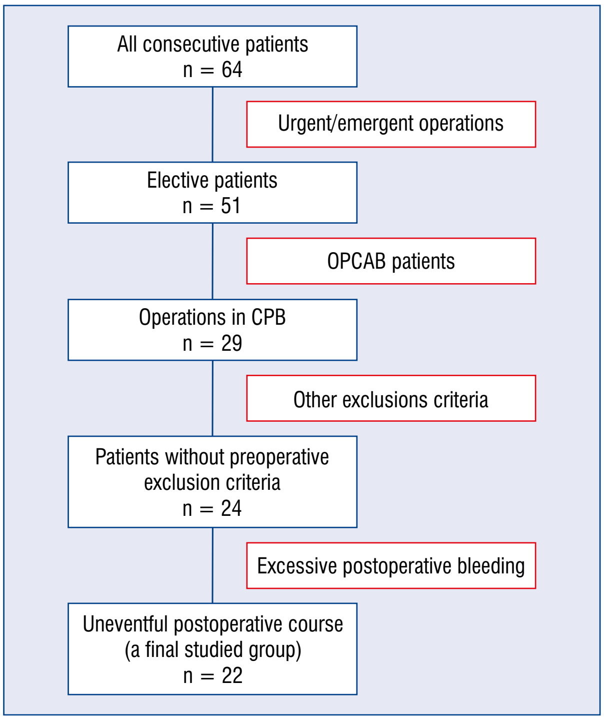

Figure 1. Recruitment process of the consecutive patients. Inclusion and exclusion criteria are indicated in the details contained in the 'Methods' section.

Table 1. Selected preoperative demographic and clinical data of the studied cardiac surgical patients (n = 22)

Parameters*	N = 22
Gender (male/female)	16/6
Height [m]	1.68 ± 0.10
Weight [kg]	82.9 ± 14.5
BMI [kg/m^2]	29.0 ± 4.1
Obesity [BMI > 30 kg/m^2]	9 (40.9)
Hyperlipidemia	16 (72.7)
Diabetes mellitus	6 (27.3)
Arterial systemic hypertension	17 (77.3)
Peripheral artery disease	5 (22.7)
CVA/TIA	2 (9.1)
CKD** 3+	2 (9.1)
COPD	4 (18.2)
ACS in history	7 (31.8)
Previous PCI	6 (27.3)

*Continuous variables are expressed as the means ± standard deviation whereas categorical as numbers and percentages; **Defined if estimated glomerular filtration rate (eGFR) was below 60 mL/min/1.73 m^2 following calculation by means of Modification of Diet in Renal Disease 4 trial equation (eGFR = 186.3 × $S_{cr}^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) × 1.21 [if African American]). ACS — acute coronary syndrome; BMI — body mass index; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CVA — cerebrovascular accident (stroke); PCI — percutaneous coronary intervention; S_{cr} — serum creatinine concentration; TIA — transient ischemic attack

was approved by the Local Bioethical Committee of the Poznan University of Medical Sciences (No. 918/15).

Surgical procedures

All study participants were operated out from a full median sternotomy. Every patient, before any surgical manipulation on the heart and big vessels received an intravenous injection of heparin in a dose of 300 IU/kg. CPB was conducted through cannulation of the ascending aorta and right atrium. Cold cardioplegic arrest and systemic moderate hypothermia (26 to 28°C) were applied as myocardial protective methods. At the end of the surgery, protamine sulfate was injected in relation 1:1 to heparin to reverse the latter one action. The anticoagulation effect's accuracy was controlled by activated clotting time measured on-site and in the operating room. The target value of activated clotting time was greater than 400 s.

Perioperative antiplatelet and anticoagulant management

All but one antiplatelet agent (ASA) was stopped at least 5 days prior to surgery. After operation, the first subcutaneous injections of LMWH in the prophylactic doses were done 6 to 8 hours after surgery (if no excessive bleeding was observed), then twice a day. While postoperative ASA (75 mg) was given in the morning of the next day and then once a day.

Perioperative laboratory examinations

Sampling points. The blood samples were drawn from a peripheral vein before surgery (on the admission day, usually one date before operation), the second one after patient's transfer from the operative room to the postoperative intensive care unit (post-ICU) (usually within 1 h after surgery) and then 24 and 48 hours later, irrespective of the patient stay (post-ICU or normal cardiac surgical ward).

Morphological platelets parameters. Besides typical laboratory examinations obligatory for safe monitoring of basic life parameters, including blood morphology and biochemistry, gases (exceptionally taken from artery), samples of 5 mL of peripheral venous blood were taken for further analysis of platelet metabolic status. Standard morphological parameters of platelets such as PLT, MPV and PDW were entered into an Excel sheet that served as a study database. Eventually, the MPV/PLT ratio was calculated.

