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Comparison of Platelet Mass Index in On-Pump and Off-Pump Coronary Artery Bypass Surgery

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ABSTRACT

Introduction: Platelet mass index (PMI) is calculated by multiplying platelet count and mean platelet volume (MPV). It demonstrates platelet activation and is thought to be associated with inflammation. Its importance for cardiac surgery has not yet fully been clarified. This study investigates whether there is a difference between PMI levels after on-pump and off-pump coronary artery bypass surgery and the relationship between early postoperative complications and PMI.

Method: In our hospital, 138 patients were included in the study retrospectively. The patients were divided into 2 groups: Group 1 (on-pump) with 80 patients (22 females, 58 males, mean age 61.54 ± 8.68) and Group 2 (off-pump) with 58 patients (15 females, 43 males, mean age 61.34 ± 10.04). In biochemical analysis, hemoglobin, platelet, white blood cell, and MPV values of the patients were evaluated in the biochemistry laboratory of our hospital with the blood taken preoperatively from the forearm veins and postoperatively on the first, third, and seventh days and, on average, after the first month.

Results: There was a statistically significant difference between postoperative first day thrombocyte (K/µL) (P = .005), postoperative first day PMI (P = .014), postoperative first day leukocyte (K/µL) (P = .001), postoperative first day Hb (g/dL) (P = .001), postoperative third day thrombocyte (K/µL) (P = .003), postoperative third day PMI (P = .031), postoperative third day leukocyte (K/µL) (P = .004), and postoperative seventh day leukocyte (K/µL) (P = .002). There was no meaningful relationship between PMI and early postoperative complications.

Conclusion: We think PMI is a more valuable indicator than MPV as an inflammation marker in cardiac surgery. In our opinion, PMI is a cheap and valuable inflammation marker that can be used in coronary surgery that can be obtained from routine hemogram test and can easily be evaluated.

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INTRODUCTION

In selected patients, coronary artery bypass surgery is a very effective method to relieve signs and symptoms of ischemic heart disease. Cardiac surgery can be performed either with (on-pump) or without (off-pump) cardiopulmonary bypass (CPB). Cardiac surgery and CPB cause alterations of systemic inflammation and oxidative stress [Paparella 2002]. Preoperatively calculated risk scores predict mortality risks, but fail to identify patients at risk for complications after cardiovascular surgery. Therefore, it is important to know which patients should closely be monitored for postoperative cardiovascular events.

Association of inflammation with many adverse results in cardiac surgery has been demonstrated [Zakkar 2015]. Although neutrophils and lymphocytes are known as the main cells in inflammation, lately the importance of platelets has been emphasized as well [Franco 2015]. The relationship of markers, such as total platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) to various diseases has been studied in the literature [Wachowicz 2016; Omar 2018; Zhang 2014; Akpinar 2014].

It has been reported that platelet mass index (PMI), which is obtained by multiplying platelet count and MPV, is a better parameter for platelet activation [Demir 2016]. However, its importance for cardiac surgery has not yet been fully clarified.

Studies investigating the relationship between postoperative PMI levels after on-pump and off-pump coronary bypass are not present. Therefore, in this study, we investigated whether there was a difference between patients undergoing on-pump and off-pump surgery, in terms of postoperative PMI levels and the relationship between early postoperative complications and PMI.

MATERIALS AND METHODS

One hundred-thirty-eight patients were included in the study retrospectively in our hospital. The patients were divided into 2 groups: Group 1 (on-pump) with 80 patients (22 females, 58 males, mean age 61.54 ± 8.68) and Group 2 (off-pump) with 58 patients (15 females, 43 males, mean age 61.34 ± 10.04). In general, patients with 2 or 3 vessels with coronary lesions on the anterior aspect of the heart, low ejection fraction, respiratory causes, and calcific ascending aorta were preferred for off-pump coronary bypass. This study was

