SOME FIBRINOLYTIC PARAMETERS IN CORONARY ARTERY DISEASE PATIENTS: FOCUS ON UNSTABLE ANGINA SUBGROUPS

Background and aim. Unstable angina is classified into new-onset, progressive, and angina at rest. Though hemostasis plays a crucial role in the pathogenesis of coronary artery disease, including unstable angina, limited data exist regarding peculiarities of fibrinolytic parameters in the above-mentioned types of unstable angina. Our study aims to investigate if there is a difference in the fibrinolytic state between the groups of patients with new-onset, progressive unstable angina in comparison with stable angina patients depending on medical history data, electrocardiographic and hemodynamic features.

Materials and methods. In our cross-sectional study, we recruited 93 coronary artery disease patients (mean age 62.32 (6.94) years, 41 males (44.1%)). They were divided into 3 groups: stable angina patients (n=22) (control), new-onset unstable angina patients (n=21), and progressive unstable angina patients (n=50). The groups were comparable by baseline characteristics. Blood samples were obtained before treatment onset. The concentrations of tissue plasminogen activator and inhibitor of plasminogen activator (type 1) were measured by the ELISA method. We registered 14 points at the admission department, particularly age, sex, body mass index, smoking, presence of the family history of cardiovascular disorders, ST-segment depression, T-wave variability, arrhythmias, left bundle branch blockage, heart rate, systolic and diastolic blood pressure, Sokolov-Lyon voltage criteria, and unstable angina type (new-onset or progressive). After comparison of fibrinolytic parameters’ concentrations among groups under investigation, we defined the main independent predictors among observed 14 parameters to create optimal regression models for assessment of fibrinolytic parameters concentrations.

Results and conclusion. The groups under investigation differ significantly in concentration of tissue plasminogen activator (P<0.001) and inhibitor of plasminogen activator (type 1) (P<0.001). The tissue plasminogen activator concentration correlated significantly with ST depression (r=0.344, P=0.001), T wave variability (r=0.233, P=0.02), systolic blood pressure (r=-0.675, P<0.001), diastolic blood pressure (r=-0.655, P<0.001), heart rate (r=-0.568, P<0.001) and clinical unstable angina subgroups (r=-0.706, P<0.001) as well as plasminogen activator inhibitor (type 1) concentration associated with age (r=-0.560, P<0.001),
body mass index (r=-0.249, P=0.049), ST-segment depression (r=0.542, P<0.001), arrhythmia (r=0.210, P=0.03), systolic blood pressure (r=0.310, P=0.04), and clinical unstable angina subgroups (r=-0.406, P<0.001). An optimal regression models for tissue plasminogen activator and its inhibitor assessment included systolic blood pressure, heart rate, unstable angina subgroup ($R^2_{adj} = 65.0\%, P<0.001$) and systolic blood pressure, unstable angina subgroup ($R^2_{adj} = 42.7\%, P<0.001$), respectively. Thus, fibrinolytic state among unstable angina clinical types differs significantly independently on observed baseline clinical, electrocardiographic and hemodynamic parameters. This finding confirms the utility of Braunwald unstable angina classification.

Keywords: tissue plasminogen activator, plasminogen activator inhibitor type 1, new-onset unstable angina, progressive unstable angina, coronary artery disease.

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Introduction

Coronary artery disease (CAD) has been passing the long history of evolution from ancient times [1] until now [2]. Though enormous research has been dedicated to this disorder, it ranks first among death causes worldwide [3] with the highest prevalence in Central and Eastern Europe [4].

According to up-to-date classification, this condition is divided into acute coronary syndrome with subgroups (myocardial infarction and unstable angina (UA)) and chronic coronary syndrome including stable angina (SA). Pathogenetic mechanisms, clinical features, diagnostic procedures and management approaches have proved high expedience of such classification [5–6].

