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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Plasma concentrations of tissue factor and its inhibitor in chronic thromboembolic pulmonary hypertension: a step closer to explanation of the disease aetiology?

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Abstract

Background: The aetiology of chronic thromboembolic pulmonary hypertension (CTEPH) is not clearly understood. In some patients, the disease is preceded by acute pulmonary embolism (APE), and is characterised by intravascular thrombosis, vasoconstriction, inflammation and remodelling of pulmonary arteries. Ensuing pulmonary hypertension leads to potentially fatal chronic right ventricle failure. Both inborn and acquired risk factors were identified. Pathogenesis of haemostatic disorders is not completely explained, and extrinsic coagulation pathway disorders may play a role in CTEPH aetiology.

Aim: To evaluate levels of tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in CETPH, and to delineate their role in the disease pathogenesis.

Methods: Plasma concentrations of TF and TFPI were evaluated in 21 CTEPH patients, in 12 patients with pulmonary arterial hypertension (PAH), in 55 APE survivors without persistent pulmonary hypertension after at least 6 months from the acute episode, and in 53 healthy volunteers (control group C). Most patients were treated with vitamin K antagonists (VKA), and some with unfractionated or low molecular weight heparin. Exclusion criteria included malignancy, inflammation, and recent operation.

Results: Tissue factor concentration was lower in CTEPH and in post-APE patients, not stratified by anticoagulation modality, as compared to control group ($p = 0.042$; $p = 0.011$) and PAH group ($p = 0.024$, $p = 0.014$). Patients with CTEPH and post-APE on adequate VKA-anticoagulation had similar TF concentration to group C. TFPI concentration was similar in CETPH and post-APE patients irrespective of anticoagulation, and higher as compared to group C (respectively, $p = 0.012$; $p = 0.024$; $p = 0.004$). TFPI concentration was similar in patients with CETPH and in post-APE group, both on adequate VKA-anticoagulation when compared to group C. In the post-APE group, there was no significant difference in TFPI concentration between patients receiving adequate and subjects without anticoagulation. Group C was significantly ($p = 0.000$) younger than any other group, and showed correlation ($r = 0.31$) between age and TFPI concentration.

Conclusions: In CTEPH there is a high consumption of TF, leading to reduction in plasma concentration of TF and increase in TFPI. Adequate VKA-anticoagulation normalises TF and TFPI plasma concentrations, as is the case of APE survivors.

Key words: chronic thromboembolic pulmonary hypertension (CTEPH), tissue factor (TF), tissue factor pathway inhibitor (TFPI), anticoagulation

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INTRODUCTION

Etiopathogenesis of chronic thromboembolic pulmonary hypertension (CTEPH) is not completely understood. In some patients, the disease is preceded by an episode of acute pulmonary embolism (APE) [1], and is characterised by vasoconstriction, inflammation, activation of the clotting system with decreased fibrinolysis as well as remodelling of pulmonary arteries [2]. Ensuing pulmonary hypertension leads to potentially fatal chronic right ventricle failure. Both inborn and acquired risk factors were identified [3–5]. Patients with CTEPH are treated in reference centres. Some patients undergo pulmonary endarterectomy with good outcome [6], whereas others, who cannot be operated on or in whom the risk connected to surgical intervention is too high, may be referred for procedures of pulmonary artery balloon angioplasty [7]. In cases of inoperable CTEPH or disease relapse after pulmonary endarterectomy, medical treatment with riociguat, a guanyl cyclase agonist is recommended (grade I B recommendation according to the 2015 guidelines of the European Society of Cardiology [ESC]) [8, 9]. Other vasodilators or remodelling inhibitors used for treatment of pulmonary arterial hypertension (PAH) may also be considered. Among those, endothelin receptor antagonist bosentan was studied the most in treatment of CTEPH (grade II B recommendation according to ESC) [9, 10]. Continuous anticoagulation remains the mainstay of treatment. Mechanisms of coagulation disturbance in CTEPH are not completely understood, there are few studies in literature, most of them in small patient groups or with contradictory results. These studies revealed increased serum concentrations of tissue plasminogen activator and inhibitor of tissue plasminogen activator type 1 but the activity of both these proteins remains unchanged [11, 12]. Moreover, selected fibrinogen gene polymorphisms were described as well as fibrinogen and fibrin structural aberrations, resulting in fibrin resistance to fibrinolytic enzymes [13–15]. Pathogenesis of haemostatic disorders is not completely explained, and extrinsic coagulation pathway disorders may play a role in CTEPH aetiology. These phenomena lead to pulmonary endothelial injury, and thus may lead to both intravascular thrombosis and pulmonary artery remodelling [16].

