Increased Thromboxane Biosynthesis in Patients With Polycythemia Vera: Evidence for Aspirin-Suppressible Platelet Activation In Vivo

By Raffaele Landolfi, Giovanni Ciabattoni, Paola Patrignani, Maria A.L. Castellana, Enrico Pogliani, Bruno Bizzi, and Carlo Patrono

Increased thromboxane (TX) production and modified aspirin sensitivity has been detected in vitro in platelets isolated from patients with polycythemia vera. To verify the relevance of these capacity-related measurements to the actual rate of TXA2 biosynthesis in vivo and its suppression by oral aspirin, we have investigated the urinary excretion of major enzymatic metabolites of TXB2 in 17 patients with polycythemia vera and 23 gender- and age-matched controls. Urinary 11-dehydro-TXB2 and 2,3-dinor-TXB2 were measured by previously validated radioimmunoassays. In addition, urinary immunoreactive leukotriene (LT) E2 was measured to explore the 5-lipoxygenase pathway of arachidonate metabolism. Polycythemic patients had significantly (P < .001) higher excretion rates of both 11-dehydro-TXB2 (1,033 ± 1,050 v 117 ± 45 pmol/mmol creatinine; mean ± SD) and 2,3-dinor-TXB2 (725 ± 676 v 82 ± 43 pmol/mmol creatinine) than controls. In contrast, urinary LTE4 was not significantly different. Enhanced metabolite excretion did not correlate with the platelet count or with the hematocrit value, and was not related to the current treatment or to a clinical history of thrombotic complications. Platelet TX receptor studies did not show any significant changes in the binding characteristics of two different ligands. A platelet-selective regimen of aspirin therapy (50 mg/d for 7 to 14 days) was associated with greater than 80% suppression in metabolite excretion in nine patients. These results are consistent with abnormal stimuli operating in polycythemia vera to induce a selective enhancement in the platelet biosynthesis of TXA2 without changes in receptor binding. This in vivo abnormality in platelet biochemistry can be largely suppressed by low doses of aspirin.

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Materials and Methods

**Study population.** Seventeen patients with polycythemia vera (9 men, 8 women; 23 to 68 years of age) and 23 healthy volunteers (12 men, 11 women; 27 to 70 years of age) were examined on several occasions between April 1988 and January 1990. Informed consent was obtained from each subject. Patients and controls were comparable for smoking habits and blood cholesterol and blood pressure levels. One patient had type II diabetes mellitus. No alterations in renal function were detected in any of the patients. An unequivocal diagnosis of polycythemia vera was made on the basis of the criteria recommended by the Polycythemia Vera Study Group. An arterial thrombotic event previously had occurred in five patients (6 months to 5 years before the study). Another patient suffered from migratory thrombophlebitis. Four patients were examined before any treatment and 13 while undergoing phlebotomy (n = 8), chemotherapy (n = 3), or both (n = 2). The various treatment regimens were individualized to keep the hematocrit value below 50%. Hydroxyurea (Onco-Carbide, Simes, Milan, Italy) was used as the chemotherapeutic agent at doses ranging between 0.5 and 1.5 g/d. At the beginning of the study, all healthy subjects, as well as the patients, were free of drugs known to affect platelet function. A complete hematologic screening was performed shortly before collecting blood and urine samples for TXB2 metabolite assays.

**Design of the studies.** In the first study, a cross-sectional comparison of TX and LT production was performed between the patients and controls. Patients and healthy volunteers were studied...
on an outpatient basis. After an overnight fast, blood samples were obtained for measurement of TXA2, LTC4 synthesis, and TXA2 receptor studies. Urine was collected during the 24 hours before blood sampling; the samples were frozen immediately and kept at −20°C until extraction. Urine samples for LTC4 measurements were added with 1 mmol/L 4-hydroxy-TEMPO (Sigma Chemicals, St Louis, MO) as an antioxidant.