Yet, UA is still being remained an ominous condition [7] despite progress in decision making in diagnostic [8] and management [9, 10, 11]. It should be pointed out that only in1989 Braunwald E. proposed the detailed UA classification by severity and clinical circumstances in which UA occurs [12]. Notably, the latter is used nowadays [13]. However, mainly 3 subgroups of UA by clinical circumstances are generally accepted and widely used, namely new-onset UA (NUA), progressive UA (PUA), and UA at rest [6]. Surprisingly, the difference between UA subgroups seems to be underinvestigated.

Undoubtedly, hemostasis plays a critical role in the occurrence and progression of CAD [14, 15], which is a pathologic process of coronary arteries narrowing commonly caused by the progression of atherosclerosis with further accumulation of deposits in the vessels walls [2]. It is clearly defined that well-balanced functioning of the fibrinolytic system provides clots dissolution and maintains vascular patency [16]. Tissue plasminogen activator (tPA) and its inhibitor (PAI-1) which are counterparts of the fibrinolytic system are mainly synthesized and secreted by endotheliocytes [16]. Consequently, the concentrations of both substances depend drastically on the endothelium state.

While analyzing enormous trials regarding CAD we have faced heterogeneity in the populations studied and a lack of data regarding peculiarities of the fibrinolytic parameters in UA subgroups. Though
the influence of multiple factors on tPA and PAI-1 is precisely investigated nothing was mentioned about differences in fibrinolytic system state among clinical types of UA, namely NUA and PUA.

Accordingly, our study aimed to compare concentrations of tPA and PAI-1 in CAD subgroups. Special attention was paid to UA subgroups, particularly NUA and PUA. Herein, we also reported analytical considerations if it is important to take into account the clinical type of UA.

Materials and methods

Research design

We observed 89 UA patients and 22 outpatients with SA.

The research was conducted according to the Declaration of Helsinki and approved by the institutional Research Ethics Committee. All patients gave written consent to participate in the study.

We included states with significant influence on the hemostatic system into the list of exclusion criteria: severe renal or hepatic disorders, hematological and endocrinological diseases, the history of malignancy, traumas or bleedings within 6 months, active infection, some cardiovascular diseases (the history of stroke, myocardial infarction, stroke, heart defects, cardiomyopathies, non-ischemic myocardial injuries, persistent form of atrial fibrillation / atrial flutter, heart failure IIB-III), exacerbation of chronic diseases.

All patients had a history taken, physical examination, electrocardiogram (ECG) at rest, quantitative troponin I testing to make a provisional diagnosis. We collected blood samples for analyzing tPA and PAI-1 concentrations before treatment onset.

Generally, 14 points were mandatory registered at the admission department, particularly age, sex, body mass index (BMI), smoking, presence of the family history of cardiovascular disorders (CVD), ST-segment depression, T-wave variability, arrhythmias, left bundle branch blockage (LBBB), heart rate (HR), systolic and diastolic blood pressure (BP) (SBP and DBP), Sokolov-Lyon voltage criteria (SLC), and UA subgroup (NUA or PUA). We analyzed such a set of criteria as it may be easily collected by the physician at the admission department.

Blood samples for routine analysis checking were taken on the next day after admission according to the schedule of the clinic. This set of analyses consisted of complete blood count, fasting glucose, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lipidogram. We performed echocardiography within 2 days of hospitalization. Consequently, some patients were excluded from the study only after a more detailed examination and follow-up period.

Population

Finally, 93 patients with CAD were consecutively enrolled in this study. They were classified into one of 3 groups: patients with SA (n=22) (control group), PUA (n=50), and NUA (n=21). We used the guidelines criteria to confirm the diagnosis of each subject [5, 6].

Clinical data

We collected data about the clinical state of patients such as the history of CVD and other disorders, previous history of hospitalizations, any medications used in 6 months before the survey by the usage of standardized documentary confirmation, symptoms while admission, results of physical examination.

Blood analysis

On the day of admission, whole blood samples were drawn by venipuncture in sodium citrate (38 g/l at the ratio of 9:1 v/v) and centrifuged for 40 minutes at 900 g. Plasma samples were stored refrigerated at -80° C until use. The tPA and PAI-1 concentrations were done by ELISA immune assays with primary and secondary antibodies from Santa Crus Biotechnology, CA, USA following instructions.