METHODS

Mean concentrations of tissue factor (TF) and its inhibitor (tissue factor pathway inhibitor [TFPI]) were studied in 21 patients with CTEPH, 12 patients with PAH, in 55 survivors of APE at least half a year after the episode and with no persistent pulmonary hypertension, and in 53 healthy subjects (voluntary blood donors, control group C). In the PAH group there were 7 patients with isolated idiopathic pulmonary arterial hypertension (IPAH), 1 patient with IPAH and lung fibrosis, 2 patients with Eisenmenger syndrome following the presence of inborn defect of interatrial heart septum, 1 patient with PAH in the course of limited systemic sclerosis, and 1 patient with mixed pre- and post-capillary pulmonary hypertension, most likely IPAH with concurrent left heart defect. Most patients were treated with vitamin K antagonists (VKA), and some received therapeutic or high prophylactic doses of unfractionated or small molecular weight heparin. Effects of anticoagulative therapy were monitored by international normalised ratio (INR) measurement, and activated partial thromboplastin time was additionally monitored in patients treated with unfractioned heparin. No patients were administered thrombin or factor Xa inhibitors. In the CTEPH groups there were no patients after undergone pulmonary endarterectomy or treated with pulmonary vasodilating agents, which were administered in some PAH patients. Exclusion criteria were the following: malignancy newly diagnosed or being treated, active inflammation, surgical intervention during the preceding weeks. Patient characteristics are presented in Table 1.

Imubind® Tissue Factor ELISA Kit from American Diagnostica Inc. (USA) was used for measurement of TF levels. The kit identifies TF-apo and TF-factor VII complexes using

Table 1. Patient characteristics in respective groups

	CTEPH	Post-APE	PAH	Control group (C)
Number of patients	21	55	12	53
Age [years ± SD]	64.81 ± 11.57	59.07 ± 16	57.92 ± 11.98	31.75 ± 11.39
Number of patients taking heparin	4	3	0	0
Number of patients taking VKA (mean INR value for patients treated with VKA)	18 (2.12)	40 (2.53)	8 (2.02)	0
Number of patients with adequate VKA anticoagulation, i.e. INR > 2 at the study onset	10	23	3	0
Number of patients not taking anticoagulants during the study	1	13	4	53

APE — acute pulmonary embolism; CTEPH — chronic thromboembolic pulmonary hypertension; INR — international normalised ratio; PAH — pulmonary arterial hypertension; SD — standard deviation; VKA — vitamin K antagonists

enzyme-linked immunosorbent assay (ELISA), with detection threshold of 10 pg/mL. Imubind® Total TFPI ELISA Kit from American Diagnostica Inc. (USA) was used for measuring TFPI concentration. This assay has detection threshold of 0.36 ng/mL, and identifies the whole and the fragmented TFPI particles as well as TFPI complexed with TF/FVIIa/TFPI, TFPI/FXa or TF/FVIIa/TFPI/FXa.

Statistical analyses

Statistical analyses were performer using Statistica 10 software (StatSoft, Tulsa, OK, USA). Results are presented in respective figures. Single factor analysis of variance (ANOVA) was used to compare mean values of patient age. Tested hypothesis was that of equal variable distribution in respective groups. When the calculated p-value was over 0.05, hypothesis of group equality could not be rejected, and thus variables in respective groups were not significantly different. For $p < 0.05$, variables in respective groups were different, and Bonferroni or least significant difference post hoc tests were performed. Correlation between patient age and concentrations of TF and TFPI was performed in group C, described by the correlation coefficient r. The level of statistical significance was adopted at $p < 0.05$.

