The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases

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SUMMARY

Background: Mean platelet volume (MPV) is arousing increasing interest as a new independent cardiovascular risk factor. Aim: To provide a comprehensive review on the biological significance, the main determinants and the prognostic implications of MPV. Methods: A literature search was performed using key terms, such as ‘MPV’ or ‘mean platelet volume’, together with ‘stroke’, ‘myocardial infarction’ and ‘diabetes and obesity’. Results: Large platelets are likely more reactive: elevated MPV values are associated with a shortened bleeding time and increased thromboxane B2 plasma levels. Thus, MPV could be considered an indicator of platelet function. Platelet size is mainly determined in the bone marrow during megakaryocyte-megakaryopoiesis, and subsequently does not substantially change. MPV is only partially regulated by thrombopoietin: in fact, growth factors and cytokines may also elicit the production of larger and more reactive platelets in the bone marrow, in the presence of conditions capable of increasing their concentrations, such as obesity, endothelial dysfunction and possibly myocardial and cerebral ischaemia. This phenomenon could play an important role in vascular diseases. In fact MPV is predictive of stroke, acute myocardial infarction (AMI) and restenosis of coronary angioplasty, is increased in the presence of obesity, diabetes mellitus, metabolic syndrome, AMI and stroke and has been shown to have a prognostic significance in patients with stroke and AMI. Conclusion: In assessing whole blood count, MPV should not be undervalued, as its increase should suggest a careful assessment of cardiovascular risk.

Introduction

Platelets are circulating, anucleate, disc-shaped cells, the count of which varies over the considerable range of 150,000 to 400,000/mm³. Their main role is to maintain the integrity of blood vessels through adequate haemostasis (1). Circulating platelets may differ in size and haemostatic potential (1,2). Larger platelets contain more granules and produce greater amounts of vasoactive and prothrombotic factors, such as thromboxane A2, serotonin and ATP; they aggregate more rapidly under the stimulus of agonists, such as ADP, collagen and adrenaline; and finally, they express a greater number of adhesion molecules, such as P-selectin and GpIIb/IIIa (3,4). All this leads to greater haemostatic efficiency: in fact, increased mean platelet volume (MPV) values are associated with shortened bleeding times (5).

The belief that platelet size decreases with platelet ageing was wrong. Indeed, platelet age and size are both determinants of platelet activity, but in an independent way (6,7). The main platelet parameters seem to be determined in megakaryocytes during platelet production. Actually, changes in platelet shape, and consequently in volume, may also occur at the sites of activation. In vitro, the contact with agonists, such as serotonin and ADP, causes important changes in shape, with the appearance of pseudopodia, in the activated platelets (8). The presence of large, more reactive (but not activated) platelets in the circulation is, however, a different phenomenon, caused by a reduced fragmentation of megakaryocytes. Megakaryocytes are polyploid cells, as they are able to multiply their DNA content by a variable number of endomitotic cycles (7,9). Platelet size and the main megakaryocyte parameters are so closely linked that they may be considered as a single system, the ‘megakaryocyte-platelet-haemostatic axis’ (MPHA) (10). Under physiological conditions, the rate of platelet production is continuously regulated...
so that the circulating ‘platelet mass’ (platelet count × MPV) is kept constant (1,11); in fact, an inverse correlation between MPV and platelet count is usually found (12). Thus, several acute inflammatory conditions, such as the relapse phases of inflammatory bowel disease and rheumatoid arthritis, are characterised by an increase in platelet count associated with a simultaneous decrease in MPV values (13–15), while in the presence of hyperthyroidism, increased MPV values may accompany a lower platelet count (16). However, MPV and platelet count can also change independently of each other (17). Experimental studies in animal models have shown that when acute platelet destruction occurs in the absence of platelet production, only an increase in MPV occurs; conversely, when platelet production is increased in the absence of platelet destruction, MPV is unaffected and, finally, when events occur that lead to the simultaneous presence of platelet production and destruction, both MPV and platelet count may increase. These observations have led to the hypothesis that MPV and megakaryocyte ploidy may be under separate hormonal control (18–23).

The most typical conditions associated with a lack of the physiological inverse relationship between MPV and platelet count are: bronchial carcinoma (increased platelet count but normal platelet volume) (24); atherosclerotic renal artery stenosis and heterozygous thalassaemia (increased MPV and normal platelet count) (25,26); diabetes mellitus and myeloproliferative disorders (increased MPV and platelet count together) (26,27).

