

# Extrinsic blood coagulation pathway and risk factors for thrombotic events in patients with essential thrombocythemia

Katarzyna Stankowska<sup>1</sup>, Grażyna Gadomska<sup>2</sup>, Joanna Boinska<sup>1</sup>,  
Małgorzata Michalska<sup>1</sup>, Alicja Bartoszewska-Kubiak<sup>3</sup>, Danuta Rość<sup>1</sup>

1 Department of Pathophysiology, Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland

2 Department of Hematology and Malignant Diseases of Hematopoietic System, Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland

3 Department of Clinical Genetics, Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland

## KEY WORDS

essential thrombocythemia, tissue factor, tissue factor pathway inhibitor

## ABSTRACT

**INTRODUCTION** The clinical course of essential thrombocythemia (ET) is varied, and some patients do not exhibit any clinical signs of the disease at the time of diagnosis. The most frequent complications that occur during the course of ET are hemostasis abnormalities manifesting as hemorrhagic or thrombotic events. The mechanism of thrombotic events in patients with ET is complex and not fully understood.

**OBJECTIVES** The aim of the study was to evaluate the concentration and activity of tissue factor (TF) and tissue factor pathway inhibitor (TFPI), depending on the most important risk factors of thrombotic complications (age >60 years, history of thrombotic episodes, presence or absence of the *JAK2 V617F* mutation, and increased leukocyte count).

**PATIENTS AND METHODS** The study group included 113 patients with diagnosed ET, and the control group, 30 healthy volunteers matched for age and sex. The concentration and activity of TF and TFPI were measured using enzyme-linked immunosorbent assays.

**RESULTS** Patients with ET had a significantly higher activity and concentration of TF and increased activity of TFPI, as compared with controls. The analysis of the studied parameters in relation to risk factors revealed that patients with ET with a history of thrombotic events had a significantly higher concentration of TF, and patients with the *JAK2 V617F* mutation had a lower TFPI activity, as compared with patients without the mutation.

**CONCLUSIONS** Our study showed that in patients with ET who have a history of thrombosis or the *JAK2 V617F* mutation, the enhanced risk of thrombosis may result from an increased TF concentration or decreased TFPI activity.

## Correspondence to:

Katarzyna Stankowska, MSc,  
Katedra Patofizjologii, Uniwersytet  
Mikołaja Kopernika w Toruniu,  
Collegium Medicum w Bydgoszczy,  
ul. Skłodowskiej-Curie 9,  
85-094 Bydgoszcz, Poland,  
phone: +48 52 585 35 91  
e-mail: stankowska\_katarzyna@wp.pl

Received: February 1, 2016.

Revision accepted: April 25, 2016.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2016;

126 (5): 340-346

doi:10.20452/pamw.3429

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**INTRODUCTION** Essential thrombocythemia (ET) belongs to Ph-negative myeloproliferative neoplasms and is characterized by an increased platelet count (>450 G/l) induced by clonal proliferation of megakaryocytes in the bone marrow. ET is mostly diagnosed between 50 and 60 years of age. The *JAK2 V617F* mutation is found in approximately 50% of patients with ET.<sup>1</sup>

Thrombotic complications are one of the most common causes of death in patients with ET and can occur in arterial vessels (cerebrovascular or cardiovascular events), venous vessels (splanchnic

vein, mesenteric, lower extremity, pulmonary embolism), or in the microcirculation (headache, paresthesia, erythromelalgia).<sup>1,2</sup> There are 2 major risk factors of thrombotic events: age above 60 years and a history of thrombotic episodes. Recent studies have indicated that platelet function abnormalities, leukocytosis, activation of platelet-leukocyte aggregates, and the *JAK2 V617F* mutation may play an important role in the development of thrombotic complications in patients with ET.<sup>3,4</sup>

