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) E4 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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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 platelet 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. The anti-TXB2 serum used was obtained in our laboratory and was described previously. Sulfidopeptide LT production (as detected by LTE4-like immunoreactivity) in whole blood stimulated with the calcium ionophore A23187 was measured as described for LTB4. The anti-LTE4 serum was a gift of Dr. Maeloud (Hospital 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 x 10^10 to 10^11 platelets were incubated for 30 minutes at 25°C with [3H]SQ29,548 (30 Ci/mmol, 5 mmol/L; Du Pont Nemours-REN 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 phosphate 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. The binding parameters of radiolabeled ligands were evaluated in the same number of platelets for patients and controls. This averaged 5 x 10^10 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. 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. Urinary excretion of both metabolites increases linearly with the rate of entry of TXB2 into the systemic circulation of healthy subjects.

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. 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. 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.

Immune reactive 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 x 15 cm; Waters Associates, Milford, MA) 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 those 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 immunoreactivity 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 serum (showing 32% cross-reaction with LTC4) diluted 1:15,000 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 immunoreactivity 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 antisera. 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 deproteinization. Serum levels of creatinine, measured on the occasion of the study, averaged 16.6 ± 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 ± 1 SD. Statistical significance was defined as P < .01.
RESULTS

Polycythemic patients had significantly (P < .001) higher 11-dehydro-TXB2 excretion than sex- and age-matched controls (1.033 ± 1.050 vs 1.175 ± 2.45 pmol/mmol creatinine; mean ± SD). Table 1 details the individual measurements of 11-dehydro-TXB2 in relation to hematologic variables, treatment, and history of thrombotic complications. All 17 patients with polycythemia vera had 11-dehydro-TXB2 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-TXB2 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-TXB2 was also significantly (P < .001) higher in patients than controls (725 ± 676 vs 82 ± 43 pmol/mmol creatinine). A highly significant linear correlation was found between the excretion rates of 11-dehydro-TXB2 and 2,3-dinor-TXB2 (Fig 1). This finding suggests that enhanced metabolite excretion in patients with polycythemia vera reflects increased TXA2 biosynthesis rather than alterations in its metabolic disposition.

At variance with TXB2 metabolite excretion, urinary LTE4 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 TXA2 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 TXA2. Whereas (1) would be reflected by changes detectable ex vivo, (2) and (3) would be compatible with unchanged capacity of platelets to synthesize TXA2 in vitro.

To assess the biosynthetic capacity of the patients platelets, we measured TXB2 production during whole blood clotting. This reflects the virtually maximal production of TXA2 by platelets exposed to endogenous thrombin.21 As shown in Table 2, serum TXB2 concentrations in patients were twofold higher than previously measured in a large (n = 177) population of healthy controls.31 However, when corrected for the platelet count, an identical value of TXB2 production was found in patients and controls. That enhanced TXB2 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-TXB2 (r = .055) or 2,3-dinor-TXB2 (r = .075). Moreover, the production of LTE4 in whole blood—a reflection of transcellular metabolism of neutrophil-derived LTA4 by other blood cells, including platelets19—was similar in polycythemic patients (10.8 ± 14.3 pmol/10⁹ white blood cells [WBCs]; n = 10) and controls (11.1 ± 7.3 pmol/10⁹ WBCs; n = 8).

To characterize the platelet versus nonplatelet origin of enhanced TXB2 metabolite excretion, we evaluated the short-term effects of a platelet-selective regimen of aspirin therapy (50 mg/d for 7 to 14 days) on the extent of suppression and time-course of recovery of metabolite

Table 1. Individual Measurements of 11-Dehydro-TXB2 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 (10⁹/L)</th>
<th>Hematocrit (L)</th>
<th>Urinary 11-Dehydro-TXB2 (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>
<td>C</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td>0.47</td>
<td>210</td>
<td>P</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>0.50</td>
<td>4,565</td>
<td>P + C</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>179</td>
<td>0.50</td>
<td>825</td>
<td>P</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td>0.48</td>
<td>1,201</td>
<td>P</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>450</td>
<td>0.51</td>
<td>1,270</td>
<td>P + C</td>
<td>Yes</td>
</tr>
<tr>
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<td>0.47</td>
<td>1,208</td>
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<td>No</td>
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<tr>
<td>8</td>
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<td>0.50</td>
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<td>P</td>
<td>No</td>
</tr>
<tr>
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<td>670</td>
<td>0.47</td>
<td>809</td>
<td>P</td>
<td>No</td>
</tr>
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<td>10</td>
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<td>0.49</td>
<td>372</td>
<td>P</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>225</td>
<td>0.48</td>
<td>310</td>
<td>C</td>
<td>Yes</td>
</tr>
<tr>
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<td>128</td>
<td>0.50</td>
<td>371</td>
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<tr>
<td>13</td>
<td>721</td>
<td>0.45</td>
<td>1,192</td>
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<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>1,097</td>
<td>0.46</td>
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<tr>
<td>15</td>
<td>696</td>
<td>0.49</td>
<td>426</td>
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<tr>
<td>16</td>
<td>360</td>
<td>0.49</td>
<td>557</td>
<td>P</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>950</td>
<td>0.47</td>
<td>339</td>
<td>P</td>
<td>No</td>
</tr>
</tbody>
</table>

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).