In these complex mechanisms of regulation, thrombopoietin (TPO) certainly plays a relevant role. It seems that TPO levels are mainly influenced by platelet mass (28). Moreover, in addition to TPO [which is synthesised in the liver (29)], several cytokines and growth factors may affect MPHA (30–36), with subsequent production of larger and more reactive platelets. These mechanisms could be involved in several vascular diseases, such as acute coronary syndromes and stroke, and could even play a role in the processes leading to the formation of atherosclerotic plaque.

This review article reports the main results obtained in the last few years on the association of MPV with the risk and prognosis of coronary and cerebrovascular diseases, and with some cardiovascular risk factors (mainly diabetes and obesity). A network of possible pathogenic links among such conditions is also proposed. The principal aim was to attract attention to a parameter that is already routinely available in many laboratories and is often disregarded, while it could sometimes suggest the need for a careful assessment of cardiovascular risk.

**Measurement of MPV**

The methods for measuring platelet volume have changed over time. Thus, variations of electrical impedance have been utilised (Beckman Coulter analysers, Fullerton, CA, USA), as well as light diffraction (Bayer Technikon analysers, Leverkusen, Germany), up to the more recent methods based on flow cytometry and the detection of two angles of laser light scatter, which allow the measurement not only of the volume, but also of the density of every single platelet (Siemens ADVIA analysers, Deerfield, IL, USA). MPV measurement is thus very accurate, and in addition platelet distribution width may be measured as the coefficient of variation of platelet volume: (standard deviation/MPV) × 100.

A technical problem arises from the fact that platelets exhibit a time-dependent swelling when blood samples are anticoagulated with ethylenediaminetetra-acetic acid (EDTA) (3), while this swelling does not occur in the presence of citrate. However, it has been shown that MPV values are independent of the anticoagulation with EDTA or citrate if the measurement is performed within 1 h of sampling (37).

**MPV and coronary artery disease**

Mean platelet volume is increased during acute myocardial infarction (AMI) and in the first subsequent weeks (38–40). This finding is often associated with a transient decrease in platelet count (38,41). Moreover, among patients with coronary artery disease, those with higher platelet volume seem to have a greater risk of AMI than those with lower MPV, regardless of the extent of the coronary lesions (42), although some authors have reported contrasting data (43).

These findings have led to the conclusion that the increase in platelet size occurs before the acute event and may play an important role in the genesis of the disease. Kristensen et al. (44) demonstrated that the bleeding time of patients with AMI is shorter than that in patients with unstable angina. This effect seems to be mediated by thromboxane, which is produced in larger quantities in the presence of high MPV values. MPV also seems to be independent of the infarct size and site (45), which reinforces the impression that this parameter is mainly determined before the acute event. However, large platelets may be released into the circulation, at least in part, also in response to myocardial ischaemia, as is suggested by the fact that MPV increases after exercise stress test in coronary patients (46).

Muscari et al. (47) found a direct association between an MPV ≥ 8.4 fl (the high tertile of its distribution) and ischaemic ECG changes, while Pizzulli
et al. (48) found higher MPV values in patients with documented coronary artery disease than that in controls, and in unstable angina more than in stable angina. In addition, among the patients with unstable angina, MPV was higher in those requiring immediate revascularisation (48). Finally, MPV may be associated with coronary syndrome X (49). Interestingly, large hyperactive platelets might be sequestered in the coronary circulation of coronary artery disease patients, as suggested by the finding of lower MPV values within the coronary sinus than in the arterial blood (50).

Other authors investigated the association of MPV with the prognosis of acute coronary syndromes and with the outcome of percutaneous coronary interventions. For example, Martin et al. (51) measured MPV 6 months after AMI in 1716 patients, who were followed up for 2 years: the patients who had a second ischaemic event had higher baseline MPV values than the patients who had no further AMI; MPV values were also higher in those who subsequently died with respect to those who did not, showing that platelet size is a risk factor and a prognostic indicator in patients with AMI.

Mean platelet volume was even found to be an effective marker of impaired reperfusion in patients who underwent coronary angioplasty (52). Some authors showed that the patients with a high MPV before the angioplasty had an increased risk of death and coronary restenosis in the following 4–8 months (53,54).