**TABLE 1** Clinical and laboratory characteristics of patients with essential thrombocythemia and control subjects

Parameter	Essential thrombocythemia (n = 113)	Controls (n = 30)	P value
mean age	61 (20–88)	49 (30–61)	NS
sex, female/male, n	41/25	17/13	–
leukocyte count, $\times 10^9/l$	9.9 (4.1–17.8)	5.9 (4.0–9.0)	<0.000001
erythrocyte count, $\times 10^{12}/l$	5.0 (2.7–9.0)	4.9 (4.0–5.6)	NS
hemoglobin, g/dl	14.5 (8.4–19.4)	13.2 (12.1–16.8)	NS
platelet count, $\times 10^9/l$	820.0 (461.0–2165.0)	250.0 (156.0–345.0)	<0.000001

Data are presented as median (min–max) unless stated otherwise.

Abbreviations: NS, nonsignificant

According to the cellular theory of blood coagulation, tissue factor (TF)-dependent extrinsic pathway is essential for the activation of blood clotting. TF is released from damaged endothelial cells and activated monocytes, macrophages, leukocytes, and platelets. Microparticles derived from endothelial cells, vascular smooth muscle cells, leukocytes, and platelets may also be the source of TF.<sup>5,6</sup>

The activity of TF is regulated by tissue factor pathway inhibitor (TFPI). TFPI is a Kunitz-type protein that is released from endothelial cells, platelets, monocytes, fibroblasts, and mesangial cells. TFPI inactivates the TF/VIIa complex in 2 steps. In the first phase, TFPI binds to activated factor X (Xa) and forms the TFPI/Xa complex. In the second step, the TFPI/Xa complex inactivates the TF/VIIa complex. TFPI may also directly inhibit the complex of TF/VIIa/Xa in the presence of calcium ions.<sup>7</sup>

The aim of the study was to evaluate the procoagulant potential reflected by TF and TFPI activity in patients with ET, with respect to the following risk factors of thrombosis: age above 60 years, history of thrombosis, presence of the *JAK2 V617F* mutation, and leukocyte count exceeding  $10 \times 10^9/l$ .

**PATIENTS AND METHODS** **Study population** The study involved 113 patients (41 women, 25 men; mean age, 61 years), diagnosed at the Hematology Clinic of the Bizieli University Hospital No. 2 in Bydgoszcz, Poland. Patients were recruited between the years 2012 and 2016. The diagnosis of ET was based on the diagnostic criteria of ET developed by the World Health Organization (2008) and the exclusion of other malignant and nonmalignant diseases manifesting with thrombocythemia. Additional exclusion criteria were as follows: newly diagnosed thrombosis, type 1 or type 2 diabetes, and pregnancy. Blood samples were collected from newly diagnosed patients (patients not previously treated with cytostatic drugs). Of 113 patients with ET, 21 (25.68%) had a history of thrombosis (at least 1 year before the diagnosis of ET). Acute coronary syndromes, myocardial infarction, transient ischemic attacks, cerebrovascular accidents, and peripheral arterial occlusive

disease were defined as major arterial thrombotic complications. Major venous thrombotic complications were defined as deep vein thrombosis and mesenteric venous thrombosis.

The control group consisted of 30 healthy volunteers (13 women, 17 men; mean age, 49 years). The study was approved by the Bioethics Committee of Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń (no. KB/396/2010). All patients were informed of the investigational nature of this study and gave written informed consent to participate.

#### Blood collection and measurement of tissue factor and tissue factor pathway inhibitor activity

Blood samples were taken from an antecubital vein, after an overnight fasting, to plastic tubes containing 3.2% sodium citrate (anticoagulant: blood, 1:9). Samples were centrifuged at  $3000 \times g$  for 20 minutes at 4°C. The obtained plasma was divided into aliquots and stored at –80°C until analysis, but no longer than 6 months. In plasma, the following tests were performed using an enzyme-linked immunosorbent assay (ELISA): concentration of TF (Imubind Tissue Factor ELISA kit, American Diagnostica Inc., Stamford, Connecticut, United States), TF activity (ACTICHROME®TF, American Diagnostica Inc.), concentration of TFPI (Imubind Total TFPI ELISA kit, American Diagnostica Inc.) and TFPI activity (ACTICHROME®TFPI Activity Assay, American Diagnostica Inc.).