A second study was designed to examine the relative contribution of platelets to enhanced excretion of TXB2 metabolites. For this purpose, nine patients were treated with aspirin (50 mg/d for 7 to 14 days), and 24-hour urine collections and blood samples (in only three patients) were obtained before and at the end of aspirin therapy and over the following 2 weeks.

In a third study, we measured TXB2 metabolite excretion in three patients undergoing phlebotomy only and phlebotomy while on low-dose aspirin therapy. Urine was obtained before and on the first (collection started 18 hours after phlebotomy), third, and fifth days after phlebotomy, both during an aspirin-free phase and again while on low-dose aspirin therapy. The study was approved by the Internal Medicine Review Boards of our institutions.

Whole blood studies. TXB2 production during whole blood clotting was measured as previously described.21 The anti-TXB2 serum used was obtained in our laboratory and was described previously.21 Sulfidopeptide LT production (as detected by LTE4-like immunoreactivity) in whole blood stimulated with the calcium ionophore A23187 was measured as described for LTB4.23 The anti-LTE4 serum was a gift of Dr J. Maclouf (Hopital Lariboisière, Paris, France) and was the same used for urinary measurements (see below).

TX receptor-binding studies. These studies were performed in four polycythemic patients and four healthy volunteers, who had not taken any nonsteroidal anti-inflammatory drugs during the previous 10 days. Platelets were obtained by differential centrifugation from peripheral blood samples and washed three times in a modified Tyrode’s buffer. Aliquots of the platelet suspension containing 5 to 10 × 10^9 platelets were incubated for 30 minutes at 25°C with [3H]SQ29,548 (30 Ci/mmol, 5 nmol/L; Du Pont Nemours-NE Instrument Research Products, Boston, MA) or [3H]U46619 (15 Ci/mmol, 20 nmol/L) and varying concentrations (10−11 to 10−5 mol/L) of competing homologous and heterologous cold ligands. The reaction was terminated by the addition of 4 mL of ice-cold 50 mmol/L Tris/100 mmol/L NaCl buffer, pH 7.4, followed by rapid filtration through Whatman GF/C glass fiber filters (Whatman Inc, Clifton, NJ). Displacement curves were fitted to a nonlinear model using the LIGAND program.24 The binding parameters of radiolabeled ligands were evaluated in the same number of platelets for patients and controls. This averaged 5 × 10^9 and 10^10 platelets for the binding of [3H]-SQ29,548 and [3H]U46619, respectively, in both groups. Although platelets of polycythemia vera patients may be larger than normal platelets, the amounts of platelet proteins measured in our studies were not significantly different in the two groups. Analysis of heterologous and homologous displacement curves best fitted the experimental data to a one-site model in both patients and controls.

Urinary 11-dehydro-TXB2 and 2,3-dinor-TXB2 assays. TXB2, the chemically stable hydrolysis product of TXA2, undergoes two major pathways of metabolism in humans.25,26 2,3-dinor-TXB2 and 11-dehydro-TXB2 have been identified as the major urinary metabolites originating via β-oxidation and dehydrogenation of the hemiacetal alcohol group at C-11, respectively.25 Urinary excretion of both metabolites increases linearly with the rate of entry of TXB2 into the systemic circulation of healthy subjects.26

After adjusting the urine pH to 4.0 with formic acid, 2,3-dinor-TXB2 and 11-dehydro-TXB2 were extracted on SEP-PAK C18 cartridges (Waters Associates, Milford, MA) and eluted with ethyl acetate. The eluates were subjected to silicic acid column chromatography and further eluted with benzene:ethyl acetate:methanol (60:40:30). These eluates were assayed for 11-dehydro-TXB2 by radioimmunoassay (RIA), as previously described.27 The same eluates were subjected to reverse-phase high-performance liquid chromatography (RP-HPLC) with the solvent system acetonitrile:water:acetic acid (27:73:0.18) at a flow rate of 0.5 mL/min to separate TXB2 from 2,3-dinor-TXB2. The latter was measured by a previously validated RIA.28 The extraction and further purification recoveries for labeled 11-dehydro-TXB2 and 2,3-dinor-TXB2 averaged 75% ± 6% and 50% ± 7% (mean ± SD, n = 32), respectively, and urinary measurements were corrected accordingly.

