Rev Bras Cardiol Invasiva.
2014;22(3):240-4

Original Article

Mean Platelet Volume as a Predictor of Major Cardiovascular Outcomes and Final Coronary Flow in Patients Undergoing Primary Percutaneous Coronary Intervention

Luiz Carlos Corsetti Bergoli, Eliza Schuck Castanho, Sandro Cadaval Gonçalves, Rodrigo V. Wainstein, Diogo Piardi, Gustavo Araújo, Márcio Mossmann, Ana Maria Krepsky, Marco V. Wainstein

ABSTRACT

Background: Platelets play a key role in the pathophysiology of acute myocardial infarction. There is evidence that higher platelet volumes may have increased prothrombotic potential. The aim of this study was to evaluate whether mean platelet volume can predict culprit coronary vessel flow and adverse cardiovascular outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. **Methods**: Primary endpoint was the composite of adverse cardiovascular events (death, stroke, myocardial infarction, stent thrombosis, class-III or IV angina and heart failure) at 30 days. The secondary endpoint was evaluated by the angiographic TIMI flow grade after the procedure. **Results**: Of the 215 patients included in the primary percutaneous coronary intervention registry, 168 (78.6%) had their mean platelet volume calculated before the procedure and were analyzed in the present study. Mean platelet volume values were stratified in tertiles, and a high value was considered as > 11 femtoliters (fL). Mean platelet volume > 11 fL was an independent predictor of cardiovascular events at 30 days (p = 0.02). It was observed that patients with final TIMI flow grade zero or 1 showed a trend towards higher mean platelet volume compared with those with final TIMI flow 2 or 3 (11.3 ± 0.9 fL vs. 10.5 ± 1.3 fL; p = 0.06). **Conclusions**: Baseline mean platelet volume is a simple, useful, and easy to measure marker to predict the risk of cardiovascular events at 30 days in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Future studies may answer whether more aggressive antithrombotic therapy results in better angiographic and/or clinical outcomes in patients with larger and more active platelets.

DESCRIPTORS: Myocardial infarction. Percutaneous coronary intervention. Mean platelet volume.

RESUMO

Volume Plaquetário Médio Como Preditor de Desfechos Cardiovasculares Maiores e Fluxo Coronariano Final em Pacientes Submetidos à Intervenção Coronária Percutânea Primária

Introdução: As plaquetas desempenham papel fundamental na fisiopatologia do infarto agudo do miocárdio. Existem evidências de que plaquetas de maior volume apresentem potencial pró-trombótico aumentado. O objetivo deste estudo foi avaliar se o volume plaquetário médio pode predizer o fluxo coronariano do vaso tratado e os desfechos cardiovasculares adversos em pacientes com infarto do miocárdio com supradesnivelamento do segmento ST submetidos à intervenção coronária percutânea primária. **Métodos**: Desfecho primário foi considerado como a ocorrência de eventos cardiovasculares adversos (morte, acidente vascular cerebral, infarto agudo do miocárdio, trombose de stent, angina e insuficiência cardíaca classes 3 ou 4) em 30 dias. Desfecho secundário foi avaliado por meio da análise angiográfica do fluxo TIMI pós-procedimento. **Resultados**: Dos 215 pacientes incluídos no registro de intervenção coronária percutânea primária, 168 (78,6%) tiveram volume plaquetário médio calculado antes do procedimento e foram analisados no presente estudo. Valores do volume plaquetário médio foram estratificados em tercis, sendo considerado um valor elevado > 11 fentolitros (fl). Volume plaquetário médio > 11 fl foi preditor independente de eventos cardiovasculares em 30 dias (p = 0,02). Observou-se que pacientes com fluxo final TIMI zero ou 1 demonstraram tendência a apresentar volume plaquetário médio maior em relação àqueles com fluxo final TIMI 2 ou 3 (11,3 ± 0,9 fl vs. 10,5 ± 1,3 fl; p = 0,06). **Conclusões**: O volume plaquetário médio basal é um marcador simples, de fácil aferição e útil para predizer risco de eventos cardiovasculares em 30 dias em pacientes com infarto do miocárdio com supradesnivelamento do segmento ST submetidos à intervenção coronária percutânea primária. Estudos futuros podem responder se a terapia antitrombótica mais agressiva resulta em melhores desfechos angiográficos e/ou clínicos nos pacientes com plaquetas maiores e mais ativas.