***JAK2 V617F* mutation analysis** The *JAK2 V617F* mutation was detected using allele-specific polymerase chain reaction (allele specific PCR amplification [AS-PCR]). Genomic DNA was isolated from peripheral EDTA blood (QIAamp DNA Mini Kit, Qiagen, Hilden, Germany) from patients with ET. The PCR reaction was performed using 100 ng of DNA, according to the method of Baxter et al.<sup>8</sup> During the AS-PCR, the reaction products were 203 bp and 364 bp in length. The 203-bp products indicated the V617F mutation, while the 364 bp products indicated the internal control.

**Statistical analysis** A statistical analysis was performed with the use of Statistica 10 software (StatSoft®, Kraków, Poland). The Shapiro–Wilk

**TABLE 2** Clinical characteristics of patients with essential thrombocythemia

Parameter	Value
history of thrombosis	21 (18.6)
arterial	16 (14.2)
venous	5 (4.4)
hepatomegaly	7 (6.2)
splenomegaly	12 (10.6)
splenectomy	1 (0.9)
JAK2 V617F mutation	
yes	75 (66.4)
no	38 (33.6)

Data are presented as number (percentage) of patients.

test was used to assess the normality of the distribution. All studied parameters had abnormal distribution and were presented as a median and lower and upper quartiles. The Mann–Whitney test was used to compare the difference between the groups. Spearman correlation coefficients were calculated to determine any correlations between the parameters. A *P* value of less than 0.05 was considered statistically significant.

**RESULTS** **TABLE 1** shows a comparison of blood cell counts between patients with ET and healthy participants. Patients with ET had a 3-fold higher median platelet count ( $820 \times 10^9/l$  vs  $250 \times 10^9/l$ ;  $P < 0.05$ ) and significantly higher leukocyte count than controls ( $9.9 \times 10^9/l$  vs  $5.9 \times 10^9/l$ ;  $P < 0.05$ ). Among 113 patients with ET, 21 (18.6%) reported the incidence of arterial and venous thrombotic history. The presence of the *JAK2 V617F* mutation was observed in 75 patients (66.4%). Data are shown in **TABLE 2**. As shown in **TABLE 3**, patients with ET had more than 2-fold higher TF concentrations and 18-fold higher TF activity, as compared with controls ( $P < 0.000001$  for both comparisons). In addition, patients with ET had a significantly higher activity of TFPI, as compared with controls ( $P < 0.05$ ). There were no significant differences in the concentration of TFPI between the groups.

**TABLE 3** Concentration and activity of tissue factor and tissue factor pathway inhibitor in patients with essential thrombocythemia and in the control group

Parameter	Study group (n = 113)	Control group (n = 30)	<i>P</i> value
TF Ag, pg/ml	363.0 (173.3; 756.5)	153.4 (110.6; 177.6)	<0.000001
TF activity, pM	49.34 (32.5; 63.8)	2.8 (0.9; 5.8)	<0.000001
TFPI Ag, ng/ml	78.7 (60.4; 101.3)	82.0 (68.8; 91.4)	NS
TFPI activity, U/ml	1.9 (1.6; 2.6)	1.7 (1.0; 2.0)	0.017

Data are presented as median and lower and upper quartiles (Q1; Q3).

Abbreviations: Ag, antigen; TF, tissue factor; TFPI, tissue factor pathway inhibitor; others, see **TABLE 1**

A detailed analysis of the studied parameters revealed that in 75 patients with ET with the *JAK2 V617F* mutation, TFPI activity was significantly lower than in patients without the mutation (**FIGURE 1**). However, there were no significant differences in the concentration of TF and TFPI as well as TF activity in patients with ET who had the *JAK2 V617F* mutation compared with the values obtained in patients without the mutation.