The routine analyses were performed by the local laboratory of the hospital. This set of analyses consisted of complete blood count, fasting glucose, creatinine, ALT, AST, lipidogram (total cholesterol, triglycerides, low-density lipoproteins cholesterol, high-density lipoproteins cholesterol) according to the standard protocol. All laboratory equipment has been calibrated. Subjects were instructed to fast for 12 h before the screening. We used the CKD-EPI formula to assess the glomerular filtration rate. BMI was calculated according to the standard formula and measured in kilograms per square meter. Troponin I was checked by chemiluminescent immunoassay with reference ranges less than 57.27 pg/ml and 36.99 pg/ml for males and females, respectively.

Instrumental procedures

We registered 12-lead ECG at rest at a speed of the tape 25 mm/s. We paid attention to ischemic signs (horizontal or downsloping ST-segment depression ≥1.5 mm in precordial leads/ ≥1 mm in
limb leads or its elevation ≥2 mm in precordial leads/ limb leads, T-wave variability, new-onset left bundle branch block) and arrhythmias, namely episodes of atrial fibrillation or supraventricular tachycardia, premature ventricular beats. HR was registered. The Sokolov-Lyon index of left ventricular (LV) hypertrophy was assessed as the voltage amplitude sum $S_{V1} + \max (R_{V5} or R_{V6})$. ECG Sokolov-Lyon sign was positive if the above-mentioned sum was ≥35 mV.

BP of patients was measured three times at admission with standardized electronic instruments. We confirmed the diagnosis of arterial hypertension (AH) if the patient had an AH history or prescription of antihypertensive medications regularly.

One sonologist conducted two-dimensional transthoracic echocardiography according to the current scanning guidelines.

Data analysis

Data were analyzed using SPSS (version 22, IBM Corp, USA). The distribution was checked by the Kolmogorov-Smirnov test. Data were expressed as absolute numbers (percentage) for nominal variables and mean (SD) or median (IQR) for continuous variables.

Differences between the two groups were checked with the Mann-Whitney U-test or post hoc Chi$^2$ or Fisher test with Bonferroni-Holm correction depending on the type of variables. The correlation between clinical variables was examined with the use of Pearson or Spearman correlation depending on the type of variables.

We used multiple linear regression to find out the most important independent parameters among 14 defined ones, to construct two models for indirect assessment of observed fibrinolytic factors. Also, we checked if a physician at the admission department should take such independent parameter as UA type into account. Of note, all criteria for appropriate multiple regression analysis usage were fulfilled. P values < 0.05 were considered to indicate statistical significance.

Results

The mean (SD) age of the entire cohort was 62.32 (6.94) years, 41 males (44.1%), 13 current smokers (13.9%), 78 patients suffered from AH (83.8%), 32 patients had family CVD history (34.4%). The mean (SD) BMI was 29.25 (4.34) kg/m$^2$.