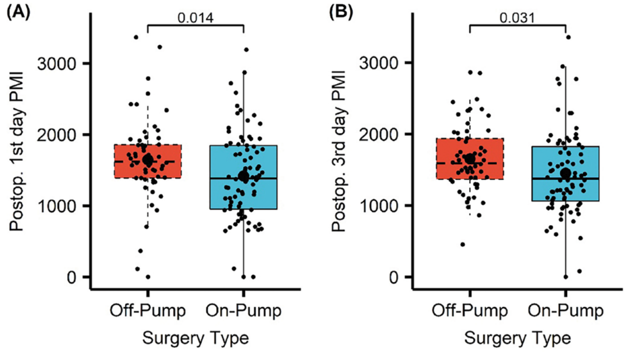

Figure 1. A, Evaluated as statistically significant postoperative first day PMI. B, Postoperative third day PMI represented as schematic view of values.

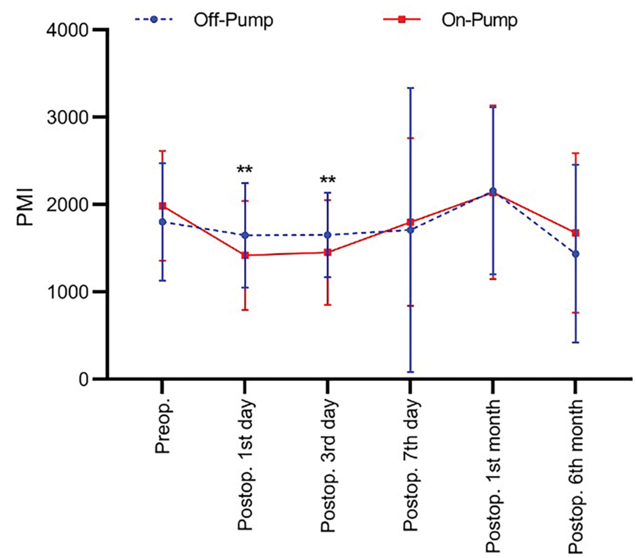

Figure 2. Variation of PMI over time.

conducted, according to the recommendations contained in the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Informed consent was obtained from all patients.

Excluded from the study were patients with active or chronic inflammatory conditions, autoimmune diseases, rheumatologic diseases, clinical evidence of active infection, malignancy, any hematological disease, anemia or recent blood transfusion, liver failure, thyroid dysfunction, developing mechanical complications of coronary artery disease (ventricular septal defect, ventricular free wall rupture, etc.), or those undergoing concomitant valvular surgery.

The data were obtained from hospital patient files and the hospital computer registry system. In our study, complications and mortality can be defined to include all days until patients were discharged from the hospital.

Low cardiac output syndrome is defined as the requirement for inotropic support for more than 48 hours or requirement for mechanical support such as intra-aortic balloon pump or extracorporeal membrane oxygenation. Stroke is defined as a sign of a new neurological deficit or transient ischemic attack confirmed by imaging test. Atrial fibrillation is diagnosed when postoperative ECG imaging reveals the absence of P waves and unequal QRS intervals in comparison to pre-operation. Postoperative infections are evaluated as pneumonia, sternal wound infection, and mediastinitis. Acute kidney injury is defined as the preoperative creatinine value increased by 2-fold or request for renal replacement study.

In biochemical analysis, preoperative and postoperative evaluations were made for the first, third, and seventh days and the first month on average, with the blood taken from the forearm veins. Approximately 5 mL to 7 mL venous blood samples were placed in sterile tubes with EDTA. Hemoglobin, thrombocyte, leucocyte, and MPV values were measured by using an Abbott Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, USA) in our hospital's biochemistry laboratory. PMI was obtained by multiplying the platelet count and MPV value.