Platelets malondialdehyde content

Platelet MDA content, one of the major products of lipid peroxidation, was to assess the effect of surgery on the platelet metabolic status. The platelets were collected in the following manner: the platelet-rich plasma was obtained by centrifugation (200 g, 12 min), transferred to acid citrate dextrose solution (1/10 vol.) and centrifuged again (900 g, 15 min).

After aspiration of plasma, platelets were suspended in distilled water (200 μL). The platelet MDA content was estimated by a commercial TBARS assay kit (Cayman Chemicals, USA) according to the manufacturer protocol and the previous studies [17]. The content was given as μM of MDA. Eventually, MDA content in a single platelet (MDA/PLT) was estimated since invasive surgical procedures can also change PLT significantly.

Data presentation and statistical analysis

First, continuous variables were tested for normality by means of the Shapiro-Wilk test. If they met the Gaussian distribution assumption, they were presented as the means ± standard deviation (SD), otherwise as medians and interquartile range (IQR). Time-related changes of all platelet indices were evaluated either by the analysis of variance (ANOVA) with repeated measurements followed, if applicable, by the *post hoc* Tukey honest significance difference test (for normally distributed continuous variables) or with the use of the Friedman repeated measures ANOVA supplemented by the Dunn multiple rank comparisons (for the other continuous data). Categorical variables were expressed as numbers (n) and percentages (%). The strength of association between platelet morphological (PLT, MPV, PDW, MPV/PLT) and functional parameters (MDA, MDA/PLT) was tested using the Spearman's correlation coefficient. The latter one was interpreted using the scale provided by Chung and Salkin, where an r between 0.8 and 1.0 (or −0.8 and −1.0) was defined as very strong, between 0.6 and 0.8 — as strong, between 0.4 and 0.6 — as moderate, between 0.2 and 0.4 — as weak relationship [18]. A p value < 0.05 was considered statistically significant. All statistical analyzes were carried out using Statistica 13.3 software (TIBCO Software Inc., Palo Alto, CA, USA).

Results

Standard platelet indices

Platelet count. PLT (223 ± 44 × 10^{12}/L at baseline [BS]) decreased significantly markedly after surgery ($p < 0.001$). The *post-hoc* test revealed significant differences between all postoperative sampling points compared to the BS count. Of note, PLT after reaching the lowest value 24 hours after the operation (166 ± 57 × 10^{12}/L) started to increase but 48 hours following surgery it was significantly lower (175 ± 60 × 10^{12}/L) than it was before (Fig. 2A).

Mean platelet volume and platelet distribution width. Although MPV increased markedly after surgery ($p = 0.041$) but further analysis revealed a significant difference only between BS (8.4 ± 0.9 fL) and the last sampling point at 48th hour following operation (9.1 ± 1.2 fL; $p = 0.021$; Fig. 2B).

Mean PDW values ranges between 54.2 ± ± 5.0% at BS and 57.1 ± 6.5% on the 1st day after surgery (Fig. 2C). However, the present calculations failed to show any changes after operations ($p = 0.364$).

MPV-to-PLT ratio. MPV/PLT index increased significantly after procedures ($p = 0.004$) and in all postoperative study time points the value of this ratio was markedly higher (peak at the 24th hour following cardiac surgical operations) than it was in the preoperative period (Fig. 2D).

MDA and MDA/PLT

A significant increase in total MDA platelet content was noted after cardiac surgical interventions ($p < 0.001$). The highest level (median with IQR) was found soon after the operation (4.3 [2.9–5.2] μM; $p < 0.001$ vs. BS), then it systematically started to decrease (24 h: 2.6 [2.1–3.2] μM; $p < 0.001$ vs. BS), and even 48 h later (2.2 [1.5–2.9] μM; $p = 0.027$) it was still higher than before the procedures (1.0 [0.6–1.5] μM).

Since surgery impacted PLT, MDA content in a single thrombocyte (MDA/PLT) was also estimated. Detailed statistical analysis revealed higher medians of MDA/PLT at all sampling points after surgery in comparison to its BS one. The details are shown in Figure 3.

Correlations between platelet morphological and functional parameters

The strongest association between platelet morphological and markers of metabolic activity were observed between MPV/PLT and MDA/PLT ($r = 0.56$; $p < 0.001$), although more significant correlations were also found (Fig. 4).