RESULTS

Mean TF and TFPI concentrations and standard deviation values in respective groups are presented in figures, with p-values given underneath.

Patients in group C were significantly younger as compared to all other groups ($p = 0.000$), with significant correlation ($r = 0.31$) between patient age and values of TFPI concentrations. No significant correlation between age and TF values was observed.

DISCUSSION

Some inborn and acquired risk factors for development of CTEPH were described [1–5] but etiopathogenesis was not completely delineated, although haemostatic aberrations seem to play a major role. Samples from patients undergoing pulmonary endarterectomy demonstrate in majority of cases presence of new or organised thromboembolic material, with only few lesions compatible with arteriopathy [6]. The latter lesions are the result of endothelial dysfunction, and present microscopically plexiform changes, thickening of intima and media, which point to vessel wall remodelling [17]. Similar arteriopathic lesions obtained from patients with PAH obtained at autopsy or lung transplantation demonstrated increased expression of TF [18]. This may suggest that even CTEPH pathogenesis may involve extrinsic coagulation pathway factors, TF and TFPI.

Tissue factor is a transmembrane protein of 47 kDa, produced by endothelial cells, monocytes, vessel smooth muscle cells, brain tissue, in lungs and in placenta. Synthesis of TF increases markedly following stimulation with proinflammatory cytokines (LPS, TNF alpha, CRP) and after mechanical tissue injury [16, 19], initiating coagulation cascade by binding TF and factor VII. Serum levels of TF in patients with pulmonary hypertension or pulmonary embolism were not studied as yet. High levels of TF were observed in arterial hypertension, hyperlipidaemia, in atherosclerotic lesions, including vessels affected by coronary heart disease and its acute episodes [20] as well as in systolic heart failure [21]. It was assumed that certain gene polymorphisms may reduce the risk of venous thromboembolic disease [22] but results published by Chinese authors speak against this hypothesis [23]. In the presented study, when TF concentrations were analysed without stratification for anticoagulation methods or efficacy (Fig. 1), lower values were observed in CTEPH and in post-APE group as compared to group C ($p = 0.042$ and $p = 0.011$, respectively). When adequate VKA-treatment in CTEPH and post-APE patients was considered (almost half of all patients in both these groups), TF concentrations were similar to those in group C (Fig. 2). Initial differences were thus most likely due to low levels of TF in patients not receiving anticoagulants (post-APE patients without anticoagulation vs. controls: $p = 0.0186$; Fig. 3). Low TF concentration post-APE may point to consumption of the factor in thrombotic lesions, which seems analogical as in patients after APE episodes who did not develop pulmonary hypertension and in patients with CTEPH. Results of the study mas suggest that adequate anticoagulation may restore normal TF concentration, and inhibit extrinsic coagulation pathway. Similar results were described by authors of the Waris II study, where long-lasting VKA treatment increased serum TF levels in patients after myocardial infarction, which was not observed in patients treated with acetylsalicylic acid [24].

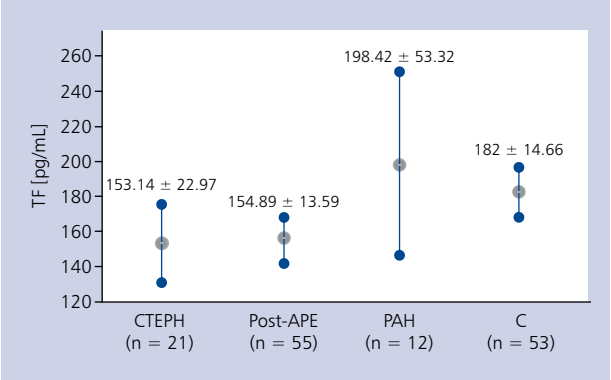

Figure 1. Mean serum concentration of tissue factor (TF) in patients with chronic thromboembolic pulmonary hypertension (CTEPH), post-acute pulmonary embolism (APE), having pulmonary arterial hypertension (PAH) and in control group (C). Significant p-values observed for the following comparisons: post-APE vs. PAH, $p = 0.014$; post-APE vs. C, $p = 0.011$; CTEPH vs. PAH, $p = 0.024$; CTEPH vs. C, $p = 0.042$.