Urinary LTE4 assay. LTE4 represents a major enzymatic derivative of LTC4 and its urinary excretion increases linearly with the rate of entry of LTC4 into the systemic circulation of healthy subjects.29

Immunoactive LTE4 was extracted from 10- to 20-mL aliquots of urine from 10 patients and 8 controls, on SEP-PAK C18 cartridges and eluted with methanol. After evaporation of the methanol to dryness, the extracts were reconstituted with 150 μL of methanol/water (1:1, vol/vol) and injected into a Nova-Pak C18 column (3.9 mm × 15 cm; Waters Associates) and eluted with a solvent system methanol:water:acetic acid (58:42:0.1, vol/vol) containing 1 mmol/L EDTA adjusted to pH 5.6 with ammonium hydroxide, at a flow rate of 1 mL/min. Fractions (1 mL) eluting with similar retention times to those of authentic LTC4 and LTE4 were collected, evaporated to dryness, and reconstituted with 0.5 mL of phosphate buffer (0.02 mol/L, pH 7.4). Radioactivity in these HPLC fractions corresponding to the retention time (11 minutes) of [3H]LTC4 (168 Ci/mmol, 6,000 disintegrations per minute [dpm] added to each urine sample) was measured by scintillation counting to determine recovery, whereas those fractions with a retention time close to that of authentic LTE4 (26 minutes) were assayed for immunoactivity by RIA. [3H]LTC4 and [3H]LTE4 (180 Ci/mmol) added to urine showed similar recovery of approximately 60%. RIA was performed by addition of 10 to 50 μL of the HPLC fractions to 1.5 mL volume of 0.02 mol/L phosphate buffer, pH 7.4; 4,000 dpm of [3H]LTE4 and an anti-LTE4 serum30 (showing 32% cross-reaction with LTC4) diluted 1:50,000 were added and the mixture incubated for 18 to 24 hours at 4°C. Separation of the antibody-bound from free [3H]LTE4 was performed by rapidly adding 0.05 mL of human plasma and 0.1 mL of a charcoal suspension (100 mg/mL), followed by subsequent centrifugation at 3,000 rpm for 10 min at 4°C. To further validate these measurements, the LTE4-like immunoactivity detected in some samples was analyzed with a different monoclonal antibody directed against LTC4 (a gift of Dr J. Rokach, Merck Frosst, Canada) that showed 35% cross-reaction with LTE4. A highly significant correlation (r = 0.93, n = 15, P < .001) was found between measurements of urinary LTE4 using the two antiserum. The IC50 values for LTE4 for the two antisera were 39 and 38 pg/mL of incubation mixture, respectively. LTE4 concentration in each urine sample was corrected by recovery of [3H]LTC4.

Other assays. The serum and urinary levels of creatinine were measured by the Jaffe’s method without deprotonization. Serum levels of creatinine, measured on the occasion of the study, averaged 89.0 ± 16.6 μmol/L (range, 69.0 to 123.8) in the 17 patients.

Statistical analyses. The results were evaluated by means of a parametric analysis of variance (ANOVA) for multiple comparisons and by Student’s t-test for single comparison. Moreover, the associations of eicosanoid measurements with other biochemical and hematologic variables were assessed by stepwise regression analysis and multiple linear regression. All values are reported as mean ± SD. Statistical significance was defined as P < .01.
THROMBOXANE BIOSYNTHESIS IN POLYCYTHEMIA VERA

