Markers of Endothelial and In Vivo Platelet Activation in Patients with Essential Thrombocythemia and Polycythemia Vera

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Abstract

We investigated endothelial and in vivo platelet activation in a cohort of 52 patients with essential thrombocythemia (ET) and polycythemia vera (PV) before and after cytoreductive treatment, 22 healthy controls, and 17 patients with acute cerebrovascular ischemia (ACVI) and normal platelet counts. We measured platelet expression of CD62P and CD63 antigens and levels of soluble vascular cell adhesion molecule 1 (sVCAM-1). We found increased in vivo platelet activation in all patients with ET and PV, both before and after cytoreductive treatment, compared with controls. In patients with arterial thrombosis, platelet expression of CD62P, and in patients with erythromelalgia, expression of both markers was higher compared with expression in patients without thrombotic complications. In patients with ET and PV before and after treatment, sVCAM-1 expression was increased compared with expression in controls but also compared with expression in patients with ACVI and normal platelet counts. In patients with arterial thrombosis and erythromelalgia, in vivo platelet activation correlated with the level of sVCAM-1. Our findings indicated that in vivo platelet activation reflects intrinsic platelet defects in patients with ET and PV, persists after cytoreductive treatment, and results in endothelial damage, probably through release of angiogenic factors and/or activation of white blood cells.

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Key words: Platelet activation; Endothelial activation; Essential thrombocythemia; Polycythemia vera; Thrombosis

1. Introduction

Hemorrhagic and thrombotic complications are common causes of morbidity and mortality in patients with myeloproliferative disorders (MPD) and associated thrombocytosis [1,2]. Identification of specific risk factors for thrombosis, particularly in patients with essential thrombocythemia (ET) and polycythemia vera (PV), is very important for defining criteria for therapeutic intervention. Risk factors that have been definitely associated with risk of thrombosis in patients with ET who are older than 60 years and have a history of thrombosis and uncontrolled thrombocytosis. In patients with PV, the degree of elevation of hematocrit (HCT) is also an indicator of risk [3-6]. The role of recognized cardiovascular risk factors in the incidence of thrombosis in these patients remains controversial [7,8].

Although many studies have addressed the question of the role of elevated platelet count and of functional abnormalities of platelets in the pathogenesis of thrombosis in patients with MPD, a clear link between these factors and the risk of thrombosis has not been demonstrated [1,2]. These data indicate that thrombosis in these patients is the result of a multifactorial process, as found in other clinical settings. Components of this process might be abnormalities of white blood cells (WBCs) or functional defects of the endothelium.

In vivo platelet activation in patients with MPD has been demonstrated by various laboratory techniques [9-17]. In most studies in vivo platelet activation has been found in the overall population of patients with ET and PV, but the investigators did not discriminate asymptomatic patients from those with a history of thrombosis [10,12,13,15]. In vivo platelet activation may reflect increased platelet responsiveness to exogenous stimuli, or it may be a marker of various
underlying mechanisms, either dependent or independent of the disease, that predispose patients to development of thrombosis.

In the recent literature, endothelial activation arises as an important factor likely to contribute to the thrombotic tendency of these patients. Serum levels of thrombomodulin and von Willebrand factor antigen have been found to be increased in the overall population of MPD patients [18,19], whereas levels of soluble E-selectin have been associated with an increased incidence of thromboembolic complications [20]. The etiology of endothelial activation in these patients is unclear. In one study it was shown that in patients with erythromelalgia there is a strong correlation between secretion of platelet activation proteins and endothelial activation. It was suggested that in this subgroup of patients, platelet activation may be the primary cause of endothelial damage [19]. In another study plasma levels of soluble P-selectin correlated with levels of markers of endothelial damage in the overall population of patients with MPD, indicating that there is an association between these values [21]. It was shown also that WBCs are activated in primary thrombocytosis, and it was suggested that this activation results in endothelial damage [22].

In untreated patients with ET and PV, we investigated in vivo platelet activation by measuring CD62P and CD63 expression on platelets and studied endothelial activation by measuring soluble vascular cell adhesion molecule 1 (sVCAM-1). We studied the correlation of these markers with other parameters of the disease and with other known risk factors for thrombosis and evaluated their predictive value for the appearance of thrombosis.