DESCRITORES: Infarto do miocárdio. Intervenção coronária percutânea. Volume plaquetário médio.

Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

Correspondence to: Luiz Carlos Corsetti Bergoli. Rua Ramiro Barcelos, 2.350 – Santa Cecília – CEP: 90035-903 – Porto Alegre, RS, Brazil
E-mail: lcbergoli@gmail.com

Received on: 06/22/2014 • Accepted on: 08/16/2014

Higher platelet volumes are metabolically and enzymatically more active, and mean platelet volume (MPV) is the most commonly used measure to assess platelet size. Platelets with larger volume contain more prothrombotic material, including thromboxane A2 and B2, P-selectin,[1] and greater expression of glycoprotein IIb/IIIa receptors.[1,2] They also have increased platelet factor 4 release[3] and platelet-derived growth factor.[4,5] Larger platelets are most commonly reticulated, which is an independent factor for worse response to dual antiplatelet therapy.[6] Finally, they show higher aggregability in response to ADP[7]and lower aggregation reduction with the use of *in vitro* prostacyclin.[8]

Therefore, MPV is a marker of platelet reactivity. Unlike all other markers of platelet activation and reactivity, it is automatically calculated by most equipment for performing blood-cell count.[9] Thus, platelet size determination through MPV is a simple, extremely inexpensive, and readily available measure in hospital and outpatient settings.[10]

This study aimed to assess whether MPV obtained from complete blood count on admission is a predictor of post-procedural coronary flow and adverse cardiovascular events at 30 days in patients with acute myocardial infarction with ST-segment elevation (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

METHODS

Study design and outcomes

Cohort, prospective study, in which the clinical outcome was the occurrence of combined adverse cardiovascular events at 30 days; a composite of death, stroke, acute myocardial infarction (AMI), need for new unplanned revascularization, heart failure class 3 or 4 according to the New York Heart Association (NYHA), or angina class 3 or 4 according to the criteria of the Canadian Cardiovascular Society (CCS). Clinical follow-up was performed by outpatient visit or telephone contact. The post-PPCI final TIMI flow was considered the angiographic outcome.

Population and procedures

Patients with signs of STEMI undergoing PPCI in the Interventional Cardiology Unit of a tertiary hospital were included. Patients with STEMI and mechanical complication and those who required urgent heart surgery were excluded from the analysis. The criteria used to define STEMI were: ST-segment elevation at J-point ≥ 2 mm in men and ≥ 1.5 mm in women, in at least two contiguous leads in leads V2-V3 and/or ≥ 1 mm in two other contiguous leads, according to the latest universal definition of myocardial infarction.[11]

Patients were pretreated with 300 to 500 mg of acetylsalicylic acid (ASA), 600 mg loading dose of clopidogrel, and unfractionated heparin intravenously at doses of 70 to 100 IU/kg. The use of glycoprotein IIb/IIIa inhibitors, the performance of aspiration thrombectomy, and percutaneous intervention strategies (pre-dilation and direct stenting post-dilation) were carried out at the surgeon's discretion. Anticoagulant use was discontinued after procedure completion (except in cases of absolute indication) and dual antiplatelet therapy use was recommended for 12 months after the event.

Basal MPV, collected at the patient's arrival in the emergency room before PPCI, was used. Patients whose blood had not been collected before the procedures were excluded from the analysis.

