Mean platelet volume and platelet count: overlooked markers of high on-treatment platelet reactivity and worse outcome in patients with acute coronary syndrome

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I would like to inform you about our experience with elementary platelet characteristics as markers of high on-treatment platelet reactivity (HTPR).

Acetylsalicylic acid (ASA, aspirin) and ADP inhibitor-based therapy is well established in coronary artery disease treatment. Despite this treatment, platelet reactivity may remain high in some patients, what results in more frequent thrombotic complications (1). In recent years, new ADP inhibitors have become widely available. Although these new drugs undoubtedly decrease the risk of thrombotic complications, they also increase the risk of bleeding complications (2, 3). In order to decrease the risk of both thrombotic and bleeding complications, it might be rational in some patients to tailor the antiplatelet treatment, as evidenced by the MADONNA study (4). It can be inferred that tailored antiplatelet treatment is effective in some high-risk groups of patients, and identification of such risks will be essential for routine clinical use.

Many intrinsic and extrinsic factors associated with increased risk of HTPR have already been identified. We focused on conditions associated with high platelet turnover and increased ADP level. These risk factors are difficult to be measured exactly, but might be approximated by basic blood count values. Mean platelet volume is higher in younger and in activated platelets (5), and therefore can be expected to correlate with platelet turnover and platelet activation. Platelet count and platelet hematocrit correlate with high level of platelet cytoplasm, which is known to be a source of potent pro-aggregatory substances.

Therefore, the primary aim of the study was to assess the relationship between mean platelet volume, platelet count, platelet hematocrit and HTPR in patients with acute coronary syndrome treated using percutaneous coronary intervention. The secondary aim was to assess the relationship between mean platelet volume, platelet count, platelet hematocrit and long-term mortality in the same group of patients.

In the period from April to December 2007, 190 patients were enrolled in the study (132 men and 58 women, average age 67.7±8.1 years). All the study patients were treated by ASA 100 mg daily with intravenous loading dose 500 mg; clopidogrel 75 mg daily with loading dose 300-600 mg; and unfractionated heparin in dose approaching 100 U/kg/ day.

In the early phase of hospitalization, the mean platelet volume, platelet count and platelet hematocrit were measured. The normal range for mean platelet volume was taken to be 7.8-11.5 fl, the normal range for platelet count 150-400×10^9/L, and the normal range for platelet hematocrit was 0.13-0.35%. The response to antiplatelet treatment was assessed using Multiplate® assay (Dynabyte GmbH, Munich, Germany) at 3rd-5th day of treatment. The assay provides a high sensitivity for anti-platelet drugs with good predicting of thrombotic complications (1). Study patients were divided into groups according to their response to antiplatelet treatment: normal response to antiplatelet treatment, "poor responsiveness to aspirin" (PRA), poor responsiveness to clopidogrel (PRC), and "poor response to both aspirin and clopidogrel [dual poor responsiveness (DPR)]. Patients in the DPR group were concomitantly included in the PRA and PRC groups.

The mortality data were obtained from Czech National Population Registry, which guarantees 100% mortality follow-up. The research was approved by the institutional ethics committee and all participants gave written informed consent.

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Table 1. Differences in platelet characteristics according to the response to antiplatelet treatment

	DPR present	DPR not present	PRA present	PRA not present	PRC present	PRC not present
Mean platelet volume, fl	11.1±0.9*	10.7±0.8	11.1±0.9***	10.7±0.8	10.9±1.0*	10.6±0.9
Platelet count, $\times 10^9$/L	254.7±60.6	222.1±67.0	242.2±71.2	220.0±63.6	244.8±73.8*	219.4±62.6
Platelet hematocrit, %	0.269±0.056*	0.234±0.070	0.268±0.080**	0.230±0.064	0.265±0.070**	0.231±0.067**

*p<0.05; **p<0.01; ***p<0.001
DPR - dual poor responsiveness; PRA - poor responsiveness to aspirin; PRC - poor responsiveness to clopidogrel

We documented increased mean platelet volume, platelet count and platelet hematocrit in patients with high on-treatment platelet reactivity (Table 1).

Mean platelet volume and platelet hematocrit were increased in patients with DPR, PRA and PRC (11.1±0.9 vs. 10.7±0.8, p<0.05 for DPR; 11.1±0.8 vs. 10.7±0.7, p<0.001 for PRA; 10.9±1.0 vs. 10.6±0.9, p<0.05 for PRC). Platelet count was increased in patients with PRC (244.8±73.8 vs. 219.4±62.6, p<0.05).

Moreover, we found mean platelet volume and platelet count to be predictors of high on-treatment platelet reactivity. Patients with mean platelet volume higher than 11.5 fl were at higher risk of DPR (22.9% vs. 9.0%; HR 2.53, 95% CI 1.15-5.37, p<0.05) and PRA than patients with mean platelet volume less than or equal to 11,5 fl (40.0% vs. 16.7%; HR 2.38, 95% CI 1.37-3.92, p<0.01). Patients with platelet count higher than 400×10^9/l were at significantly higher risk of PRC (44.4% vs. 19.9%; HR 2.60, 95% CI 1.07-4.33, p<0.05) in comparison with patients with lower platelet count.

Another important finding was that the three-year mortality was increased in patients with high mean platelet volume (25.7% vs. 13.5%, p<0.05; Fig. 1).

Our results are in concordance with results of previous studies. There are several reports regarding the association between mean platelet volume and resp. HTPR or mortality in patients with acute coronary syndrome (6). Reports regarding the association between platelet count and HTPR are rare (7). We did not find any report describing association of platelet hematocrit to HTPR. No previous study described the association of mean platelet volume to both HTPR and mortality simultaneously.

We would like to highlight the fact that the easily available platelet characteristics can be used as markers of high on-treatment platelet reactivity. This is important especially now, when new ADP antagonists are available and first evidence of tailored antiplatelet treatment benefits was published. It can be concluded that patients with increased mean platelet volume or platelet count might be good candidates for antiplatelet treatment monitoring.

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