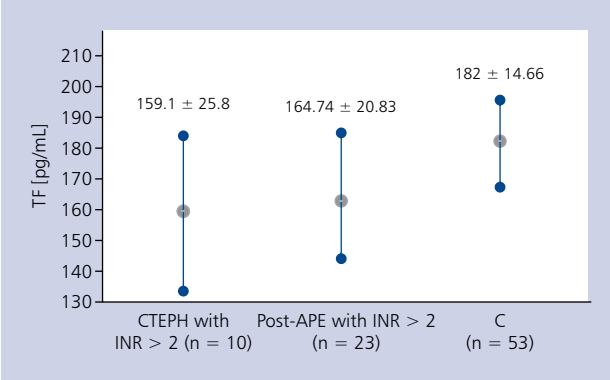

Figure 2. Mean serum concentration of tissue factor (TF) in chronic thromboembolic pulmonary hypertension (CTEPH) patients with adequate vitamin K antagonists (VKA) anticoagulation, post-acute pulmonary embolism (APE) patients with adequate VKA anticoagulation and in control group (C). No statistical significance was observed for these comparisons (NS)

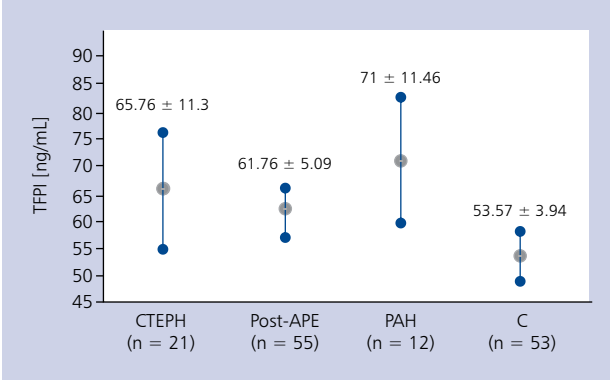

Figure 4. Mean serum concentration of tissue factor pathway inhibitor (TFPI) in patients with chronic thromboembolic pulmonary hypertension (CTEPH), post-acute pulmonary embolism (APE), having pulmonary arterial hypertension (PAH) and in control group (C). Significant p-values observed for the following comparisons: CTEPH vs. C, p = 0.012; post-APE vs. C, p = 0.024; PAH vs. C, p =0.004.

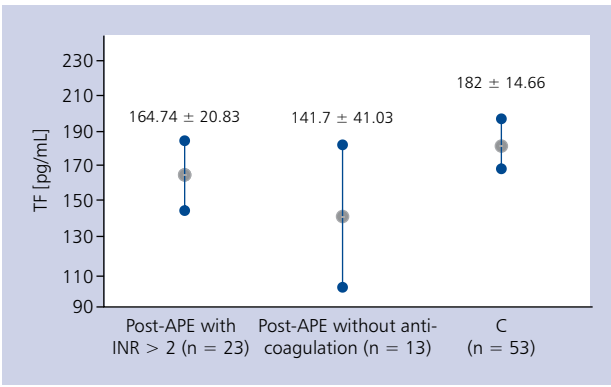

Figure 3. Mean serum concentration of tissue factor (TF) in post-acute pulmonary embolism (APE) patients with adequate vitamin K antagonists anticoagulation, post-APE patients without anticoagulation and in control group (C). Statistical significance was observed only for the comparison post-APE with no anticoagulation vs. C, p = 0.0186.

When concerning etiopathogenetic particularities of CTEPH and PAH, it was observed that TF concentration in the PAH group, where only 3 of 12 patients had adequate anticoagulation, was significantly higher than in patients with CTEPH or post-APE (p = 0.024 and p = 0.014, respectively) but no such difference was observed as compared to group C, although trend to increasing TF values was observed (Fig. 1). The group of patients with PAH was small, which impedes definitive interpretation of results. However, in these patients extrinsic coagulation pathway seemed to be less involved.