Angiographic analysis

Angiographic analysis was performed to determine the initial and final TIMI flow, as well as evaluation of the anatomical complexity using the angiographic SYNTAX score. To calculate the SYNTAX score, each coronary lesion with luminal obstruction > 50% in vessels ≥ 1.5 mm were scored and at the end, all lesions were added, according to the specific recommendations (www.syntaxscore.com). The score was calculated based on the initial angiography before any therapeutic approach, and considered the patency of the artery responsible for the AMI. Thus, in the presence of initial TIMI flow zero or 1, the culprit lesion was scored as total occlusion with thrombus.

Statistical analysis

All data were analyzed using SPSS, version 17.0. Continuous variables were described as means and standard deviations and compared using Student's *t*-test for independent variables or Mann-Whitney test, according to their distribution. Categorical variables were presented as percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. After the univariate analysis, multivariate logistic regression was performed to determine the degree of influence and independence of predictive factors of adverse cardiovascular events at 30 days. The logistic regression included the variables with significant association in the univariate analysis and those predictive of outcomes in previous studies. The results were expressed as relative risk (RR) and 95% confidence interval (95% CI). Significance was considered at a two-tailed level of $p < 0.05$.

RESULTS

Patients and procedures

Of 215 patients included in the PPCI registry in this service with clinical follow-up, 168 (78.6%) had MPV calculated before the procedure and were analyzed in the present study. MPV values ranged from 6.8 to

Rev Bras Cardiol Invasiva.
2014;22(3):240-4

14.0 femtoliters (fL). These values were stratified into tertiles, with the first tertile representing 6.8 to 10.0 fL; the second, from 10.1 to 11.0 fL; and the third, from 11.1 to 14.0 fL. Upper tertile values were considered high MPV values, i.e. MPV > 11.0 fL.

Basal demographic and clinical characteristics were similar between groups with MPV ≤ 11 fL and > 11 fL, as shown in Table 1. The mean age of patients was 60.7 ± 12.7 years, and 66.3% were males. There was a rate of diabetes mellitus of 15.4% and 60.9% of the patients were hypertensive. Previous or current history of smoking was observed in 68% of the analyzed population. There was a predominance of anterior wall AMI, which occurred in 47.3%.

Table 2 shows the baseline and procedure-related angiographic characteristics. Initial TIMI flow 0 or 1 was observed in 78.1% of cases. The mean SYNTAX score was 15.4 ± 8.5 and did not differ between groups (14.6 ± 8.2 vs. 15.9 ± 9.0; p = 0.46).

The mean number of stents used per patient was 1.2 ± 0.7, and the volume of contrast medium used was 208 ± 88 mL. The transradial approach was used in 49.7% of cases (47.3% vs. 54.2%; P = 0.39). Aspiration thrombectomy was used in 65.7% vs. 57.6% of cases, p = 0.27.

Clinical and angiographic outcomes

When in-hospital death was assessed, an overall incidence of 11.2% was observed. In the group of patients with MPV > 11 fL, the rate of hospital death was higher, but without statistical significance (9.1% vs. 15.3%; p = 0.20).

Thirty-day follow-up was obtained in 100% of cases. The rate of adverse cardiovascular events at 30 days was 23.1% and significantly higher in patients with high MPV (17.3% vs. 33.9%; p = 0.021). Multivariate analysis identified MPV> 11 fL (RR = 2.92; 95% CI: 1.08 to 7.88; p = 0.03) and functional Killip class > 2 (RR = 1.80; 95% CI: 1.09 to 2.98; p = 0.02) as independent predictors of adverse cardiovascular events at 30 days (Table 3).

Regarding the analysis of the final coronary flow (Figure), patients with final TIMI flow 0 or 1 showed tendency to have higher MPV compared to those with final TIMI flow grade 2 or 3 (11.3 ± 0.9 fLvs. 10.5 ± 1.3fL; p = 0.06).