**MPV and cerebrovascular disease**

Several studies have investigated the relationships of MPV with stroke and its prognosis. O’Malley et al. (55) noticed an increase of MPV in all subtypes of ischaemic stroke. This increase was already detectable in the acute phase (within 48 h of the onset of symptoms) and persisted long after the stroke (the second measurement was performed after 6 months). This finding led to the conclusion that increased MPV values were probably pre-existent to the acute event, and were potentially involved in the genesis of the disease, considering, in particular, that mean platelet life is only 8 days. Most studies found a greater MPV increase in cortical strokes than in lacunar strokes (56,57).

Importantly, in patients with previous cerebrovascular diseases, the PROGRESS study (58) showed that MPV could predict the risk of a second stroke up to 4 years before the acute event, documenting an 11% increase of the relative risk of stroke for each femtoliter of MPV increment.

Mean platelet volume can even provide some information about the prognosis of stroke patients (56–59). Greisenegger et al. (59) subdivided 776 patients with stroke in quintiles according to the MPV values obtained within 3 days of the onset of the symptoms. A week after the event, the patients were evaluated with the modified Rankin Scale (mRS). The subjects within the highest quintile of MPV had the most severe strokes and the worst prognosis. Similarly, Butterworth and Bath (56) found that the patients who were dead or dependent (mRS 3–6) at 3 months poststroke had high basal MPV values. Muscari et al. (57) examined the spontaneous variability of MPV during the acute phase of ischaemic stroke, showing that this parameter, in non-lacunar strokes, tends to increase progressively in the first week, although with a different timing according to the severity of the disease. In particular, the MPV increase was earlier in patients with a greater neurological impairment than in those with a less compromised clinical picture. Thus, the authors suggested that the temporal factor should be considered in the assessment of the prognostic value of MPV, because a late MPV increment occurs even in the less severe ischaemic strokes. Other studies, however, did not find any significant relationship between MPV and stroke outcome (55,60). These discordances could be due to the number of enrolled patients and to the utilisation of different outcomes.

**MPV, other cardiovascular diseases and antiplatelet drugs**

In pregnant women, an increase in MPV values is predictive of pre-eclampsia 4.6 weeks before the diagnosis (61). Moreover, the longitudinal monitoring of MPV may identify the women who will benefit from intensification of antiplatelet treatment (62).

Increased MPV, C-reactive protein and erythrocyte sedimentation rate values have been reported in the presence of paroxysmal atrial fibrillation (AF) (63), and MPV values are higher in permanent than in paroxysmal AF (64). These findings may contribute to explain the prothrombotic state associated with this arrhythmia.

Finally, hypertensive patients with stenosis of a renal artery may also present increased MPV values (25). At present, no data are available concerning a possible association of MPV with peripheral artery disease. Similarly, only limited data are available regarding the relationships between antiplatelet drugs and large platelets. In particular, aspirin does not seem to significantly affect platelet volume, either in vitro or in vivo (65). Conversely, large platelets may have an increased reactivity even in patients with stable coronary artery disease undergoing dual antiplatelet therapy with aspirin and clopidogrel (66).
**MPV and diabetes mellitus**

Several studies showed that MPV is increased in the presence of diabetes mellitus (67–71) and in patients with impaired fasting glucose (although less than that in diabetic subjects) (72).

Sharpe and Trinick (67) demonstrated that MPV values do not differ between the genders or between type 1 and type 2 diabetes, and that they are not related to the duration of the disease. These observations lead to the conclusion that the increase in MPV is caused by the diabetic state itself, being detectable from the early phases and persisting for the entire duration of the disease.

A recent study (69) considered two groups of diabetic subjects, i.e. 35 patients with glycated haemoglobin (HbA1c) levels ≤ 7%, and 35 patients with HbA1c > 7%. The patients of the latter group were invited to undergo monthly visits to improve their diabetic control. The study showed a positive correlation between HbA1c and MPV, as well as a decrease in MPV values in the patients who achieved improved diabetic control. No difference was found between patients with and without vascular complications. The latter observation was not confirmed by another investigation (70) that studied 265 patients with type 2 diabetes and 151 subjects with type 1 diabetes, finding that the patients with microvascular complications (retinopathy, microalbuminuria) had higher MPV values than those without such conditions.

Recently, Muscari et al. (47) performed a systematic search for MPV determinants in a non-selected elderly population, showing that blood glucose, body fat and ischaemic electrocardiographic changes were the main factors independently associated with an elevated MPV (≥ 8.4 fl).