Surgical technique - on-pump surgery: Median sternotomy was performed when the patient was under general anesthesia. Arterial and venous grafts were prepared. LIMA was removed as standard arterial graft in each patient. LAD was preferred to bypass the artery. The saphenous vein was removed as venous graft. It was generally used during coronary artery bypass grafting except for LAD. Cannulas were placed in the aorta and right atrium after systemic heparinization (300 IU/kg). During the operation, the activated clotting time (ACT) was maintained for over 450 seconds. Cardiopulmonary bypass was started by using a roller pump and membrane oxygenator. Patients routinely were cooled to 28-30°C. Myocardial protection was provided by antegrade cold crystalloid cardioplegia after cross clamping, and it was repeated every 20 minutes. During cardiopulmonary bypass, flow was 2.2-2.5 L/min/m^2, mean perfusion pressure was between 50-mm and 80-mm Hg, and hematocrit level was maintained at 20-25%. Distal anastomoses were performed under cross-clamp and proximal anastomoses under lateral clamp by grafting the aorta.

Off-pump surgery: After median sternotomy under general anesthesia, LIMA and saphenous vein grafts were prepared. LIMA again was preferred for LAD and the saphenous vein graft for other vessels. After the pericardium was opened, the heart was suspended by sutures placed in the pericardium. Systemic heparinization was performed at a dose of 1-2 mg/kg ACT for 250-300 seconds. Distal anastomoses were performed with the aid of Octobus 4 (Medtronic Inc, Minneapolis, MN, USA). The intracoronary shunt (Clearview intracoronary shunt, Medtronic Inc., USA) was generally placed in accordance with the coronary artery diameter to provide a bloodless area during anastomosis. The shunt was removed through the coronary artery near the end of the anastomosis. Proximal anastomoses were then performed under the lateral clamp. In all patients, the

Table 1. Results of the analysis of the differences between the two groups as regards the demographic variables

Parameters	Off-Pump	On-Pump	*P*
Average age (years)	61.34 ± 10.04	61.54 ± 8.68	ns
BMI (kg/m^2)	25.10 (1.99–29.41)	23.67 (1.86–29.38)	ns
Preoperative left ventricular EF (%)	60.21 ± 7.69	62.02 ± 9.27	ns
Systolic blood pressure (mmHg)	128.33 ± 11.09	130.09 ± 12.96	ns
Diastolic blood pressure (mmHg)	75.73 ± 10.82	75.28 ± 9.50	ns
Heart rate (beats/minute)	76.27 ± 7.81	78 ± 7.03	ns
EuroSCORE	2.77 ± 2.05	3.84 ± 2.39	.008
Total cholesterol (mg/dL)	181.71 ± 38.19	185.24 ± 42.91	ns
Triglyceride (mg/dL)	135 (99–204)	143 (112.50–196.50)	ns
HDL cholesterol (mg/dL)	38.36 ± 8.42	39.63 ± 7.95	ns
LDL cholesterol (mg/dL)	110.20 ± 32.04	110.10 ± 33.29	ns
Fasting blood glucose (mg/dL)	99.50 (88–123)	107 (92–130)	ns
BUN	16 (13–20)	16 (13–20)	ns
Creatine	0.87 (0.73–1.02)	0.84 (0.76–1.02)	ns
Uric acid (mg/dL)	5.31 ± 1.05	5.25 ± 1.59	ns
CRP (mg/dL)	3.91 (1.61–7.90)	4.84 (2.40–9.70)	ns

Values are presented as mean ± standard deviaton or median (interquartile range)

P-value: student's t test or Mann Whitney-U test

BMI: body mass index, BUN: blood urea nitrogen, HDL cholesterol: high density lipoprotein, LDL: low density lipoprotein, CRP: C-reactive protein, EF: ejection fraction, ns: not significant

sternum was closed according to the subcutaneous and cutaneous anatomy.