Discussion

The most crucial finding of this study was the proven association, which was revealed for the

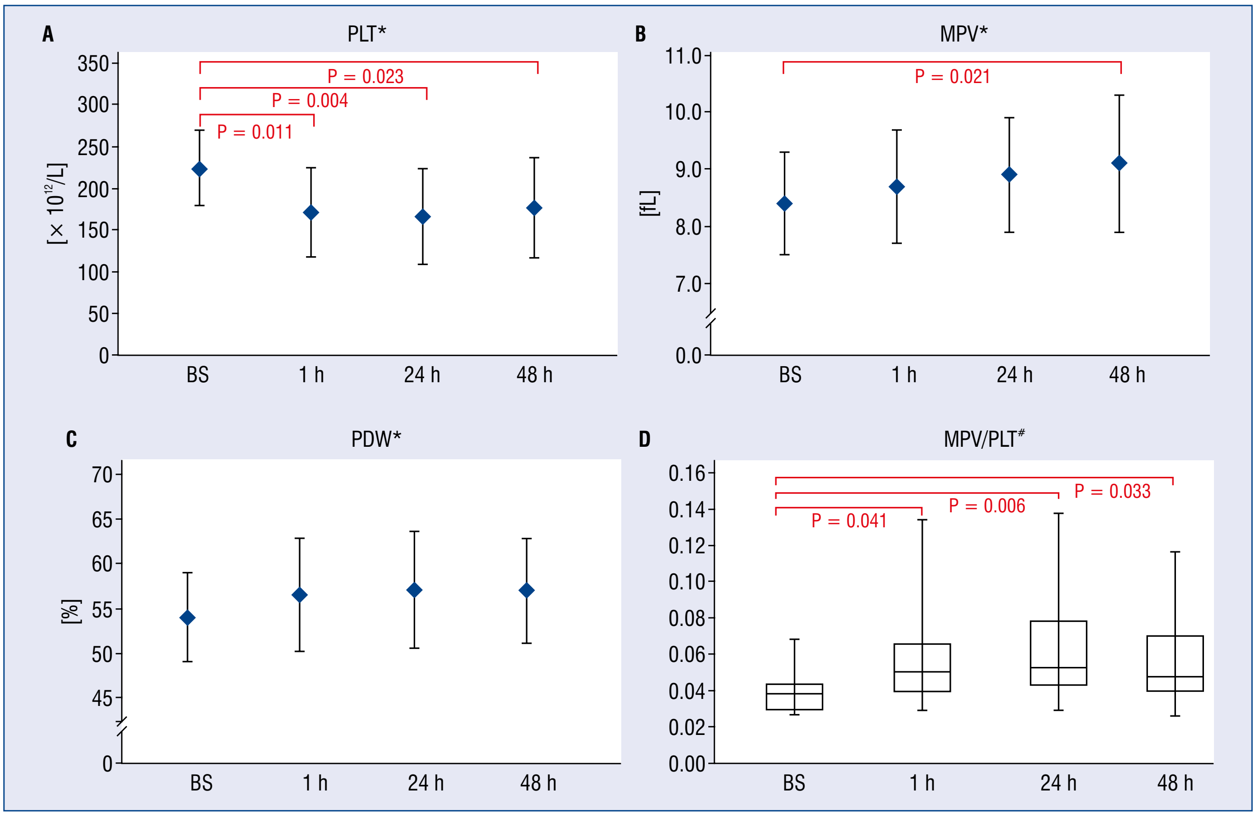

Figure 2. Basic morphological parameters of examined cardiac surgical patients (n = 22). Individual points method of presentation (the means with a standard deviation) was applied for parametric data (*; platelet count [PLT; **A**], mean platelet volume [MPV; **B**], platelet distribution width [PDW; **C**]) whereas box plots (the medians with interquartile ranges and total ranges) for nonparametric data (#; MPV/PLT; **D**). Only p values of significance in post-hoc tests are on the graphs; BS — baseline.

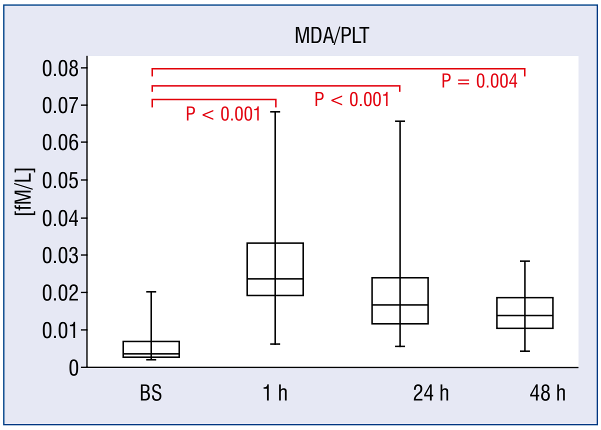

Figure 3. Time-related changes of malondialdehyde (MDA) content in single platelets in the perioperative period in cardiac surgical patients (n = 22). MDA/PLT as nonparametric data are presented as the medians with interquartile ranges and total ranges (minimum--maximum); BS — baseline; PLT — platelet count.