As shown in **FIGURE 2**, the TF concentration was significantly higher ( $P < 0.05$ ) in patients with ET with a history of thrombotic episodes, compared with patients without such episodes (**FIGURE 2**).

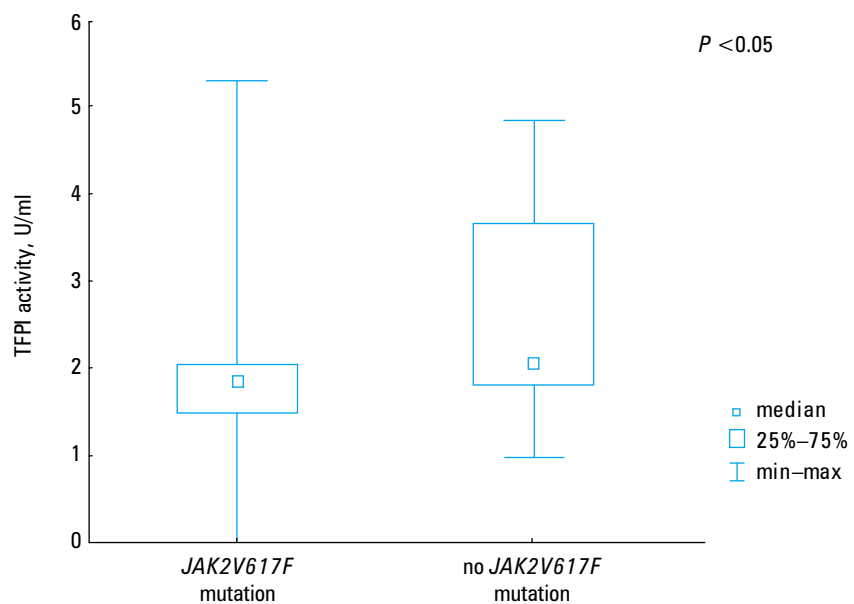
There were no significant differences in the activity of TF in patients with a history of thrombosis compared with patients without such history. The concentration and activity of TFPI in patients with a history of thrombotic episodes did not differ significantly from the values obtained in patients with no history of thrombotic events.

There were no significant differences in the concentration and activity of TF and TFPI between patients aged 60 years or older (71 patients) and those younger than 60 years of age (42 patients). Moreover, the concentration and activity of TF and TFPI in patients with ET were not related to leukocyte count. Data are presented in **TABLE 4**.

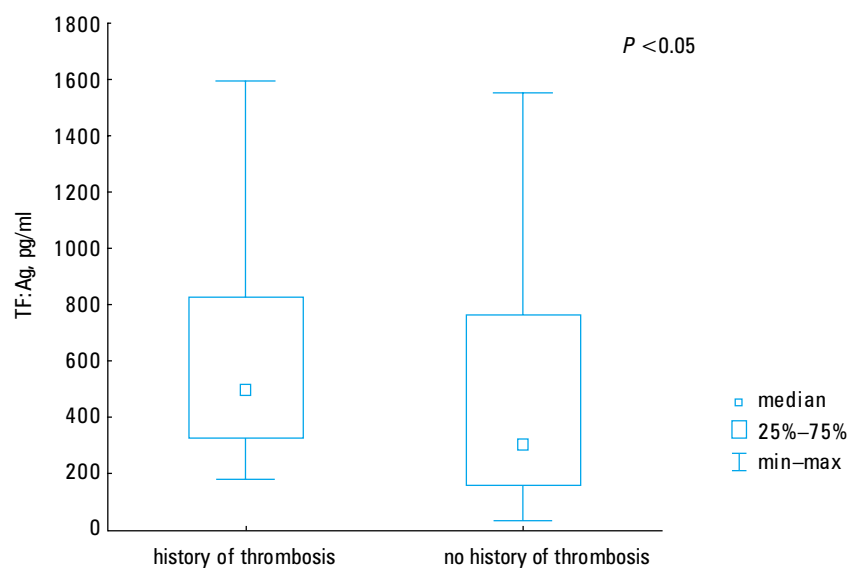
**DISCUSSION** TF is a glycoprotein with a molecular weight of 47 kDa, produced by the brain, lung, placenta, and heart muscle cells. IT occurs in the blood of healthy subjects only in small amounts. Increased concentrations of TF can result from vascular endothelial damage or blood cell activation (platelets, granulocytes). According to recent studies, TF is a major activator of the blood coagulation process.<sup>9,10</sup>