Table 1 – Baseline characteristics of observed patients’ groups

| Parameter             | SA, n = 22 | PUA, n = 50 | NUA, n = 21 | P  |
|-----------------------|------------|-------------|-------------|----|
| Age, years (years)    | 62.5 (58.0-69.0) | 67.0 (60.0-69.0) | 66.0 (55.0-67.0) | 0.22 |
| Males, abs. no. (%)   | 11 (50.0) | 16 (32.0)* | 14 (66.7) | 0.03 |
| BMI, kg/m$^2$         | 28.6 (26.2-31.9) | 31.6 (25.7-34.1) | 25.0 (24.6-36.0) | 0.52 |
| Smokers, abs. no. (%) | 0          | 7 (14.0)   | 6 (28.6) | 0.02 |
| Family CVD history, abs. no. (%) | 10 (45.5) | 17 (34.0) | 6 (28.6) | 0.48 |
| ST segment depression, abs.no. (%) | 2 (9.1)* | 27 (54.0) | 16 (76.2) <0.001 |
| T wave variability, abs. no. (%) | 4 (18.2)* | 18 (36.0) | 12 (57.1) | 0.03 |
| LBBB, abs. no. (%)    | 1 (4.5)   | 11 (22.0)  | 0          | 0.047 |
| Arrhythmia, abs. no. (%) | 10 (45.5) | 30 (60.0) | 9 (42.9) | 0.29 |
| SBP, mm Hg            | 140.0 (122.5-165.0)* | 150.0 (129.5-170.0)* | 169.0 (162.0-176.0) | 0.005 |
| DBP, mm Hg            | 80.0 (74.5-98.0)* | 92.0 (84.0-98.5)* | 98.0 (93.5-104.5) <0.001 |
| HR, beats/min.        | 73.0 (70.0-80.5)* | 81.0 (73.0-92.0) | 84.0 (78.0-11.0) | 0.02 |
| SLC, mm               | 22.0 (14.0-26.5) | 24.0 (21.0-25.0) | 21.0 (17.0-34.0) | 0.71 |

Notes: abs. no. – absolute number, BMI – body mass index, CVD – cardiovascular disease, LBBB – left bundle branch blockage, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, SLC – Sokolov-Lyon criteria, SA – stable angina, PUA – progressive unstable angina, NUA – new-onset unstable angina, P – probability, * – significant difference between Groups NUA and PUA after post-hoc analysis, † – significant difference between Groups PUA and SA after post-hoc analysis, ‡ – significant difference between Groups NUA and SA after post-hoc analysis.
We presented the baseline patients’ characteristics in Table 1. No difference was registered among the groups regarding age, BMI, family CVD history, arrhythmia, SLC. Females prevailed in PUA group because of the relatively higher frequency of males with MI history in contrast to the NUA group. Although a significant difference in AH comorbidity was registered between SA and UA (19 patients (86.4%) versus 68 patients (95.7%), P=0.03), UA subgroups were comparable regarding AH history (P=0.09) and signs of heart remodeling. Remarkably, the highest BP was registered in NUA patients, while HR in patients of both UA groups exceeded the one in patients with SA.

ECG at rest findings were typical of the established diagnosis. No difference was registered in the frequency of arrhythmias between groups, including ventricular premature beats, paroxysms of atrial fibrillation and supraventricular tachycardia (P=0.29). We do not assess the longevity of AH history in patients. To diminish this limitation we compared SLC which may indirectly indicate the AH history duration.

In this article, the results of echocardiography and above-mentioned laboratory tests are not presented. However, we highlight that all exclusion criteria were fulfilled.

The concentrations of tPA and PAI-1 among CAD subgroups are demonstrated in Figure 1 and Figure 2. A significant difference in tPA concentration was found between all observed subgroups (P=0.001). In contrast, while PAI-1 concentrations between PUA and NUA differ drastically (P=0.001), the concentrations of this factor in PUA and SA patients were comparable (P=0.07). In general, the PUA patients were characterized by remarkably increased levels of both fibrinolytic factors comparing with the NUA group (P=0.001 and P<0.001, respectively).

Additionally, we decided to assess the importance of gathered at admission department parameters for assessment of fibrinolytic potential in patients with UA and check if there is a utility in taking into consideration the UA type.

For this purpose firstly, we checked the correlation between tPA, PAI-1 and 14 independent factors. As it is shown in Table 2, tPA concentration correlated with ST-segment depression, T-wave variability, SBP, DBP, HR. The correlations between PAI-1 concentration and age, BMI, ST-segment depression, arrhythmia, SBP were found out. Of note, the correlation of very high statistical significance was registered between both fibrinolytic factors and UA type, particularly the strong one between tPA and UA type, and the correlation of moderate strength was detected between PAI-1 concentration and UA type. For appropriate interpretation of results, it should be mentioned that NUA was encoded as 1 and PUA – 0.