2. Materials and Methods

2.1. Patients and Controls

A cohort of 52 patients with ET and PV with associated thrombocytosis followed in 2 institutions (University and District Hospital of Patras) entered the study from August 1997 to March 2002. The diagnoses of ET and PV were made according to the recommendations of the Polycythemia Vera Study Group [23,24]. Patients receiving anticoagulant treatment or medications affecting platelet function were excluded. In all patients the investigations were repeated after 6 months.

Thirty-two healthy volunteers underwent studies for establishing a reference range for CD62P, CD63 platelet expression, and serum sVCAM-1 levels. None of these subjects had received aspirin or any medication that affects platelet function for at least 15 days prior to blood collection.

Another group of 17 patients with acute cerebrovascular ischemia (ACVI) and normal platelet count admitted to the neurology department of the University Hospital participated in the study, and their results were compared with those from MPD patients. Tests were performed on the ACVI patients within 48 hours of admission and 30 days after the onset of the disease. All ACVI patients started antplatelet treatment the third day after admission. The study was approved by the ethics committee of the University Hospital. All patients and controls entered the study after giving informed consent. The characteristics of patients with MPD, patients with ACVI, and controls are shown in Table 1.

2.2. Diagnosis of Thrombotic and Hemorrhagic Events

The recognition criteria of previous arterial or venous thrombosis were obtained with validated questionnaires [25]. Thrombotic events during the follow-up period were objectively documented. Venous thrombosis included deep venous thrombosis and pulmonary embolism diagnosed by Doppler ultrasound or phlebography and ventilation perfusion scan, respectively. Arterial thrombosis included transient ischemic attack (episodes of focal cerebral ischemia resolved within 24 hours), myocardial infarction diagnosed on the basis of symptoms plus elevation of cardiac enzyme level and diagnostic changes in the electrocardiogram, ischemic stroke diagnosed by computed tomography or nuclear magnetic resonance imaging, and erythromelalgia.

### Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ET Group (n = 40)</th>
<th>PV Group (n = 12)</th>
<th>ACVI Group (n = 17)</th>
<th>Controls (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51</td>
<td>59</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>Range</td>
<td>19-88</td>
<td>30-88</td>
<td>42-77</td>
<td>22-74</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>19/21</td>
<td>4/8</td>
<td>7/10</td>
<td>22/10</td>
</tr>
<tr>
<td>Platelets, ( \times 10^{9} /L )</td>
<td>944</td>
<td>760</td>
<td>193</td>
<td>251</td>
</tr>
<tr>
<td>Mean</td>
<td>308</td>
<td>428</td>
<td>68</td>
<td>45</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.3</td>
<td>15.5</td>
<td>13.2</td>
<td>13.4</td>
</tr>
<tr>
<td>Mean</td>
<td>2.2</td>
<td>2</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>White blood cells, ( \times 10^{9} /L )</td>
<td>8.6</td>
<td>15.6</td>
<td>9.7</td>
<td>7.44</td>
</tr>
<tr>
<td>Mean</td>
<td>5.2</td>
<td>10.6</td>
<td>2.2</td>
<td>1.28</td>
</tr>
<tr>
<td>Cigarette smoking, n</td>
<td>11/40 (27.5%)</td>
<td>4/12 (33%)</td>
<td>10/17 (59%)</td>
<td>15/32 (46%)</td>
</tr>
<tr>
<td>Other cardiovascular risk factors, n</td>
<td>17/40 (42%)</td>
<td>2/12 (16.6%)</td>
<td>15/17 (88%)</td>
<td></td>
</tr>
</tbody>
</table>

*ET indicates essential thrombocytahemia; PV, polycythemia vera; ACVI, acute cerebrovascular ischemia.
diagnosed on the basis of the presence of painful burning and red congested extremities. Unexplained headache and dizziness were not considered in the analysis. Bleeding was classified as major if it necessitated hospitalization or blood transfusion. All other episodes of bleeding were classified as minor [26].

2.3. Cardiovascular Risk Factors

Information concerning major risk factors for vascular disease (hypertension, cigarette smoking, diabetes mellitus, hyperlipidemia, and obesity) was recorded with the use of a standard questionnaire.