Our study demonstrated a 2-fold higher concentration of TF in patients with ET than in healthy subjects. We determined the procoagulant activity of TF, which is the best indicator of the activation of the blood coagulation process (TF activity). TF activity was nearly 18-fold higher in patients with ET than in healthy subjects.

**FIGURE 1** Tissue factor pathway inhibitor (TFPI) activity in the subgroups of patients with essential thrombocythemia with or without the *JAK2 V617F* mutation



**FIGURE 2** Concentrations of tissue factor (TF) in patients with essential thrombocythemia with and without a history of thrombosis



A review of the available literature has shown that there are only a few studies assessing the concentration of TF in patients with ET. Panova-Noeva et al<sup>11</sup> observed a significantly higher expression of TF on platelets in patients with ET compared with controls. The authors observed the generation of thrombin in the calibrated automated thrombogram assay in platelet-rich plasma and isolated platelets, but it was absent in platelet-free plasma. According to the authors, platelets (which are the main source of TF) are responsible for the occurrence of a hypercoagulable state in patients with ET.<sup>11</sup> Falanga et al<sup>12</sup> also observed a significantly increased expression of TF on platelets in patients with ET in comparison with the control group. Different results were obtained by Arellano-Rodrigo et al,<sup>9</sup> who did not observe significant differences in the expression of TF on platelets and its concentrations between patients with ET and healthy subjects.

In the current study, we analyzed the concentration and activity of TF and TFPI depending on

a history of thrombosis, patients' age, leukocyte count, and the presence of the *JAK2 V617F* mutation. We showed significantly higher TF concentrations in patients with ET with past thrombotic episodes. Different results were obtained by Arellano-Rodrigo et al,<sup>9</sup> who found no significant differences in the concentration of TF between patients with ET with and without a history of thrombotic episodes.

Procoagulant activity of TF is inhibited by TFPI, an inhibitor of the TF pathway whose primary source is the vascular endothelium. In the present study, we observed an increased activity of TFPI in patients with ET, as compared with the control group ( $P = 0.017$ ). The TFPI concentration and activity in patients with ET were also measured by Cacciola et al,<sup>13</sup> who found significantly higher levels of TFPI in these patients ( $n = 17$ ). Elevated concentrations of TFPI have also been observed in patients with advanced pancreatic, colorectal, stomach, breast, and prostate cancers.<sup>14</sup> It is believed that the increased level of TFPI can

**TABLE 4** Concentration and activity of tissue factor and tissue factor pathway inhibitor in patients with essential thrombocythemia depending on age and leukocyte count

Parameter	Age		P value	Leukocyte count		P value
	<60 years (n = 42)	≥60 years (n = 71)		<10×10 <sup>9</sup> /l (n = 65)	≥10×10 <sup>9</sup> /l (n = 48)	
TF Ag, pg/ml	262.7 164.3; 686.9	413.0 (180.2; 795.4)	NS	412.0 (181.4; 783.4)	299.7 (173.3; 693.0)	NS
TF activity, pM	48.0 30.1; 61.8	49.4 (37.7; 67.2)	NS	49.8 (34.2; 69.6)	47.6 (26.1; 57.1)	NS
TFPI Ag, ng/ml	78.0 55.0; 102.3	81.6 (62.4; 100.2)	NS	78.4 (62.8; 102.3)	82.9 (56.1; 107.6)	NS
TFPI activity, U/ml	1.9 1.4; 2.1	1.9 (1.6; 3.0)	NS	1.9 (1.6; 2.2)	1.9 (1.5; 3.2)	NS

Data are presented as median and lower and upper quartiles (Q1; Q3).