first time according to available research, between metabolic activity of platelets and some basic morphological parameters such as MPV, PDW or MPV//PLT that are routinely monitored in the early period after cardiac operations. Therefore, such information about likely metabolic excitation may be easily made available within a short time. The other findings regarding postprocedural changes of morphological parameters, such as temporary decline in PLT as well as increase in MPV are not novel. Up till now, particularly the latter one has been studied extensively (usually together with PDW) in patients with coronary artery disease or after PCI, but not following cardiac operations. Of interest, the easily calculated MPV-to-PLT ratio, in the current study corresponds best with the metabolic activity of platelets, and has aroused scientific interest relatively recently.

Previous reports that PLT usually drops soon after cardiac surgical procedures are supported

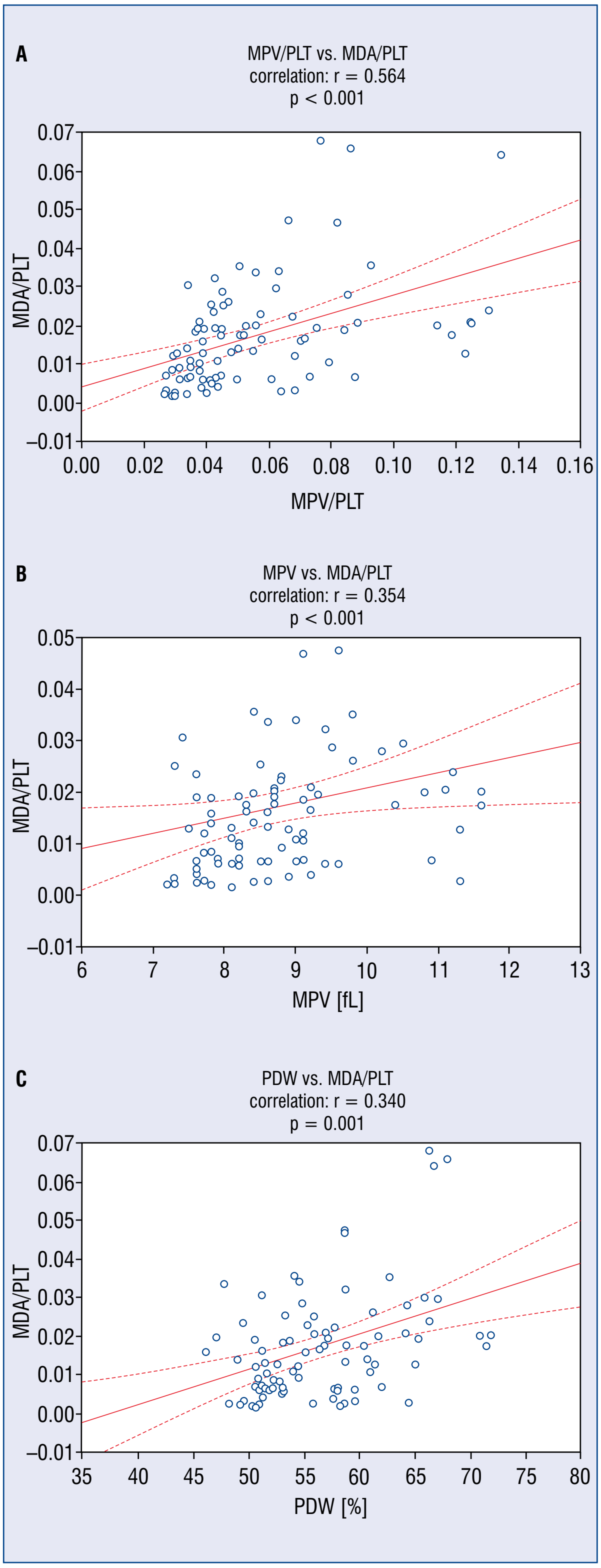

Figure 4. Significant correlation coefficients between platelet morphological parameters and their metabolic activity. Correlations of statistical significance were found between MDA/PLT vs. MPV/PLT (**A**), vs. MPV (**B**) as well as vs. PDW (**C**); MDA — malondialdehyde; MPV — mean platelet volume; PDW — platelet distribution width; PLT — platelet count.