2.4. Blood Collection

Blood from each patient was collected between 8 AM and 10 AM to avoid circadian variations. Venipuncture was performed with minimal stasis with a 21-gauge butterfly needle, and the first 2 mL of blood was collected in an EDTA tube for full blood count. The tourniquet was released, and 10 mL of blood was collected and divided into siliconized tubes without anticoagulant for measurement of endothelial markers, into siliconized tubes containing trisodium citrate (1:9 vol/vol) for clotting screening, and into special tubes (Diastase H; Diagnostica Stago, Parsippany, NJ, USA) containing citrate and the platelet antiaggregants theophylline, adenosine, and dipyridamole for platelet activation studies.

2.5. Flow Cytometry

Double immunolabeling was performed by incubating the samples with saturating concentrations of phycoerythrin-labeled antibodies (Immunotech, Marseilles, France) against CD62P (clone CLBThromb/6) or CD63 (clone CLBGran12) as well as with CD41-FITC (clone P2; Immunotech). The method used was a modification of a previously described one [27]. In brief, 5 μL of whole blood was added within 1 hour of collection to 50 μL of filtered N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid (HEPES)-buffered saline solution (0.145 mol/L NaCl, 0.005 mol/L KCl, 0.001 mol/L MgSO₄, 0.01 mol/L HEPES, pH 7.4) containing the appropriate dilution of antibodies. Samples were incubated for 20 minutes at 22°C to 26°C and mixed with 500 μL of 0.2% (vol/vol) formyl saline. Isotopic negative controls were prepared as appropriate. After immunolabeling, the samples were analyzed with an Epics-XL-MCL cytometer (Coulter, Miami, Florida, USA) within 2 hours of collection, and the data were processed with XL-2 software. Platelets were discriminated from the other blood cells on the basis of light-scatter characteristics and specific expression of CD41a antigen. At least 10,000 platelets from each sample were analyzed, and the results were expressed as percentages.

2.6. Human sVCAM-1

The levels of sVCAM-1 were measured in the serum of patients and controls by enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA). All samples were stored at −80°C until assayed. The assay was performed according to the instructions of the manufacturer. Each sample was assessed in duplicate. The levels of sVCAM-1 were calculated by reference to a standard curve constructed using standards with known concentrations provided by the manufacturer. The minimum detectable level of sVCAM-1 was typically less than 2.0 ng/mL.

2.7. Statistical Analysis

The data are given as mean ± SD. Comparisons between 2 sample populations were performed by Student t test with Welch correction when necessary. P values less than .05 were considered significant. For correlation between the various parameters Pearson coefficient was calculated with the corresponding value.

3. Results

3.1. Patient Demographics

Of the 52 patients with MPD, 22 patients had newly diagnosed disease and 30 had previously diagnosed disease but had not received cytoreductive treatment (median time after diagnosis was 56 months; range, 6-99 months). At diagnosis 13 (25%) of the patients had a history of arterial thrombosis, 1 (1.9%) of venous thrombosis and 2 (3.8%) of bleeding complications. These data are shown in Table 2. Thirty (58%) of the 52 patients were given cytoreductive treatment. For patients with ET, indications for treatment were platelet count >1 × 10⁹/μL, age older than 65 years, and/or previous thromboembolic complications [26]. For patients with PV, an additional indication was HCT >55% that did not respond to phlebotomy.

For all patients the median follow-up period from the time of first investigation was 39 months (range, 15-68 months). During follow-up, 2 untreated patients and 3 patients undergoing cytoreductive treatment developed thrombotic complications. These data are shown in Table 2. One of the untreated patients suffered a myocardial infarction, and the other developed portal vein thrombosis. Of
Table 3.
Markers of Endothelial and In Vivo Platelet Activation in Patients and Controls*