DISCUSSION

The main findings were the following: in patients undergoing primary PCI for treatment of STEMI, MPV assessed on patient arrival at the hospital was able to predict major cardiovascular events at 30-day follow-up. Although not statistically significant, the rate of in-hospital death was higher in subjects with high MPV (> 11 fL).

TABLE 1
Clinical characteristics

Variable	MPV ≤ 11 fL (n = 109)	MPV > 11 fL (n = 59)	*p*-value
Age, years	61.2 ± 12.7	59.9 ± 12.7	0.55
Male gender, %	66.4	67.2	> 0.99
Arterial hypertension, %	60.6	62.7	0.87
Diabetes mellitus, %	12.8	20.7	0.19
Smoking, %	65.1	74.6	0.23
Previous AMI, %	6.4	8.5	0.75
Previous stroke, %	5.5	5.1	> 0.99
Previous heart failure, %	0.9	1.7	> 0.99
Previous PCI, %	8.2	12.1	0.63
Anterior wall STEMI, %	42.7	55.9	0.11
Killip classification > 2, %	9.1	15.3	0.31
Previous creatinine, mg/dL	1.00 ± 0.90	1.05 ± 0.54	0.68
Quantitative ECC, mL/min	86.2 ± 24.6	80.8 ± 27.0	0.20

MPV: mean platelet volume; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; STEMI: acute myocardial infarction with ST-segment elevation; ECC: endogenous-creatinine clearance.

TABLE 2
Angiographic and procedural characteristics

Variable	MPV ≤ 11 fL (n = 109)	MPV > 11 fL (n = 59)	*p*-value
Transradial approach, %	47.3	54.2	0.39
Intra-aortic balloon, %	6.4	8.5	0.62
Glycoprotein IIb/IIIa inhibitor, %	56.1	61.4	0.51
SYNTAX score	14.7±8.2	15.9±9.1	0,46
Door-to-balloon time, minutes	70.5±27.2	67.9±22.5	0.60
Pre-PCI TIMI flow 0 or 1, %	75.5	83.1	0.25
Aspiration thrombectomy, %	65.7	57.6	0.27
Stent length, mm	24.2±13.1	26.0±15.4	0.42
Number of stents	1.25±0.7	1.25±0.7	0.99
Direct stenting, %	31	34.5	0.65
Post-dilation, %	52.4	54.4	0.81
Contrast volume, mL	201.4±75.4	220.3±106.9	0.20

MPV: mean platelet volume; PCI: percutaneous coronary intervention.

TABLE 3
Predictors of adverse cardiovascular events at 30 days

Variable	RR	95%CI	*p*-value
Killip Classification > 2	1.80	1.09-2.98	0.02
MPV > 11 fl	2.92	1.08-7.88	0.03
Diabetes mellitus	1.72	0.49-6.03	0.40
Male gender	1.16	0.37-3.65	0.79
Transradial approach	0.98	0.35-2.75	0.96
SYNTAX score	1.01	0.95-1.08	0.68
Age	1.02	0.98-1.07	0.36
Door-to-balloon time	0.98	0.98-1.02	0.94
Previous creatinine	1.02	1.02-0.58	0.95

RR: relative risk; 95% CI: 95% confidence interval; MPV: mean platelet volume.

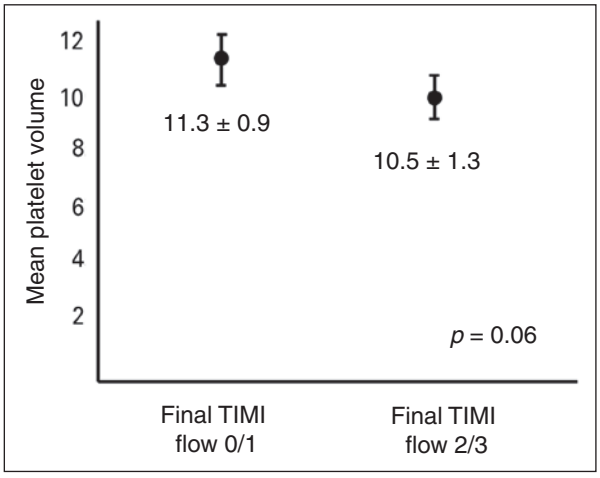

Figure – Final TIMI flow and mean platelet volume. TIMI: Thrombolysis in Myocardial Infarction.