RESULTS

Polycythemic patients had significantly ($P < .001$) higher 11-dehydro-TXB$_2$ excretion than sex- and age-matched controls (1.033 ± 1.050 v 117 ± 45 pmol/mmol creatinine; mean ± SD). Table 1 details the individual measurements of 11-dehydro-TXB$_2$ in relation to hematologic variables, treatment, and history of thrombotic complications. All 17 patients with polycythemia vera had 11-dehydro-TXB$_2$ excretory rates 2 SD higher than the normal mean. Enhanced metabolite excretion did not correlate with platelet count or with the hematocrit value, and was not related to the current treatment or to a clinical history positive for thrombotic complications. The rate of excretion of 11-dehydro-TXB$_2$ was relatively stable when assessed repeatedly on different days (intrasubject coefficient of variation: 18.4% ± 9.0%, mean ± SD; n = 8). The urinary excretion of 2,3-dinor-TXB$_2$ was also significantly ($P < .001$) higher in patients than controls (725 ± 676 v 82 ± 43 pmol/mmol creatinine). A highly significant linear correlation was found between the excretion rates of 11-dehydro-TXB$_2$ and 2,3-dinor-TXB$_2$ (Fig 1). This finding suggests that enhanced metabolite excretion in patients with polycythemia vera reflects increased TXA$_2$ biosynthesis rather than alterations in its metabolic disposition.

At variance with TXB$_2$ metabolite excretion, urinary LTE$_4$ was not significantly different in patients (9.3 ± 6.1 pmol/h; n = 10) and controls (10.9 ± 7.3 pmol/h; n = 8), thus implying a selective alteration of arachidonate metabolism via the cyclooxygenase pathway. Enhanced TXA$_2$ biosynthesis might be a consequence of (1) alterations in platelet biochemistry (eg, increased substrate availability) or number; (2) abnormal stimuli to platelet activation; or (3) increased extraplatelet production of TXA$_2$. Whereas (1) would be reflected by changes detectable ex vivo, (2) and (3) would be compatible with unchanged capacity of platelets to synthesize TXA$_2$ in vitro.

To assess the biosynthetic capacity of the patients platelets, we measured TXB$_2$ production during whole blood clotting. This reflects the virtually maximal production of TXA$_2$ by platelets exposed to endogenous thrombin. As shown in Table 2, serum TXB$_2$ concentrations in patients were twofold higher than previously measured in a large (n = 177) population of healthy controls. However, when corrected for the platelet count, an identical value of TXB$_2$ production was found in patients and controls. That enhanced TXB$_2$ metabolite excretion found in polycythemia vera does not merely reflect increased platelet numbers is indicated by the lack of any statistically significant correlation between platelet counts and urinary 11-dehydro-TXB$_2$ ($r = .055$) or 2,3-dinor-TXB$_2$ ($r = .075$). Moreover, the production of LTE$_4$ in whole blood—a reflection of transcellular metabolism of neutrophil-derived LTAs by other blood cells, including platelets—was similar in polycythemic patients (10.8 ± 14.3 pmol/10$^9$ white blood cells [WBCs]; n = 10) and controls (11.1 ± 7.3 pmol/10$^9$ WBCs; n = 8).

Table 1. Individual Measurements of 11-Dehydro-TXB$_2$ Excretion in 17 Patients With Polycythemia Vera, in Relation to Hematologic Variables, Treatment, and History of Thrombotic Complications

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Platelet Count (10$^9$/L)</th>
<th>Hematocrit (%)</th>
<th>Urinary 11-Dehydro-TXB$_2$ (pmol/mmol creatinine)</th>
<th>Treatment</th>
<th>Thrombotic Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>0.45</td>
<td>756</td>
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<tr>
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<td>567</td>
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<tr>
<td>17</td>
<td>950</td>
<td>0.47</td>
<td>339</td>
<td>—</td>
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</table>

Table 2. Whole Blood TXB$_2$ Production in Relation to Platelet Count in Patients With Polycythemia Vera and Healthy Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum TXB$_2$ (nmol/L)</th>
<th>Blood Platelets (10$^9$/L)</th>
<th>Serum TXB$_2$ (nmol/10$^9$ Platelets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls*</td>
<td>(n = 177)</td>
<td>811 ± 292</td>
<td>212 ± 42</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>patients (n = 13)</td>
<td>1,678 ± 1,899</td>
<td>434 ± 294</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*Normal values are from Alessandrini et al.25

Abbreviations: C, chemotherapy; P, phlebotomy (urine collection was started at least 18 hours after phlebotomy).