herein, for both adults and in children [19, 20]. Many factors have been suggested which contribute to low PLT, particularly when CPB is applied this includes; mechanical damage, hemodilution, hypothermia and perioperative treatment with platelet-inhibiting agents [21]. Moreover, blood loss is inevitable during such invasive procedures, especially if more complex procedures with longer CPB time are carried out [22, 23]. Of note, this effect is usually temporary and not uncommon post 24 hours, at least a partial recovery is usually observed [24]. The latter finding was also confirmed by the present observations. The other basic platelet indices such as MPV and PDW were found to be elevated after procedures associated with iatrogenic injury [25, 26]. Higher values of MPV and PDW after surgical procedures may be a net result of two biological processes both driven by tissue damage. The trauma-induced mixture of cytokines and reactive oxygen species provokes bone marrow for production and release of platelets to the vascular system due to a differentiation of megakaryocytes [27]. Newly released platelets tend to be larger than mature forms and MPV is often considered a reflection of the average age of these cells. However, the aforementioned reaction of bone marrow in response to surgical trauma may not be harmful. Miceli et al. [26] found that aortic valve replacement in CPB resulted in thrombocytopenia, higher PDW and MPV in the early postoperative period but in the absence of adverse clinical events. On the other side, circulating platelets respond to vessel injury by changes in morphological shape, secretion of granule contents, and aggregation to prevent blood loss. It was previously proved that large size platelets manifested increased enzymatic and metabolic activity as well as prothrombotic potential [28]. Our study supports earlier reports regarding MPV but not PDW. We cannot exclude that recruitment of a larger volume of patients would have revealed more changes of statistical significance.

Monitoring of platelets activity as well as their metabolic status is of importance after medical procedures with extensive iatrogenic tissue damage and SIRS. To assess the metabolic activity of platelets, we have chosen the content analysis of MDA, a product of thromboxane synthase and the marker of lipid peroxidation, oxidative stress and redox imbalance [17]. Oxidative stress altering platelets redox state may lead to their activation and eventually thrombus formation. It was previously observed that increased intraplatelet MDA content was also shown to be related to higher platelet activity, including aggregation [14, 29]. This association was confirmed by the other studies that found suppression of platelet MDA levels resulted in inhibition of arachidonate- and collagen-induced aggregation [30]. Therefore, pronounced changes in platelet metabolic status may play a role in the functional pathologies responsible for either excessive bleeding or thrombo-embolic adverse events [4, 7].

Of note, some basic morphological platelet indices have been suggested to be of clinical prognostic value after both coronary artery bypass grafting (CABG) and acute coronary syndrome patients treated with PCI [31–34]. One of them, MPV was previously found to predict not only the development of saphenous vein graft disease but also mortality and morbidity (e.g., atrial fibrillation) following CABG) [31, 32] Wang et al. [33] showed dynamic changes of MPV during the acute phase of myocardial infarction and higher MPV in patients with high Killip class, suggesting its predictive value in ventricular dysfunction and adverse clinical outcome after angioplasty for acute coronary syndrome. In their study, antiplatelet treatment with pre-used clopidogrel resulted in significant MPV reduction on admission. Not only MPV, but also PDW was found to be associated with no-reflow phenomenon after primary PCI, and may be one of the mechanisms responsible for a poor prognosis if the platelet were hyperactive (reflected by rapid elevation of MPV and PDW) [34]. Herein, among platelet indices, the strongest correlation with platelet metabolic activity (MDA) was found for MPV/PLT ratio. The latter one was shown to predict long-term adverse outcomes in patients with STEMI undergoing PCI [16]. In another study, a high MPV/PLT ratio was associated with early vein-graft occlusion and poor postoperative outcomes, including both early and late reduced survival rates [35].

Limitations of the study

Some limitations of the present study should be stressed. Firstly, the number of patients participating in this clinical study was relatively small. However, even the small group size did enable revealing significant findings. Of course, one cannot exclude the that recruitment of a higher number of individuals would have increased the practical value of the examined parameters. On the other side, the primary stress is put on the findings in the laboratory studies. At least one of them is not routine and requires experienced staff and a well--equipped research laboratory. In the vast majority of studies, such a number is considered sufficient to make the conclusions that follow. There is an awareness that the present findings must be further supported by the clinical outcomes of patients undergoing cardiac surgical procedures. Therefore, it must be stressed that the present research results are treated as groundwork for further prospective clinical studies.

Conclusions

Heart surgeries as complex and invasive procedures have significant impact on both morphological parameters and indices of their metabolic status. Among basic morphological parameters and indices, the MPV-to-PLT ratio best reflects the metabolic status of platelets in cardiac surgical patients.

Conflict of interest: None declared

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