<table>
<thead>
<tr>
<th></th>
<th>All Pts with ET</th>
<th>All Pts with PV</th>
<th>All Pts with MPD</th>
<th>Pts without Thrombosis</th>
<th>Pts with Arterial Thrombosis</th>
<th>Pts with Erythromelalgia</th>
<th>Pts with ACVI without MPD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 40)</td>
<td>(n = 12)</td>
<td>(n = 52)</td>
<td>(n = 35)</td>
<td>(n = 16)</td>
<td>(n = 5)</td>
<td>(n = 17)</td>
<td>(n = 32)</td>
<td></td>
</tr>
<tr>
<td>CD63P, %</td>
<td>3.1 ± 2.1</td>
<td>3.9 ± 2.2</td>
<td>3.3 ± 2.1</td>
<td>3.1 ± 2.2</td>
<td>4.2 ± 1.8</td>
<td>4.22 ± 0.4</td>
<td>4.85 ± 3</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.0001</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD63, %</td>
<td>2.3 ± 1.9</td>
<td>2.6 ± 2.1</td>
<td>2.4 ± 1.9</td>
<td>2.1 ± 1.9</td>
<td>2.71 ± 1.3</td>
<td>2.74 ± 1.45</td>
<td>3.1 ± 2.75</td>
<td>1.45 ± 1.16</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
<td>NS</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>1065 ± 565</td>
<td>1283 ± 419</td>
<td>1101 ± 545</td>
<td>1041 ± 564</td>
<td>1223 ± 529</td>
<td>1666 ± 140</td>
<td>632 ± 234§</td>
<td>488 ± 118</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.0001</td>
<td>&lt;.005</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD. P is for comparisons between patients and controls. Pts indicates patients; ET, essential thrombocytopenia; PV, polycythemia vera; MPD, myeloproliferative disorders; ACVI, acute cerebrovascular ischemia; NS, not significant; sVCAM, soluble vascular cell adhesion molecule.

CD62P expression in patients with arterial thrombosis and erythromelalgia and CD63 expression in patients with erythromelalgia were significantly increased compared with the values in patients without thrombotic complications, P < .05.

sVCAM-1 in patients with erythromelalgia was significantly increased compared with the value in MPD patients without thrombotic complications, P < .001.

§sVCAM-1 in patients with MPD was significantly increased compared with the value in patients with ACVI without MPD, P < .0001.

the patients receiving treatment, 1 developed ACVI while the platelet count was 800 x 10^3/µL. Another patient developed acute myocardial infarction, and another, deep venous thrombosis; both of these patients had a platelet count <400 x 10^3/µL.

Patients with ACVI and normal platelet count had a higher percentage of known cardiovascular risk factors compared with patients with MPD. These data are shown in Table 1.

3.2. In Vivo Platelet Expression of CD62P and CD63 Antigens

In vivo platelet expression of CD62P and CD63 antigens was significantly increased in all patients with ET and PV with thrombocytosis compared with controls. These results are shown in Table 3. Expression of these antigens did not differ between patients with ET and those with PV. In ET patients with arterial thrombosis, the mean percentages of platelets expressing CD62P and CD63 antigens were 3.28 ± 0.91 and 2.64 ± 1.66, respectively, whereas in those without thrombotic complications the percentages were 3.1 ± 0.7 and 2.25 ± 0.4, respectively, differences that were not statistically significant. In PV patients with arterial thrombosis, the mean percentages of platelets expressing CD62P and CD63 were 4.25 ± 1.25 and 2.15 ± 0.97, respectively, whereas in those without thrombotic complications, the percentages were 3.55 ± 3.2 and 3.2 ± 3, respectively, again differences that did not reach statistical significance. When results for all patients with MPD were analyzed together, however, in vivo platelet expression of CD62P antigen was increased in patients with arterial thrombosis compared with expression in subjects without thrombotic complications (P < .05), whereas expression of CD63 did not show any difference. When results for patients with erythromelalgia were analyzed separately, mean expression of CD62P and CD63 was significantly increased compared with that in patients without thrombotic complications, P < .05 for both parameters. These results are shown in Table 3. When results for the ET and PV patients were analyzed together, patients with arterial thrombosis had significantly increased expression of platelet CD62P antigen compared with subjects without thrombotic complications. This finding contrasted with the results obtained when this comparison was made in the separate subgroups, probably because of the small number of patients with arterial thrombosis in each subgroup.