Abbreviations: see TABLE 1

be the result of endothelial damage or increased procoagulant activity of TF.<sup>15</sup>

The analysis of TFPI depending on the *JAK2 V617F* mutation revealed differences in the activity of TFPI between the subgroups with and without the mutation. We found a significantly reduced TFPI activity in patients with ET with the *JAK2 V617F* mutation, compared with patients without the mutation. Data from the literature suggest that reduced activity of TFPI is associated with an increased risk of thromboembolic incidents.<sup>16-18</sup> Taken together, the decreased activity of TFPI in patients with the *JAK2 V617F* mutation indicates that this subgroup can be particularly vulnerable to the risk of thrombosis. Campbell et al<sup>19</sup> found that the incidence of thrombotic complications in the veins was higher in patients with ET with the *JAK2 V617F* mutation, as compared with patients without the mutation. However, the authors did not observe significant differences in arterial thrombotic events between patients with and without the *JAK2* mutation.<sup>19</sup> Antonioli et al<sup>20</sup> reported no relationship between the presence of the *JAK2 V617F* mutation and the incidence of thrombotic events.

According to prospective and retrospective studies, one of the main risk factors of thrombosis in patients with ET is age above 60 years.<sup>21</sup> In the present study, we did not observe any significant differences in TF and TFPI activity and concentration in the subgroups of patients aged less than 60 years and those aged 60 years or older. Thrombotic potential increases with age in healthy subjects. It is associated with vascular endothelial damage, impaired fibrinolysis, and increased concentrations of most procoagulant factors. Therefore, it is believed that risk factors such as age above 60 years and a history of thromboembolic events are associated with abnormalities in the vessels regardless of myeloproliferative neoplasm.

The analysis showed no significant differences in the activity and concentration of TF and TFPI depending on the leukocyte count in the blood of patients with ET. It is well known that high

leukocyte count at diagnosis is a poor prognostic factor and is associated with worse survival.<sup>22</sup> High leukocytosis is also linked to more frequent progression of ET to acute leukemia or myelofibrosis. Carobbio et al<sup>23</sup> observed that the risk of thrombotic events in patients with ET with an increased leukocyte count (above median) was 2-fold higher than that in patients with lower white blood cell count. Based on these results, the authors found that the number of leukocytes can be a useful parameter in evaluating the risk of thrombotic events in patients with ET.<sup>23</sup> Similar conclusions were drawn by Wolanskyj et al,<sup>24</sup> who also reported a relationship between the elevated levels of leukocytes and the incidence of thrombotic events in patients with ET.

In conclusion, the study showed that increased blood coagulation observed in patients with ET may be related to elevated TF concentrations and remarkably increased TF activity. Moreover, in patients with ET with a history of thrombosis or the *JAK2 V617F* mutation, an enhanced risk of thrombosis may be a result of increased TF concentration or decreased activity of TFPI.

**Contribution statement** KS and GG were responsible for collecting the material for research, analysis, and interpretation of the results. KS and DR were responsible for interpretation of the results and preparation of the manuscript. JB, MM, and AB-K were responsible for the measurement of the parameters. JB was responsible for statistical analysis and preparation of the manuscript.