Table 2. Whole Blood TXB2 Production in Relation to Platelet Count in Patients With Polycythemia Vera and Healthy Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum TXB2 (nmol/L)</th>
<th>Blood Platelets (10⁹/L)</th>
<th>Serum TXB2 (nmol/10⁹ Platelets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls*</td>
<td>811 ± 292</td>
<td>212 ± 42</td>
<td>3.8 ± 2.4</td>
</tr>
<tr>
<td>(n = 177)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>1,678 ± 1,899</td>
<td>434 ± 294</td>
<td>3.8 ± 1.4</td>
</tr>
<tr>
<td>patients (n = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*Normal values are from Alessandrini et al.26
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 arachidonate metabolism have been reported. Thus, Shafer described a selective deficiency of platelet lipoxygenase activity in 10 of 22 patients with polycythemia vera, whereas this enzyme activity was normal in patients with reactive thrombocytosis or secondary polycythemia. Interestingly, lipoxygenase-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-lipoxygenase 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 aggregeometric 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 ple-
THROMBOXANE BIOSYNTHESIS IN POLYCYTHEMIA VERA

1969

Although the biosynthetic capacity of human platelets to produce TXA₂ when challenged in vitro, the actual rate of TXA₂ biosynthesis in vivo is very low under physiologic circumstances, possibly because of the low frequency and/or intensity of stimuli to its production. The discrepancy between the two is several thousand fold, with the platelets contained in 1 mL of human whole blood being capable of generating approximately the same amount of TXB₂ produced by the whole body, i.e., 420 ng/h. Thus, capacity-related indexes do not necessarily reflect changes in the stimuli to TXA₂ biosynthesis occurring in vivo. Moreover, as recently reviewed by George and Shattil, in addition to technical variables, platelet aggregate responses among normal persons can vary with mental stress, age, sex, race, diet, and hematocrit level, and a person may have different responses on repeated determinations.

Thus, the present study sought to determine the actual rate of TXA₂ biosynthesis in patients with polycythemia vera by measuring two major urinary enzymatic metabolites, i.e., 11-dehydro-TXB₂ and 2,3-dinor-TXB₂, noninvasive indexes of arachidonate metabolism via the cyclooxygenase/TX-synthase pathway. All of our patients excreted 2 to 40 times the level of metabolites excreted by controls matched for sex and age. The finding of a linear correlation between the two metabolites (Fig 1), originating through the 11-hydroxy-dehydrogenase and the β-oxidation pathways, respectively, suggests that the enhanced metabolite excretion detected in patients with polycythemia vera reflects a change in the biosynthesis of TXA₂ rather than a shift in its metabolic disposition. The finding of unchanged excretion of LTE₄, a major metabolite of LTC₄ in humans, excludes a generalized abnormality of arachidonate metabolism by blood cells of polycythemic patients. Moreover, our observation of similar LTE₄ production in whole blood samples of patients and controls is consistent with the recent finding of Stenke et al of unaltered LTC₄ production in WBC preparations from polycythemia vera patients. Enhanced TXA₂ biosynthesis in our patients was associated with unchanged biosynthetic capacity of circulating platelets, as assessed by measurement of TXB₂ production during whole blood clotting (Table 2). Moreover, TXB₂ metabolic excretion did not correlate with the platelet count to any statistically significant extent, thus excluding thrombocytosis as the primary cause of this abnormality.

Urinary metabolites do not necessarily reflect a specific site of cicosanoid biosynthesis. To distinguish between platelet and nonplatelet sites of TXA₂ synthesis, we exploited the capacity of aspirin to acetylate platelet prostaglandin G/H-synthase selectively when it is administered daily in low doses. Other sites of cyclooxygenase activity, such as the kidney, that can be involved in enhanced TXA₂ production under pathophysiologic circumstances are largely unaffected by doses of aspirin in the range of 30 to 50 mg/d. The greater than 80% reduction in TXB₂ metabolite excretion in nine patients after they received low doses of aspirin for 1 to 2 weeks as well as the slow rate 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, as well as in patients with episodically or persistently 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 occurring 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 coronary and peripheral 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, non-insulin-dependent diabetes mellitus, and type IIa hypercholesterolemia. Thus, TXA₂-dependent platelet activation may represent a transduction mechanism linking these various risk factors to the enhanced risk of vascular occlusive complications.

An elevated hematocrit value and increased blood viscosity clearly play a role in the pathogenesis of thrombotic complications in polycythemia vera. As reviewed by Sayer, 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. 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 dipryidamole 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 reassessing 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 µg 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 polycythemia vera.

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