Tissue factor protein inhibitor is a glycoprotein produced mainly by endothelial cells but also by platelets, activated fibroblasts, monocytes and megakaryocytes. The protein inhibits factor and TF/FVIIa complexes, thus inhibiting generation of thrombin. Moreover, TFPI has an anti-proliferative and anti-inflammatory effect [16]. In the presented study, all patient groups (CTEPH, post-APE and PAH) had similarly higher TFPI serum concentrations as compared to group C, when anticoagulation was not considered (Fig. 4; p = 0.012, p = 0.024 and p = 0.004, respectively). Increased serum TFPI concentration was observed in other entities where coagulation cascade was activated, including ischaemic heart disease, atherosclerotic artery occlusions, Buerger disease, hyperlipidaemia, diabetes, in inflammatory conditions, whereas decreased TFPI concentrations were found in subjects with protein C deficiency and in women using hormonal contraception [13]. Altman et al. [25] described decreased TFPI concentrations in 22 patients with pulmonary hypertension. Their results differ from the presented study, which might be due to different patient selection, as those authors did not study CTEPH patients, and included only a single patient with PAH. Anticoagulation may affect TFPI concentrations. In the presented study, patients receiving adequate VKA after CTEPH and post-APE had similar concentrations of TFPI, which did not significantly differ from those in group C (Fig. 5) and from not anticoagulated post-APE patients (Fig. 6). There was a trend to decreasing TFPI concretrations on adequate anticoagulation in post-APE patients comparing to not anticoagulated APE survivors (Fig. 6). Results presented herein seem to be the first ever to demonstrate effect of VKA anticoagulation on TFPI concentrations. Previously, heparin was noted to release a fraction of TFPI to the serum, thus increasing its concentration [26]. In the presented study, 4 patients with CTEPH (19% of all studied subjects) and 3 post-APE (5%) used heparin, alone or in combination with VKA. It is difficult to establish to what extent heparin usage increased TFPI concentrations in respective patient groups or whether this reflects endogenous aberrations. If the values in patients on heparin do not significantly affect the entire group values as

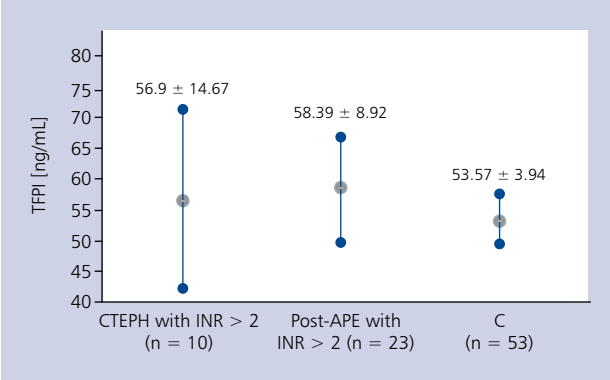

Figure 5. Mean serum concentration of tissue factor pathway inhibitor (TFPI) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and adequate vitamin K antagonists (VKA) anticoagulation, in patients post-acute pulmonary embolism (APE) with adequate VKA anticoagulation and in control group (C). No statistically significant differences were observed (NS)

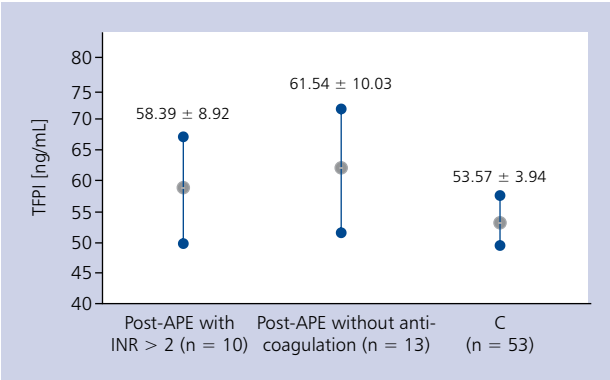

Figure 6. Mean serum concentration of tissue factor pathway inhibitor (TFPI) in patients post-acute pulmonary embolism (APE) and adequate vitamin K antagonists anticoagulation, in patients post-APE without anticoagulation and in control group (C). No statistically significant differences were observed (NS)