![Figure 1 – TPA concentration among observed groups of CAD patients](image)

Notes: TPA – tissue plasminogen activator, SA – stable angina, PUA – progressive unstable angina, NUA – new-onset unstable angina, P – probability, χ² – chi-squared, df – degrees of freedom
Secondly, we selected all independent parameters correlated with observed fibrinolytic factors and built 2 regression models for tPA and PAI-1. Model 1 included all selected independent parameters without UA type, while Model 2 – with UA type as an independent predictor. As it is presented in Table 3, the optimal Model 1 for tPA included two independent factors, namely SBP and HR, while only one independent predictor out of 13 was selected for PAI-1 prediction. The models with other predictors were inappropriate as not all criteria for the linear regression model were fulfilled. Both models showed low predictive ability.

Table 2 – Correlation between hemostatic factors and parameters collected immediately at admission department in UA patients

| Parameter                        | TPA, r (P)       | PAI-1, r (P)       |
|----------------------------------|------------------|-------------------|
| Age, years                       | 0.121 (0.28)     | -0.560 (< 0.001)  |
| Sex, abs. no.                    | -0.011 (0.91)    | 0.052 (0.61)      |
| BMI, kg/m2                       | -0.09 (0.44)     | -0.249 (0.049)    |
| Smokers, abs. no.                | -0.178 (0.09)    | 0.097 (0.34)      |
| Family CVD history, abs. no.     | -0.045 (0.66)    | 0.085 (0.41)      |
| ST segment depression, abs. no.  | 0.344 (0.001)    | 0.542 (< 0.001)   |
| T wave variability, abs. no.     | -0.233 (0.02)    | -0.053 (0.61)     |
| LBBB, abs. no.                   | 0.009 (0.93)     | -0.052 (0.61)     |
| Arrhythmia, abs. no.             | -0.022 (0.82)    | 0.210 (0.03)      |
| SBP, mm Hg                       | -0.675 (< 0.001) | 0.310 (0.04)      |
| DBP, mm Hg                       | -0.655 (< 0.001) | 0.108 (0.51)      |
| HR, beats/ min.                  | -0.568 (< 0.001) | 0.005 (0.97)      |
| Sokolov-Lyon index, mm           | -0.066 (0.64)    | -0.027 (0.85)     |
| Clinical type of UA (NUA vs PUA) | -0.706 (< 0.001) | -0.406 (< 0.001)  |

Notes: such points of data as male, smoker, positive family CVD history, presence of ST segment depression, T wave variability, LBBB, arrhythmia at admission (Lawn 2 and higher grade, paroxysm of supraventricular tachycardia or atrial fibrillation), NUA were encoded as “1”, other points – “0”; abs. no. – absolute number, BMI – body mass index, CVD – cardiovascular disease, LBBB – left bundle branch blockage, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, UA – unstable angina, NUA – new-onset unstable angina, PUA – progressive unstable angina, TPA – tissue plasminogen activator, PAI-1 – plasminogen activator inhibitor (type 1), r – regression coefficient, P – probability
Notes: abs. no. – absolute number, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, TPA – tissue plasminogen activator, PAI-1 – plasminogen activator inhibitor (type 1), β – standardized regression coefficient, VIF – variance inflation factor, P – probability, R^2_adj – adjusted coefficient of determination

It is demonstrated in Table 4, that taking into consideration the factor of UA clinical type increased the value of models for tPA and PAI-1 assessment by 13.8% and 23.1%, respectively (P<0.001 for both).

Table 4 – Linear regression Model 2

| Predictor independent | TPA          | PAI-1         |
|-----------------------|--------------|---------------|
| Systolic blood pressure, mm Hg | β | P | VIF | β | P | VIF |
| Heart rate, beats/ min. | -0.404 | < 0.001 | 1.318 | 0.596 | < 0.001 | 1.226 |
| Unstable angina subgroup (NUA vs PUA) | -0.435 | < 0.001 | 1.365 | 0.664 | < 0.001 | 1.226 |

R^2_adj = 65.0%, P<0.001, R\(^{2}\) change = 13.8

Notes: TPA – tissue plasminogen activator, PAI-1 – plasminogen activator inhibitor (type 1), β – standardized regression coefficient, VIF – variance inflation factor, P – probability, R^2 – coefficient of determination, R^2_adj – adjusted coefficient of determination, NUA – new-onset unstable angina, PUA – progressive unstable angina, NUA was encoded as “1”, PUA as “0”

**Discussion**

Enormous studies are devoted to the role of fibrinolytic system parameters, namely tPA and PAI-1, in patients with CAD [17, 18, 19]. However, the peculiarities of clinical types of UA regarding fibrinolytic system state are underinvestigated.