Statistical analysis: All statistical analyses were performed using R Version 3.6.0 (www.r-project.org). $P < .05$ was considered statistically significant. Anderson Darling test was carried out to assess data normality, and Levene's test was performed to test variance homogeneity. Fisher's exact test was used to determine significance among categorical variables. To compare continuous variables, student's t and Mann Whitney-U tests were used. Categorical data were summarized through counts (N) and percentages (%), and continuous data through mean ± standard deviation or median (interquartile range). Pearson correlation analyses were performed between postoperative first day PMI, postoperative third day PMI, and variables in univariate analysis. Multiple regression analyses were performed to evaluate the relationship between postoperative first day PMI, postoperative third day PMI, and variables found significant with them in univariate analysis. Stepwise method was used for variable selection method.

RESULTS

The mean age was determined as 61.54 ± 8.68 years for Group 1 and 61.34 ± 10.04 years for Group 2 (*P* = ns). In terms of preoperative demographic data, there was no statistically significant difference between the other variables except Euroscore (*P* = .008) (Table 1).

In terms of hemogram data, there was statistically meaningful difference between postoperative first day thrombocyte (K/μL) group ½ [164 (124-222)/204 (174-233)] (*P* = .005), postoperative first day PMI group ½ [1383.07 (949.64-1846.91)/1618.11 (1388.91-1859)] (*P* = .014), postoperative first day leukocyte (K/μL) group ½ [11.80 (9.81 to 14.30)/10 (8.25 to 11.60)] (*P* = 0.001), postoperative first day Hb (g / dL) group ½ [10.80 (10.20-11.80)/11.80 (10.60-12.80)] (*P* = 0.001), postoperative first day C-reactive protein (CRP) (mg/L) group ½ [83.03 (69.30–123.30)/117.40 (83–152.90)], postoperative third day thrombocyte (K/μL) group ½ [162 (122-235)/197.50 (171-234)] (*P* = .003), postoperative third day PMI group ½ [1451.25 ± 600.88/1652.24 ± 482.84] (*P* = .031), postoperative third day leukocyte (K/μL) group ½ [10.32 ± 3.30/8.76 ± 2.77] (*P* = .004), postoperative seventh day leukocyte (K/μL) group ½ [9.91 (8.07-12.10)/8.24 (7.33-9.74)] (*P* = .002). No difference was found between postoperative first day MPV (fL), postoperative third day MPV (fL) and Hb (g/dL), CRP (mg/L), postoperative seventh day PMI, platelet (K/μL) and MPV (fL), CRP (mg/L) and Hb (g/dL), postoperative first month MPV (fL), thrombocyte (K/μL), PMI, leukocyte (K/μL), CRP (mg/L), Hb (g / dL) values (*P* = ns). The postoperative first and third day PMI values and the change of PMI values over time are shown (Figures 1 and 2).

As for operative and postoperative data, there was statistical

Table 2. Postoperative first day PMI

Parameters	Univariate		Multiple (Stepwise)	
	R	*P*	β	*P*
EuroSCORE	-0.195	.023	-	-
Preop. thrombocyte (K/µL)	0.398	<.001	-	-
Preop. leukocyte (K/µL)	0.253	.003	-	-
Postop. 1st day MPV (fL)	0.353	<.001	0.534	<.001
Postop. 1st day thrombocyte (K/µL)	0.865	<.001	0.871	<.001
Postop. 1st day leukocyte (K/µL)	0.268	.002	-	-
Postop. 3rd day thrombocyte (K/µL)	0.594	<.001	0.103	.003
Postop. 7th day thrombocyte (K/µL)	0.328	<.001	-	-
Postop. 1st month thrombocyte (K/µL)	0.311	<.001	-0.060	.027
Postop. 1st month leukocyte (K/µL)	0.310	.001	-	-
Full blood (units)	-0.363	<.001	-	-
Plasma	-0.241	.005	-	-