these patients were few, it could be assumed that underlying diseases increase serum TFPI concentration in CTEPH patients and post-APE as compared to healthy persons. Pulmonary arterial hypertension bears pathophysiological similarities to CTEPH but TFPI seemed to be the highest (Fig. 4). None of these patients was using heparin, and only 25% of them had adequate VKA anticoagulation. It should be noted that adequate treatment with VKA decreases pathologically elevated TFPI concentration in CTEPH and post-APE or even restores it to normal.

Limitations of the study

Small numbers of patient with CTEPH and PAH are the limitation of the presented study, which is related to rarity of these diseases and concommitant exclusion criteria (involving conditions that could potentially affect TF and TFPI levels). The estimated incidence of CTEPH following an APE episode is 0.5–3.8% [27], and PAH is described as an "orphan disease". Other limitations included necessity of continuous anticoagulation in some patients, mostly in CTEPH group as well as a significant age difference between patients and controls ($p = 0.000$ for all groups). In the presented study, weak correlation ($r = 0.31$) between age and TFPI concentration was observed. Other authors did not find correlations between age and concentrations of TF or TFPI [28].

CONCLUSIONS

The presented study points to activation of the extrinsic coagulation cascade in CTEPH, as reflected by decreased TF concentration due to its consumption, increased TFPI concentration, and normalisation of these parameters under adequate anticoagulative treatment. Concentrations of TF and TFPI, and the effect of anticoagulation were similar in post-APE patients, who did not have pulmonary hypertension. This finding suggests a similar pathogenesis of both entities but does not identify patients after an APE episode who are at risk of developing CTEPH. The observed TF concentrations suggest a lower activity of extrinsic coagulation pathway in PAH as compared to CTEPH. Verification of these findings in bigger patient groups is warranted, with analysis of age impact and effect of various anticoagulation modalities on TF and TFPI concentrations. Evaluation of TF and TFPI concentrations in samples obtained from endarterectomy procedures and in autopsy material could shed more light on the role of these factors in development of CTEPH.

Conflict of interest: *none declared*

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Stężenia osoczowe czynnika tkankowego i jego inhibitora w przewlekłym zakrzepowo-zatorowym nadciśnieniu płucnym: krok ku poznaniu etiopatogenezy choroby?

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Streszczenie

Wstęp: Etiopatogeneza przewlekłego zakrzepowo-zatorowego nadciśnienia płucnego (CTEPH) nie jest dokładnie poznana. Rozwój CTEPH u części chorych wiąże się z przebyciem ostrej zatorowości płucnej (APE), a istotą choroby jest wazokonstrykcja, procesy zapalne, aktywacja układu krzepnięcia i osłabienie fibrynolizy oraz przebudowa naczyń w tętniczej części płucnego łożyska naczyniowego. Nadciśnienie płucne, które rozwija się w wyniku powyższych zmian, prowadzi do przewlekłego przeciążenia i niewydolności prawej komory, a w konsekwencji do zgonu. Zidentyfikowano już kilka wrodzonych i nabytych czynników rozwoju CTEPH. Zaburzenia hemostazy są niewątpliwie silnie wyrażone, choć nie do końca poznane. Nie wiadomo, czy w rozwoju i przebiegu CTEPH mogą mieć znaczenie zaburzenia wstępnego etapu zewnątrzpochodnej ścieżki krzepnięcia. Potencjalnie procesy te, związane z uszkodzeniem śródbłonka tętniczych obszarów naczyń płucnych, mogłyby mieć udział zarówno w zakrzepicy wewnątrznaczyniowej, jak i w przebudowie naczyń płucnych.

Cel: Celem pracy było zbadanie zachowania się czynnika tkankowego (TF) i jego inhibitora (TFPI) w CTEPH oraz ustalenie ich potencjalnej roli w patogenezie tego schorzenia.