There was also a tendency for patients with higher final coronary flow to have smaller-volume platelets.

It was observed that the SYNTAX score before PCI was similar between patients regardless of MPV, which supports previous findings that demonstrated no association between MPV and the extent of coronary artery disease.[12] Increased platelet reactivity found in higher-volume platelets has been shown to result in clinical symptoms in different scenarios of coronary disease, both in the short and long term. A study by Gonçalves et al.[13] in an unselected population of 1,432 patients undergoing PCI demonstrated that MPV > 9 fL measured before the procedure was independently associated with the incidence of death or myocardial infarction at the 1 year follow-up. Another recent study demonstrated that elevated MPV was independently associated with myocardial infarction without ST-segment elevation, low ejection fraction, and culprit lesion severity in patients with acute coronary syndrome without ST-elevation.[14] A meta-analysis that included 24 studies and more than 6,000 individuals confirmed the hypothesis that high MPV is a risk factor for cardiovascular disease. Three findings of this meta-analysis must be mentioned: a significant difference was observed between MPV of individuals with and without myocardial infarction, mainly when patients with myocardial infarction were compared with those with stable cardiovascular disease or without coronary disease; elevated MPV was associated with higher mortality after myocardial infarction; and, among patients undergoing PCI, MPV was significantly higher among those who developed restenosis.[15]

In the scenario of myocardial infarction, it has been shown that the MPV measured six months after the event was able to predict recurrent infarction and mortality in 2 years.[16] In 2005, Huczek et al.[17] demonstrated in 398 patients undergoing PPCI that MPV measured before the procedure was a strong independent predictor of reperfusion failure and mortality in 6 months. No-reflow phenomenon was observed in 21.2% vs. 5.5% ($p = 0.0001$), when comparing patients with MPV greater to or equal and lower than 10.3 fL, respectively. Another study also demonstrated, in the context of primary PCI, that increased MPV was a predictor of both basal coronary flow and mortality at 30 days only in patients that were not treated with glycoprotein IIb/IIIa inhibitors.[18] Furthermore, two studies published in 2014 demonstrated an association between individuals that were no-responders to clopidogrel and increased MPV in patients with acute coronary syndrome,[19,20] further supporting the hypothesis that increased platelet activity and decreased platelet inhibition are the mechanisms acting as mediators of worse cardiovascular outcomes in individuals with increased MPV.

Although this index has been increasingly confirmed as a risk marker, a cut-off value is yet to be defined. Considering that MPV is higher in patients with AMI, it is likely that the cut-off varies according to the clinical scenario. Finally, a relevant question is whether a more aggressive-antithrombotic and antiplatelet-aggregation therapy in individuals with high MPV can result in improved cardiac outcomes.

Study limitations

This study has limitations, some of which are inherent to observational studies. A small sample of patients was analyzed; however, it was enough to demonstrate, with statistical significance, the association between MPV and major cardiovascular outcomes. Individuals were enrolled from a single interventional cardiology center. This is a referral hospital to the treatment of patients with STEMI, with most patients treated through the Brazilian Unified Health System (Sistema Único de

Saúde – SUS) and coming from the metropolitan area; thus, they are a fairly representative sample of this population. Finally, late follow-up of patients was not performed, although significant results were observed in the short-term outcome. These patients are currently being followed and future studies, with a longer follow-up period, should be performed.

CONCLUSION

In patients with myocardial infarction submitted to primary percutaneous coronary intervention, basal mean platelet volume was a simple marker, easy to measure and useful to predict increased risk of major cardiovascular events at 30 days.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING SOURCES

None.