difference between ventilation time (hrs) group ½ [5.50 (4.50-9)/4.50 (3.50-8)] (*P* = .046), the period of hospitalization (days) group ½ [7 (6-9)/5 (4-7)] (*P* < .001), full blood (units) group ½ [3 (2-4)/1 (1-2)] (*P* < .001), plasma (units) group ½ [5 (4-6)/4 (2-5)] (*P* = .001). There was no difference between the 2 groups, in terms of postoperative drainage (*P* = ns). In terms of postoperative early adverse events, there was a difference in pleural effusion between the 2 groups (*P* = .023). Ratio of pleural effusion was higher in group 1 (66/10, no/yes respectively) compared to group 2 (57/1, no/yes respectively). There were no significant differences in revision due to bleeding, sternal infection, pulmonary infection, mediastinitis, acute renal failure, and atrial fibrillation (*P* = ns).

Factors affecting the postoperative first day PMI include postoperative first day MPV (fL) (*P* < .001), postoperative first day thrombocyte (K/µL) (*P* < .001), postoperative third day thrombocyte (K/µL) (*P* = .003) and postoperative first month thrombocyte (K/µL) (*P* = .027), variables were statistically significant in multivariant analysis (Table 2).

Postoperative third day PMI are found to be affected by postoperative third day thrombocyte (K/µL) (*P* < .001) variable with significance (Table 3).

DISCUSSION

For the first time in the literature, our study found that PMI values were found to be higher on the first and third days postoperatively in patients, who underwent off-pump surgery compared with those who had undergone on-pump surgery. There was no significant difference between the 2 groups, in terms of postoperative adverse events except pleural effusion. In addition, no correlation was found between postoperative complications and PMI (Tables 2 and 3).

Cardiac surgery usually is performed using cardiopulmonary bypass. The patient is connected to the heart-lung machine by various lines. Blood is cleaned after contact with foreign surfaces and given back to the patient. Cardiopulmonary bypass, a non-physiological method, is associated with many adverse events in the body. It causes formation and increase of inflammation. In more detail, there are several possible explanations for inflammation in cardiac surgery patients. For example, hemolysis, blood loss, hypothermia, ischemia and perfusion injury and neutrophil activation during CPB play an important role in activation associated with oxidative stress and inflammation. Ischemia and reperfusion injury, especially during cardiac surgery, can lead to the formation of pro-inflammatory mediators [Christen 2005; Zakkar 2015; Laffey 2002; Pearson 2003; Lehmann 2019].

One method used to reduce inflammation, especially in coronary surgery, is to bypass the heart while it is working; this is called off-pump. Cardiopulmonary bypass is not used in this technique. Technically, it is more difficult than on-pump surgery. Although the anterior aspect of the heart generally is revascularized, other aspects of the heart also have started to be revascularized with the help of surgical experience and technology in heart stabilization. Especially in elderly and high-risk patients, it reduces the undesirable complications that may be caused by cardiopulmonary circulation, such as neurological complications, inflammatory response and myocardial ischemia [Yoon 2017].

Platelets actively participate in the process of inflammation, atherogenesis, and thrombus formation through the production and release of various cytokines and chemokines [Langer 2008]. Although neutrophils are known to be the main cells in inflammation, thrombocyte-neutrophil interaction is emphasized in the formation of infection, inflammation and thrombosis, and studies on this subject recently have been conducted [Lisman 2018].

MPV is a simple and easy method for evaluating platelet function. MPV is associated with undesirable clinical events. In various studies, the subject has been investigated in literature. For example, a positive correlation was found

Table 3. Postoperative third day PMI

Parameters	Univariate		Multiple (Stepwise)	
	R	*P*	β	*P*
Preop. thrombocyte (K/μL)	0.472	<.001	-	-
Preop. leukocyte (K/μL)	0.284	.001	-	-
Postop. 1st day thrombocyte (K/μL)	0.626	<.001	-	-
Postop. 3rd day thrombocyte (K/μL)	0.912	<.001	0.935	<.001
Postop. 7th day leukocyte (K/μL)	0.191	.042	-	-
Postop. 7th day thrombocyte (K/μL)	0.695	<.001	-	-
Postop. 1st month thrombocyte (K/μL)	0.441	<.001	-	-
Postop. 1st month leukocyte (K/μL)	0.299	.001	-	-
The period of hospitalization (days)	-0.189	.029	-	-
Full blood (units)	-0.213	.030	-	-
Plasma (units)	-0.248	.004	-	-