Thus, MPV increase might contribute to the diabetes-associated vascular damage, especially considering that, in this disease, platelets are not only larger, but also circulate in an activated state, as demonstrated by the presence of markers of platelet activation (71), by higher plasma and urinary concentrations of thromboxane A2 (73) and by an increased spontaneous platelet aggregation (74).

**MPV and obesity**

Obesity is a complex condition characterised by chronic metabolic alterations, and associated with a high cardiovascular risk (75). Coban et al. (76) demonstrated that MPV is increased in obese patients, independently of the presence of other cardiovascular risk factors or of haematological and renal diseases, and that there is a positive correlation between body mass index (BMI) and MPV. The MPV increment could therefore contribute to increasing the cardiovascular risk in obese subjects. Another study demonstrated that percent body fat is one of the parameters independently associated with MPV in the elderly population (47). Finally, in addition to confirming the increment of MPV values in the obese subjects, a study that involved 30 obese women and 30 non-obese healthy women showed a significant decrease in platelet size after a diet-induced weight loss (77). Similar results had already been obtained by earlier studies (78). Thus, weight loss may lead to an improvement of cardiovascular risk even through a decrease in platelet size and reactivity. Overall, no significant difference in platelet count was found between obese and non-obese subjects.

**MPV and other risk factors**

The metabolic syndrome is a clinical condition characterised by the coexistence of multiple cardiovascular risk factors, such as hypertension, dyslipidaemia and obesity. This syndrome is associated with insulin resistance, with a prothrombotic and proinflammatory state and with a threefold increased risk of cardiovascular impairment compared with individuals without the syndrome (79,80). A recent study (81) showed that MPV was increased in the presence of the metabolic syndrome and, more precisely, that MPV values were independently associated with the number of components of the syndrome, being especially correlated with waist circumference, BMI, fasting blood glucose and blood pressure. A relationship between blood pressure and MPV was also reported by other studies (82,83), but sometimes this relationship was not confirmed (47,51,69).

Similar contrasting results have been obtained of hypercholesterolaemia: although the aforesaid study (81) and others (51,76) were unable to find any relationship with MPV, Coban and Afacan (84) reported higher MPV values in patients with hypercholesterolaemia than that in healthy controls. Moreover, these authors noted an MPV decrement after 12 weeks of rosuvastatin treatment. There was, however, no correlation between the changes in MPV levels and the changes in plasma lipids, which could be caused by the intrinsic antiplatelet or anti-inflammatory actions of statins.

**Possible mechanisms involved**

A number of factors, in addition to TPO, could influence megakaryocytopenesis, such as granulocyte-macrophage colony-stimulating factor, a series of cytokines, such as interleukin (IL) 1, IL-3, IL-6, IL-8,
IL-11, IL-18 and nitric oxide (30–36). The plasma concentrations of these or other similar substances might increase in the presence of disorders such as obesity and endothelial dysfunction (36,85–88) (Figure 1). Similarly, insulin resistance, diabetes mellitus and other risk factors associated with endothelial dysfunction might trigger the same mechanisms. The cytokines produced by the adipose tissue and by the dysfunctioning endothelium may stimulate the bone marrow to produce large platelets that, in turn, would favour the occurrence of thrombosis and ischaemic events. As an increase in MPV has been documented during the acute phase of ischaemic stroke (57) and after exercise stress test in coronary patients (46), we suggest that ischaemic tissues may also release cytokines, with a subsequent further increase in circulating large platelets. This phenomenon would be proportional to the severity of the ischaemic events, which could also explain, at least in part, the prognostic significance of MPV. The hormonal factors involved in the increase in platelet volume, however, might not coincide with the classical inflammatory cytokines, as suggested by the low MPV values reported in some acute inflammatory diseases (13–15) and by the lack of correlation between MPV and some markers of inflammation (47).

Conclusions
Under some pathological conditions, larger and more reactive platelets are generated. This phenomenon seems to play an important role in several vascular diseases. In fact MPV is increased in diabetes mellitus, obesity, metabolic syndrome, AMI and stroke; it is predictive of stroke, AMI and restenosis of coronary stent, and has a prognostic significance in stroke and AMI. Thus, among the many parameters provided by whole blood count, MPV should not be disregarded, and its increment should suggest a careful assessment of cardiovascular risk.

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Paper received January 2009, accepted February 2009