PAI-1 as a classical pro-inflammatory adipocytokine associated with CAD is used for the diagnosis and risk assessment in CAD patients [20]. Additionally, PAI contributes to the formation of atherosclerotic plaques [21]. The tPA concentration is connected tightly with inflammation and endothelial cell damage [22]. In our study, while the PAI-1 concentration was statistically significantly higher in UA in comparison with SA, the tPA concentration was lower. This trend demonstrates the increase in thrombogenic potency in UA patients, which indicates the increased risk in major adverse cardiac events [18] and is corresponding with previous studies [23]. Also, the concentrations of both observed biomarkers were higher in patients with PUA in comparison with NUA (P<0.001). Such finding may be connected with a longer duration of endothelium damaged by the atherosclerotic process in PUA patients. Moreover, it seems that fibrinolytic potency in NUA patients is lower than in the PUA group leading to a higher coagulability of blood plasma in the former group.

In our study, the strongest association was registered between fibrinolytic factors and hemodynamic parameters (BP, HR). This data confirms the statement that close relationships exist between the vascular wall and blood components controlling blood flow and hemostasis, including the fibrinolytic system [24]. We suspect it is due to
both-sided interaction. On the one hand, wall share stress modulates vascular remodeling, including expression of some genes [25], and platelets activation [26]. On the other hand, fibrinolytic markers are also characterized by influence on hemodynamic. Thus, in the experimental study of Heyman et al., it was shown that tPA infusions cause progressive fall in BP as it is characterized by a pro-vasodilatory effect, while vasoconstriction is typical of PAI-1 [25]. However, it depends on the baseline condition of the organism as Liu et al. demonstrated a negative association between SBP and PAI-1 in dialysis patients [27].

Though Braunwald E. calls in question the necessity of this diagnosis [28], new facts have been revealed regarding supporting of it. Jia et al. have demonstrated that Braunwald A, B, C groups are independently associated with death, myocardial infarction, and in-stent thrombosis [13]. In our study, we have shown that clinical types of UA influence independently from other observed factors on fibrinolytic parameters (tPA and PAI-1).

This finding may be among the possible explanations of Braunwald classification’s usefulness and its correspondence with UA outcomes.

Our study has some limitations, particularly AH comorbidity. However, all recruited subjects had an AH history with antihypertensive medications prescription. Moreover, no significant difference in interventricular septum thickness was registered. We may suspect a relatively similar tie of AH history. Additionally, patients had different histories of medications intake. Some of them may influence on parameters under the question.

A strong feature of our study was the comparison of fibrinolytic parameters among subgroups of UA (NUA vs PUA) and control group (SA). Unfortunately, no patients with UA at rest were observed. It is connected with population specificity, particularly age, comorbidity. Also, we tried to exclude the vast majority of conditions with evident impact on investigated parameters or make the groups comparable by such conditions.

Conclusions

Concentrations of fibrinolytic factors differ significantly among the groups of patients with different UA clinical types independently on observed baseline clinical, electrocardiographic and hemodynamic parameters. This data call for further investigation in hemostasis among clinical types of UA which may elucidate additional information regarding pathogenetic peculiarities among CAD course.

Prospects for future research

It looks worthy to analyze the extent of other parameters’ influence (e.g. complete blood count and biochemical tests, structural peculiarities of the heart) on the difference between fibrinolytic factors’ concentrations among the patients with different UA clinical types.

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Conflict of interest
The authors declare no conflict of interest.

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