REFERENCES

1. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. Eur Heart J. 2001;22(17):1561-71.
2. Giles H, Smith RE, Martin JF. Platelet glycoprotein IIb-IIIa and size are increased in acute myocardial infarction. Eur J Clin Invest. 1994;24(1):69-72.
3. Kaplan KL, Owen J. Plasma levels of beta-thromboglobulin and platelet factor 4 as indices of platelet activation in vivo. Blood. 1981;57(2):199-202.
4. Casscells W. Smooth muscle cell growth factors. Prog Growth Factor Res. 1991;3(3):177-206.
5. Ferns GA, Raines EW, Sprugel KH, Motani AS, Reidy MA, Ross R. Inhibition of neointimal smooth muscle accumulation after angioplasty by an antibody to PDGF. Science. 1991;253(5024):1129-32.
6. Guthikonda S, Alviar CL, Vaduganathan M, Arikan M, Tellez A, DeLao T, et al. Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. J Am Coll Cardiol. 2008;52(9):743-9.
7. Karpatkin S, Khan Q, Freedman M. Heterogeneity of platelet function: correlation with platelet volume. Am J Med. 1978;64(4):542-6.
8. Jakubowski JA, Adler B, Thompson CB, Valeri CR, Deykin D. Influence of platelet volume on the ability of prostacyclin to inhibit platelet aggregation and the release reaction. J Lab ClinMed. 1985;105(2):271-6.
9. Michelson AD. Methods for the measurement of platelet function. Am J Cardiol. 2009;103(3 Suppl):20A-26A.
10. Boos CJ, Lip GY. Assessment of mean platelet volume in coronary artery disease- what does it mean? Thromb Res. 2007;120(1):11-3.
11. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.
12. Güvenç TS, Hasdemir H, Erer HB, İlhan E, Özcan KS, Çalık NA, et al. O volume plaquetário médio abaixo do normal está associado com extensão reduzida de doença arterial coronariana. Arq Bras Cardiol. 2013;100(3):255-60.
13. Gonçalves SC, Labinaz M, Le May M, Glover C, Froeschl M, Marquis JF, et al. Usefulness of mean platelet volume as a biomarker for long-term outcomes after percutaneous coronary intervention. Am J Cardiol. 2011;107(2):204-9.
14. Dogan A, Aksoy F, Icli A, Arslan A, Varol E, Uysal BA, et al. Mean platelet volume is associated with culprit lesion severity and cardiac events in acute coronary syndromes without ST elevation. Blood Coagul Fibrinolysis. 2012;23(4):324-30.
15. Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost. 2010;8(1):148-56.
16. Tekbas E, Kara AF, Ariturk Z, Cil H, Islamoglu Y, Elbey MA, et al. Mean platelet volume in predicting short- and long-term morbidity and mortality in patients with or without ST-segment elevation myocardial infarction. Scand J Clin Lab Invest.2011;71(7):613-9.
17. Huczek Z, Kochman J, Filipiak K, Horszczaruk GJ, Grabowski M, Piatkowski R, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. J Am Coll Cardiol. 2005;46(2):284-90.
18. Estévez-Loureiro R, Salgado-Fernández J, Marzoa-Rivas R, Barge-Caballero E, Pérez-Pérez A, Noriega-Concepción V, et al. Mean platelet volume predicts patency of the infarct-related artery before mechanical reperfusion and short-term mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Thromb Res. 2009;124(5):536-40.
19. Asher E, Fefer P, Shechter M, Shechter M, Beigel R, Varon D, et al. Increased mean platelet volume is associated with non-responsiveness to clopidogrel. Thromb Haemost. 2014;112(1): 137-41.
20. Uzel H, Ozpelit E, Badak O, Akdeniz B, Barış N, Aytemiz F, et al. Diagnostic accuracy of mean platelet volume in prediction of clopidogrel resistance in patients with acute coronary syndrome. Anadolu Kardiyol Derg. 2014;14(2):134-9.