*Normal mean is 117 ± 45 pmol/mmol creatinine (range, 53 to 210).
excretion in nine patients. Before aspirin administration, urinary 11-dehydro-TXB₂ and 2,3-dinor-TXB₂ averaged 688 ± 692 and 467 ± 428 pmol/mmol creatinine, respectively. The drug was well tolerated by all patients and no untoward effects were recorded during the study. As shown in Fig 2, aspirin administration was associated with greater than 80% reduction in metabolite excretion and virtually maximal suppression in platelet TXB₂ production. The time-course of recovery of TXA₂ biosynthesis was linear over the next 2 weeks, consistent with the time-dependent maximal suppression in platelet TXB₂ production. The biosynthetic capacity to the systemic circulation on withdrawal of aspirin administration (data not shown).

Because all of the previously mentioned findings are consistent with enhanced platelet biosynthesis and release of TXA₂ in response to stimuli operating in vivo, we assessed the interaction of two different ligands with the platelet TXA₂ receptor(s) of patients and controls with the aim of detecting a possible downregulation of TXA₂ receptor binding. As detailed in Table 3, washed platelets from polycythemic patients were characterized by similar equilibrium dissociation constants (k_d) and binding capacity (B_max) for the receptor antagonist SQ29,548 and for the agonist U46619 as measured in healthy controls.

To clarify the nature of stimuli to platelet activation in polycythemia vera, we also evaluated the short-term effects of phlebotomy on 11-dehydro-TXB₂ and 2,3-dinor-TXB₂ excretion in three patients. As shown in Fig 3, metabolite excretion was only marginally reduced after phlebotomy, whereas it was completely suppressed during low-dose aspirin treatment.

**DISCUSSION**

When compared with other myeloproliferative disorders, patients with polycythemia vera are particularly prone to develop thrombotic complications. This is especially true in patients over 70 years old with a prior thrombotic event. A number of factors have been suggested to contribute to such increased thrombotic risk. These factors include an elevated hematocrit value, increased blood viscosity, thrombocytosis, as well as qualitative platelet abnormalities. In addition to several platelet receptor defects, alterations in arachidonic metabolism have been reported. Thus, Shafer described a selective deficiency of platelet lipoxigenase activity in 10 of 22 patients with polycythemia vera, whereas this enzyme activity was normal in patients with reactive thrombocytosis or secondary polycythemia. Interestingly, lipoxigenase-deficient platelets generated higher levels of TXA₂ than control platelets, a finding possibly related to increased substrate availability for the cyclooxygenase pathway and to diminished formation of 12-hydroperoxy-5,8,10,14-eicosatetraenoic acid. Because we did not measure 12-lipoxigenase activity, our measurements of platelet TXB₂ production ex vivo cannot be directly compared with those in the study of Shafer. Moreover, the nature of the stimulus used in the latter and in the present studies was different, ie, exogenously added arachidonate versus endogenously released substrate, respectively.

In the patient studied by Mehta et al, serum TXB₂ was numerically increased when expressed in nanograms per milliliter, but perfectly normal when corrected for the high platelet count. In vitro studies of platelet function have shown either diminished or enhanced aggregation to various stimuli. The latter finding is consistent with increased platelet-fibrinogen affinity, as shown by both the aggregometric technique and by measuring the platelet binding of 125I-labeled fibrinogen.

A major limitation of platelet studies performed in vitro is that they only examine capacity-related indexes of platelet studies.
of recovery of TXA2 production on withdrawal of aspirin administration are consistent with a role for platelets as the major source of enhanced TXA2 biosynthesis in polycythemia vera. This degree of suppression of TXB2 metabolite excretion is comparable to that achieved by daily doses of aspirin (40 to 80 mg) in healthy subjects,38 as well as in patients with episodically79 or persistently17,18 enhanced TX biosynthesis. The fact that enhanced TXA2 biosynthesis was not related to a clinical history of thrombotic complications is not surprising, inasmuch as these had occurred to five patients 6 months to 5 years before the study.