Metody: W badaniu porównano stężenia TF i TFPI u 21 pacjentów z CTEPH ze stężeniami tych białek u 12 pacjentów z tętniczym nadciśnieniem płucnym (PAH), u 55 chorych po przebytej co najmniej pół roku wcześniej APE bez przetrwałego nadciśnienia płucnego oraz u 53 zdrowych osób (grupa kontrolna C). Większość pacjentów otrzymywała antagonistów witaminy K (VKA), a niektórzy (19% w grupie CTEPH i 5,5% po APE) — heparynę niefrakcjonowaną lub drobnocząsteczkową w dawkach terapeutycznych lub wysokich profilaktycznych. Aby ocenić skuteczność leczenia, u wszystkich badanych oznaczano wartość międzynarodowego wskaźnika znormalizowanego (INR), a u osób stosujących heparynę niefrakcjonowaną — także czas częściowej tromboplastyny po aktywacji. Odsetek pacjentów z INR > 2 sięgnął 47,6% w grupie CTEPH, 41,8% w grupie po APE i 25% w grupie PAH. Żaden z badanych nie stosował inhibitorów trombiny ani czynnika Xa. Wśród chorych na CTEPH nie było leczonych metodą endarterektomii płucnej ani nowoczesnymi wazodylatatorami łożyska płucnego. Leki te stosowali natomiast niektórzy pacjenci z PAH. Kryteriami wykluczenia były: nowotwór złośliwy w trakcie terapii, stan zapalny, przebyta w ostatnich tygodniach operacja.

Wyniki: Przy badaniu materiału bez uwzględnienia prowadzenia i skuteczności antykoagulacji stężenie osoczowe TF okazało się porównywalnie niższe w grupie CTEPH i po APE niż w grupie C (odpowiednio $p = 0,042$ i $p = 0,011$). Po wyodrębnieniu skutecznie leczonych VKA pacjentów z CTEPH i po APE stężenia TF okazały się porównywalne do grupy C. Stężenia TF u osób niepoddanych antykoagulacji po APE było istotnie niższe niż w grupie C ($p = 0,0186$). Stężenie TF w grupie PAH okazało się znamiennie wyższe niż u chorych na CTEPH i po APE (odpowiednio $p = 0,024$ i $p = 0,014$) oraz nieistotnie wyższe niż w grupie C. Bez uwzględnienia antykoagulacji u pacjentów z CTEPH, po APE i z PAH stwierdzono porównywalne i istotnie wyższe niż w grupie C stężenia osoczowe TFPI (odpowiednio $p = 0,012$; $p = 0,024$; $p = 0,004$). U poddanych skutecznej antykoagulacji za pomocą VKA chorych na CTEPH i po APE zanotowano porównywalne do grupy C stężenia TFPI. Stężenia TFPI u skutecznie antykoagulowanych osób po APE były nieistotnie niższe niż u pacjentów po APE niepoddanych antykoagulacji. Grupa C okazała się istotnie ($p = 0,000$) młodsza w odniesieniu do wszystkich grup pacjentów. W grupie tej stwierdzono słabą ($r = 0,31$) korelację między wiekiem a stężeniem TFPI.

Wnioski: Wyniki badania wskazują na wzmożoną aktywność zewnątrzpochodnej ścieżki krzepnięcia w CTEPH, wyrażającą się istotnym obniżeniem stężenia TF w wyniku jego zużycia, wzrostem stężenia TFPI oraz normalizacją tych czynników hemostazy pod wpływem skutecznej antykoagulacji. Stężenia TF i TFPI zachowują się podobnie u chorych po APE, u których nie rozwinęło się nadciśnienie płucne. Wskazuje to na podobną etiopatogenezę schorzeń, ale i nie pozwala na wyodrębnienie chorych po epizodzie APE, po którym rozwinie się CTEPH. Wyniki badania stężenia TF mogą wskazywać na mniejszą aktywność zewnątrzpochodnej ścieżki krzepnięcia w PAH niż w CTEPH.

Słowa kluczowe: przewlekłe zakrzepowo-zatorowe nadciśnienie płucne, czynnik tkankowy, inhibitor zewnątrzpochodnego toru krzepnięcia, antykoagulacja

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