In all patients with MPD, expression of both markers did not differ between the first and second measurements (data not shown). In the group of patients who started cytoreductive treatment during follow-up, in vivo platelet expression of CD62P and CD63 antigens, 3.3% ± 2.1% and 2.4% ± 1.9% versus 3.8% ± 1.8% and 2.2% ± 1.6%, respectively, did not differ before and after treatment. Compared with controls, patients with ACVI and normal platelet count within 48 hours of admission had increased platelet expression of both CD62P and CD63 antigens. These results are shown in Table 3. In these patients, 30 days after the onset of the disease, platelet expression of both antigens returned to that of controls (data not shown). These results in combination with the fact that patients with ACVI and normal platelet count had a higher percentage of cardiovascular risk factors indicated that in these patients platelet activation reflects the ongoing thrombotic process and is not a marker of known cardiovascular risk factors.

3.3. Endothelial Activation Markers

The level of sVCAM-1 was significantly increased in all patients with ET and PV at entry to the study compared with the level in controls. In patients with erythromelalgia, the levels of sVCAM-1 were significantly increased compared with that in patients without thrombotic complications (P < .001), whereas in patients with arterial thrombosis, the levels did not show any difference. These results are shown in Table 3.

An interesting finding was that levels of sVCAM-1 were also very significantly increased in patients with ET and PV compared with the values in the group of patients with ACVI without MPD (P < .0001). This increase remained statistically significant when patients without thrombotic complications, with arterial thrombosis and erythromelalgia, were
compared separately with patients with ACVI. The levels of sVCAM-1 after cytoreductive treatment did not differ from those prior to it (data not shown).

3.4. Correlation of Platelet Activation to Other Biological Parameters

In the overall population of MPD patients in the study, none of the markers of platelet activation correlated with patient age, platelet count, HCT, or WBC count. However, expression of CD62P antigen correlated with duration of disease ($r = 0.34, P < .05$). In patients with arterial thrombosis, CD62P expression correlated inversely with platelet count ($r = -0.54, P < .05$). In the group of patients with erythromelalgia, CD62P expression strongly correlated with WBC count ($r = 0.9, P < .05$).

The levels of sVCAM-1 did not correlate with patient age, platelet count, WBC, or HCT. A strong correlation was found between sVCAM-1 level and percentage of platelet CD62P expression when MPD results for patients with arterial thrombosis and erythromelalgia were analyzed separately ($r = 0.7, P < .05$ and $r = 0.9, P < .05$, respectively).

3.5. Risk of Thrombosis

Calculation of odds ratio in the entire population of patients with MPD did not show increased risk of development of thrombotic complications in patients having in vivo platelet expression of CD62P greater than 2.7% (>mean + 2 SD of controls) or expression of CD63 greater than 3.8% (>mean + 2 SD of controls).

The 3 patients, however, who developed arterial thrombosis during follow-up had consistently increased in vivo CD62P platelet expression >2.7%. At entry to the study, the 2 patients who developed venous thrombosis had CD62P expression <2.7%, which, however, increased during the acute phase of thrombosis and gradually returned to the levels of controls.

Although investigation of in vivo platelet expression after treatment with aspirin or other antiplatelet agents was not a purpose of our study, in patients with erythromelalgia, treatment with aspirin reduced platelet activation in all except 1 patient. During follow-up that patient developed acute myocardial infarction.

The data suggested that a persistent increase of in vivo expression of platelet CD62P may have prognostic significance for the development of arterial complications during follow-up.

4. Discussion

In the present study we found, by measurement of platelet expression of the CD62P and CD63 antigens with flow cytometry, an increased percentage of in vivo activated platelets in all patients with newly diagnosed and untreated ET and PV. Demonstration of in vivo platelet activation in previous studies has been criticized on the grounds that platelets can be easily activated by ex vivo laboratory manipulation [28]. Assessment of in vivo platelet activation by a whole-blood method minimizes manipulation while allowing study of platelets in their physiological milieu [29]. In addition, in our study, blood was collected in tubes containing anticoagulants and antiaggregant agents that minimize further artifacts related to sample manipulation. These differences in technique can explain the lower percentage of platelet activation markers in our study and control populations compared with studies in previous studies [15,17].