Thus, the present findings provide the following novel information on in vivo arachidonate metabolism in polycythemia vera: (1) a biochemically selective alteration exists in all the examined patients, involving the cyclooxygenase/TX-synthase pathway; (2) platelets provide the major source of enhanced TXA2 biosynthesis; and (3) this aspirin-suppressible persistent abnormality is not related to increased platelet count and is likely to reflect stimuli to platelet activation operating in vivo. Atherosclerotic vascular disease may be associated with accelerated platelet-vascular interactions and provide triggers to platelet activation in vivo. However, it should be noted that stable manifestations of coronary40 and peripheral39 vascular disease are not associated with detectable changes in TXB2 metabolite excretion. Because none of our patients had acute manifestations of vascular occlusion at the time of the study, it is unlikely that vascular disease contributed to the observed changes in platelet arachidonate metabolism. Persistently elevated platelet TXA2 biosynthesis has been characterized in association with several cardiovascular risk factors, such as cigarette smoking,41 non-insulin-dependent diabetes mellitus,17 and type IIA hypercholesterolemia.18 Thus, TXA2-dependent platelet activation may represent a transduction mechanism linking these various risk factors to the enhanced risk of vascular occlusive complications.42

An elevated hematocrit value and increased blood viscosity clearly play a role in the pathogenesis of thrombotic complications in polycythemia vera. As reviewed by Shaffer,1 an increased hematocrit value may permit platelets to achieve more intimate contact with the vessel wall as a function of the axial migration of red blood cells. In the present study, TXA2 biosynthesis was not related to the hematocrit, although in a relatively narrow range of values (Table 1). Moreover, a 5% to 6% reduction in the hematocrit value associated with phlebotomy did not modify appreciably the rate of TXB2 metabolite excretion in three patients studied repeatedly (Fig 3). Although phlebotomy may acutely and transiently increase TXA2 production as a result of the attending trauma and rapid intravascular volume depletion, this is unlikely to be reflected in metabolite excretion measured 18 hours after the procedure, given the 45-minute half-life of 11-dehydro-TXB2 in the human circulation.53 Thus, the mechanisms responsible for enhanced platelet synthesis and release of TXA2 in polycythemia vera remain to be investigated further. Verification of the pathophysiologic significance of this abnormality would require a controlled trial of low-dose aspirin prophylaxis.
The potential antithrombotic effect of aspirin has been evaluated previously by the Polycythemia Vera Study Group. Thus, 166 patients were randomized to receive either phlebotomy plus aspirin (300 mg three times a day) and dipyridamole or 32P. There were nine "severe thrombotic complications" in the entire group (seven in the aspirin-treated patients) after a maximum of 3.4 years of follow-up (median, 1.2 years), which is an overall incidence of approximately 5%. Without addressing the issue of the adequacy of the control group, it is obvious that the sample size was too small to test any realistic hypothesis of risk reduction by aspirin (eg, 20% to 30%, as suggested by the overview of the Antiplatelet Trialists' Collaboration). The apparently negative efficacy data and the excess of gastrointestinal hemorrhagic complications reported in this study have discouraged them and other investigators from reasessing the efficacy and safety of aspirin in polycythemia vera. In this context, we believe that the present findings are useful in establishing (1) that these patients do have enhanced TXA2 biosynthesis in vivo; and (2) that such an abnormality can be corrected by a platelet-selective dosage of aspirin that is only a small fraction (50 v 900 mg/d) of that used by the Polycythemia Vera Study Group. The recent demonstration that the antithrombotic effect of doses as low as 30 to 75 mg is comparable to that of much higher doses of aspirin and is associated with reduced gastrointestinal toxicity and bleeding provides the conceptual and practical framework for reassessing the efficacy and safety of antiplatelet therapy in polycythemveral.

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Increased thromboxane biosynthesis in patients with polycythemia vera: evidence for aspirin-suppressible platelet activation in vivo [see comments]

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