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# Zewnątrzpochodny proces krzepnięcia krwi a wybrane czynniki ryzyka powikłań zakrzepowych u chorych na nadpłytkowość samoistną

Katarzyna Stankowska<sup>1</sup>, Grażyna Gadomska<sup>2</sup>, Joanna Boinska<sup>1</sup>,  
Małgorzata Michalska<sup>1</sup>, Alicja Bartoszevska-Kubiak<sup>3</sup>, Danuta Rość<sup>1</sup>

1 Katedra Patofizjologii, Uniwersytet Mikołaja Kopernika w Toruniu, Collegium Medicum w Bydgoszczy, Bydgoszcz

2 Oddział Kliniczny Hematologii i Chorób Rozrostowych Układu Krwiotwórczego, Uniwersytet Mikołaja Kopernika w Toruniu, Collegium Medicum w Bydgoszczy, Bydgoszcz

3 Katedra i Zakład Genetyki Klinicznej, Uniwersytet Mikołaja Kopernika w Toruniu, Collegium Medicum w Bydgoszczy, Bydgoszcz

## SŁOWA KLUCZOWE

czynnik tkankowy,  
inhibitor drogi  
krzepnięcia zależnej  
od czynnika  
tkankowego,  
nadpłytkowość  
samoistna

## STRESZCZENIE

**WPROWADZENIE** Przebieg kliniczny nadpłytkowości samoistnej (*essential thrombocythemia* – ET) jest zróżnicowany, a część pacjentów w momencie diagnozy nie przejawia żadnych objawów klinicznych choroby. Najczęstszymi powikłaniami występującymi w przebiegu ET są zaburzenia hemostazy ujawniające się pod postacią incydentów krwotocznych lub zakrzepowych. Mechanizm incydentów zakrzepowych u chorych na ET jest złożony i nie został do końca poznany.

**CELE** Celem pracy było zbadanie stężenia i aktywności czynnika tkankowego (*tissue factor* – TF) i inhibitora drogi krzepnięcia zależnej od czynnika tkankowego (*tissue factor pathway inhibitor* – TFPI) w zależności od najważniejszych czynników ryzyka wystąpienia powikłań zakrzepowych (wiek >60. rż., epizody zakrzepowe w wywiadzie, obecność lub brak mutacji *JAK2 V617F* oraz podwyższona liczba leukocytów).

**PACJENCI I METODY** Do grupy badanej włączono 113 pacjentów ze zdiagnozowaną ET, a do grupy kontrolnej – 30 zdrowych osób dobranych pod względem wieku i płci do grupy badanej. Stężenie i aktywność TF i TFPI oznaczono za pomocą testów immunoenzymatycznych.

**WYNIK** Chorzy na ET mieli istotnie wyższą aktywność i stężenie TF oraz podwyższoną aktywność TFPI w porównaniu z grupą kontrolną. Analiza badanych parametrów zależnie od czynników ryzyka wykazała, że u chorych na ET z dodatnim wywiadem w kierunku incydentów zakrzepowych występuje istotnie wyższe stężenie TF, a u chorych z mutacją *JAK2 V617F* niższa aktywność TFPI w stosunku do chorych bez mutacji.

**WNIOSKI** Nasze badanie wykazało, że u pacjentów z ET z dodatnim wywiadem w kierunku zakrzepicy lub obecnością mutacji *JAK2 V617F* zwiększone ryzyko zakrzepowe może być wynikiem zwiększonego stężenia TF lub zmniejszonej aktywności TFPI.

Adres do korespondencji:

mgr Katarzyna Stankowska,  
Katedra Patofizjologii, Uniwersytet  
Mikołaja Kopernika w Toruniu,  
Collegium Medicum w Bydgoszczy,  
ul. Skłodowskiej-Curie 9,

85-094 Bydgoszcz, tel.: 52 585 35 91,

e-mail: stankowska\_katarzyna@wp.pl

Praca wpłynęła: 01.02.2016.

Przyjęta do druku: 25.04.2016.

Nie zgłoszono sprzeczności  
interesów.

Pol Arch Med Wewn. 2016;

126 (5): 340-346

doi:10.20452/pamw.3429

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Kraków 2016