We showed that platelet activation in these patients was persistent, in contrast to findings in patients with ACVI and normal platelet counts, in whom platelet activation was detected during the acute phase of the disease and returned to the levels of healthy controls within 30 days. In ET and PV patients, in vivo platelet activation did not correlate with other hematological parameters, such as platelet count, HCT, and WBC count. Furthermore, treatment with hydroxyurea and anagrelide, despite reducing platelet count, did not have an effect on platelet activation. This finding supported data showing that treatment with anagrelide, despite normalizing platelet count, does not correct the functional and chemical defects of platelets in patients with ET [30]. The finding also supported clinical data showing that in MPD patients cytoreduction with hydroxyurea and anagrelide reduces but does not eliminate the risk of thrombosis [26,31], whereas treatment with aspirin is effective in the prevention of these complications [32]. The above data taken together indicate that platelet activation characterizes ET and PV and reflects platelet hyperactivity due to intrinsic defects, such as increased responsiveness to thrombopoietin [33] or other stimuli.

We also found significantly increased endothelial activation in the overall population of patients with ET and PV. This activation persists even after cytoreductive treatment. Furthermore, levels of sVCAM-1 were significantly increased in these patients compared with patients with ACVI and normal platelet counts despite the fact that the latter group of patients had a higher percentage of cardiovascular risk factors. The levels of sVCAM-1 strongly correlated with both markers of platelet activation studied in patients with large-vessel thrombotic complications and in patients with erythromelalgia, although not in the overall MPD population, probably because of the size of the sample. These data collectively indicate that in patients with MPD endothelial activation is characteristic of the disease and is associated with platelet activation.

The mechanisms of endothelial damage in patients with primary thrombocytosis are unknown. One mechanism of endothelial activation in these patients may be the release of angiogenic growth factors from activated platelets. Vascular endothelial growth factor (VEGF) [34,35] has been shown to activate the endothelium to express tissue factor and become prothrombotic, inducing platelet adhesion to the endothelium [36]. Increased levels of VEGF have been demonstrated in patients with MPD [37,38]. Activated platelets in these patients can also result in WBC activation, a mechanism involved in both clotting activation and endothelial damage [39]. Increased numbers of platelet-leukocyte aggregates have been found in patients with MPD [17,40], while in a recent study the levels of these aggregates correlated with the rate of thrombotic complications [41]. WBC activation has been found in primary thrombocytosis,
and it has been suggested that WBC activation may be related to endothelial damage [22].

The strong correlation between percentages of in vivo circulating activated platelets and duration of disease might reflect the effect of a vicious circle involving activated platelets and activated endothelium.

Although increased endothelial and in vivo platelet activation was found in all patients in our study, the activation profiles of these markers differed between subgroups of patients. In patients with erythromelalgia, expression of both platelet activation markers and the level of sVCAM-1 were significantly increased compared with the findings in patients without thrombotic complications. In patients with large-vessel arterial thrombosis, only expression of CD62P antigen showed a difference.

The significant platelet activation in patients with erythromelalgia underlines the importance of platelets in the pathogenesis of the syndrome [19], and platelet activation is clearly associated with the observed endothelial activation. In these patients, as confirmed in our study, detection of in vivo platelet activation can be used as a marker for following response to treatment with aspirin [42].

The different platelet and endothelial activation profiles of patients with large-vessel arterial thrombosis, however, compared with those with erythromelalgia, indicates involvement of other factors in the thrombotic process. For discrimination of the latter subgroup of patients, markers of endothelial and in vivo platelet activation probably should be added to other investigations, such as studies of platelet function [16] and of WBC activation.

In conclusion, our findings of increased in vivo platelet and endothelial activation in the overall population of patients with MPD at presentation and after cytoreductive treatment indicated that both signs are characteristic of the disease. We suggest that in vivo platelet activation is mainly due to intrinsic platelet defects and results in endothelial damage by release of angiogenic factors and/or by activation of WBCs. Different platelet and endothelial activation profiles discriminate subgroups of MPD patients at risk of development of thrombotic complications. These markers may prove useful in monitoring the antithrombotic effect of treatment of MPD patients.

References