between MPV and acute ischemic cerebrovascular cases. High MPV has been shown to be associated with a worse outcome for acute ischemic cerebrovascular cases, independent of other clinical parameters [Greisenegger 2004]. In addition, increased MPV has a prognostic role in cardiovascular disease. In a study, it was found to be associated with high mortality following myocardial infarction [Boos 2007]. Another recent prospective study found that MPV can be used to predict the onset of venous thromboembolism, especially in those of non-provoked origin. In patients with MPV 9.5 and above, the risk of developing non-provoked venous thromboembolism was significantly increased 1.5-fold compared with those with MPV <8.5 [Braekkan 2010]. For Li et al, MPV was found to be independently associated with the presence of colon cancer. It has been shown that MPV values are higher and decrease postoperatively in patients with colon cancer compared with the control group [Li 2014]. In all these and similar publications, inflammation, which is the basis of diseases, can be interpreted as increasing the numerical value of MPV.

In our study, no difference was found between the 2 groups, in terms of MPV values for any time frame. This information shows us that MPV for CABG perhaps is not valuable enough to be an inflammation marker. In our study, it was found that platelet counts significantly were lower in the on-pump group on the postoperative first and third days, but improved over time, and no difference was found between the 2 groups after the postoperative seventh day. It can be concluded that platelets easily are affected by cardiopulmonary bypass used in on-pump surgery. As a result, many elements in the blood traveling in a foreign environment are activated. And, this leads to the breakdown of platelets, reducing their number. In addition, the dilution of platelets decreases due to the use of prime solution.

Many markers of inflammation such as leukocytes, C-reactive protein, neutrophils, and lymphocytes are known. PMI also is one of the clinical parameters that can be found recently by detailed analysis of the hemogram. PMI is a newly emerged marker of inflammation when compared with MPV. Normally, a low-number and high-volume inverse relationship between platelet count and platelet volume generally is considered to provide a balanced saving of PMI and thus maintain platelet function. Different studies have suggested that PMI may be a better inflammation marker when compared with MPV [Demir 2016; Okur 2016; Korkmaz 2017].

In a related literature study, 46 patients were evaluated for a highly mortal disease known as Fournier's gangrene. Low PMI values were found to be a poor prognostic factor [Girgin 2018]. In another study conducted for ductus arteriosus in recent years, no difference was found between MPV and PMI values among infants whose duct was closed and remained open [Kahvecioglu 2018].

In another study for the presence and severity of calcific AD, platelet count x platelet count/mean platelet volume/10^7 was found to be significantly higher in advanced AD group compared with mild and moderate AD groups [Çakmak 2016]. In our study, PMI values were found to be higher in the off-pump group compared with the on-pump group on the postoperative first and third days. This difference was statistically significant (*P* = .014, 0.031, respectively). After the seventh day, there was no difference between the 2 groups.

CONCLUSION

PMI, which has been investigated as an inflammation marker for many diseases, can be considered as a negative inflammation marker, due to the low detection of on-pump CABG. In other words, it should be kept in mind that patients with low postoperative PMI values should be more careful and more aggressive treatments should be considered when necessary. Nevertheless, low PMI values should be investigated in different subjects in order to be an indicator of inflammation for cardiac surgery. For instance, the relationship between PMI and inflammation, such as postoperative AF and renal failure, and PMI should be investigated in a large number of prospective studies.

Limitations of the study: Our study is a retrospective study, and the number of patients is relatively low. The results should be supported by more comprehensive, prospective studies. Furthermore, it can be a confusing factor that postoperative blood transfusion is significantly higher in the on-pump group compared with the other group.

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