Early effects of paroxysmal atrial fibrillation on plasma markers of fibrinolysis

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Abstract

There are no studies to date on the early changes in the hemostasis profile of patients with paroxysmal atrial fibrillation (PAF).

Given the key role of the fibrinolytic system in maintaining blood fluidity, our aim was to examine its activity in patients with clinical manifestation of the disease <24 hours.

We studied 51 nonanticoagulated patients with a first episode of the disease (26 men, 25 women; mean age 59.84 ± 1.60 years) and 52 controls (26 men, 26 women; mean age 59.50 ± 1.46 years) who matched the patients in terms of gender, age, comorbidities, and conducted treatment. Using enzyme-linked immunosassays and colorimetric assays we assessed the plasminogen activity, tissue plasminogen activator level (t-PA), plasminogen activator inhibitor 1 activity (PAI-1), a2-antiplasmin activity (a2-AP), D-dimer level, and vitronectin level. Blood samples were collected immediately after hospitalization.

Patients were hospitalized between the second and twenty four hours (mean 8.14 ± 0.76 hours) after the onset of PAF. Compared to controls, plasminogen (159.40 ± 4.81 vs 100.2 ± 2.88%, P < 0.001) and t-PA levels (11.25 ± 0.35 vs 6.05 ± 0.31 ng/mL, P < 0.001) were significantly higher in the patient group. PAI-1 activity (7.33 ± 0.37 vs 15.15 ± 0.52 AU/mL, P < 0.001) and a2-AP (112.9 ± 2.80 vs 125.60 ± 3.74%, P < 0.05) as well as vitronectin plasma levels (134.7 ± 5.83 vs 287.3 ± 10.44 mcg/mL, P < 0.001) were lower in the PAF group. Conversely, the levels of D-dimer in patients were significantly higher (0.53 ± 0.07 vs 0.33 ± 0.02 ng/mL, P < 0.05).

Early changes in the fibrinolytic system occur in PAF, suggesting their close relationship with the manifestation of the disease. There is high plasma fibrinolytic activity, during the very first 24 hours of the disease, which is most likely a pathophysiological response to the intensified procoagulation process.

Abbreviations: a2-AP = a2-antiplasmin activity, FDPs = fibrin degradation products, PAF = paroxysmal atrial fibrillation, PAI-1 = plasminogen activator inhibitor type 1, t-PA = tissue plasminogen activator, u-PA = urokinase-type plasminogen activator.

Keywords: a2-antiplasmin, D-dimer, PAI-1, paroxysmal atrial fibrillation, plasminogen, t-PA, vitronectin

1. Introduction

The fibrinolytic system plays a crucial role in maintaining the hemostasis balance in the human body. It is a complex and multicomponent system and it strictly controls the opposing processes of activation and inhibition of proteolytic degradation of fibrin in order to restore and maintain normal blood flow.[11]

A key molecule for fibrinolysis is the freely circulating in plasma plasminogen.[12] Plasminogen is the zymogen form of the active serine protease plasmin, which initiates the cleavage of the fibrin network in the blood clot.[13] Plasminogen is converted into plasmin by the action of 2 immunologically distinct physiological activators, namely t-PA and urokinase-type plasminogen activator (u-PA), the latter operating mainly in the extravascular space.[4,3]

In the dissolution of intravascular thrombi, t-PA-mediated plasminogen activation plays the most important role.[6] This defines t-PA as a major initiator of fibrinolysis, in the course of which the fibrin network is cleaved into a series of soluble fibrin degradation products (FDPs) including D-dimer.[7,8] FDPs are also obtained in the decomposition of other coagulation proteins such as fibrinogen. Unlike them, D-dimer is a degradation product solely from crosslinked (by factor XIII) fibrin. In this respect, D-dimer is a specific marker of endogenous fibrinolysis, and more precisely of intravascular fibrin formation and its subsequent cleavage.[9]

The fibrinolytic process can be inhibited through 2 main mechanisms: plasminogen activation inhibition by plasminogen activator inhibitors (PAIs) or plasmin inhibition by a2-AP.[10] Several types of PAIs are known, the most physiologically important PAI-1. Its active form binds to t-PA in a stoichiometric manner, rapidly and irreversibly inhibiting t-PA.[11] Vitronectin is a plasma glycoprotein with a key role in the function of active PAI-1. The interaction between them leads to stabilization of the structure and extends the life of active PAI-1.[12]

a2-AP, similar to PAI-1, is a member of the serpine family of enzyme inhibitors.[13] It has the ability to rapidly inactivate the...
plasmin, forming with it a stable inactive complex, plasmin-α2-AP.[14] It is believed that α2-AP is responsible for about 90% of plasmin inhibition.

According to data from epidemiological studies PAF accounts for 25% to 60% of all AF cases, most likely the actual prevalence being higher due to the presence of asymptomatic episodes.[15] Despite the short duration (up to 7 days), the disease has a high incidence of thromboembolic complications, similar to chronic AF.[16,17] These facts give rise to clinical interest in the hemostasis profile in PAF and in particular to fibrinolysis as its essential element.

2. Aim

Given the key role of the fibrinolytic system in maintaining blood fluidity, our aim was to examine its activity in patients with clinical manifestation of the disease <24 hours.

3. Materials and methods

3.1. Study design

Only patients with sudden manifestation of symptomatic episodes of AF, with the onset within the first 24 hours before hospitalization, were selected. They determined the start of the arrhythmia as a feeling of palpitation, continuing up to blood sampling. The diagnosis was confirmed by ECG performed immediately after admission to the ward. Patients who could not confidently define the onset of AF were excluded from the study.

A control group was formed from volunteers who visited their GPs for their annual examination. The control group matched the patients in terms of age, gender, comorbidities, and performed medical treatment. The selection process aimed at the utmost degree to equalize the factors affecting the hemostasis profile between the 2 groups.

Six indicators of fibrinolysis were examined once in each participant: plasminogen activity, t-PA level, PAI-1 activity, α2-AP activity, as well as vitronectin and D-dimer plasma levels. Blood samples were collected in patients immediately after hospitalization and prior to administration of drugs. Blood was taken in controls during prophylactic outpatient examinations.

Participants were included after previously signing an informed consent to participate.

3.2. Study population

The study was conducted in the Cardiac Intensive Care Unit of the First Cardiology Clinic at the University Hospital St. Marina —Varna for the period October 2010–May 2012 after approval by the Ethics Committee of Research (35/29.10.2010) at the same hospital and in accordance with the Declaration of Helsinki.[18]

From a total of 338 screened patients, 51 were selected with a first episode of PAF (26 men and 25 women; mean age 59.84 ± 1.60 years) that was successfully terminated by propafenone. The drug was administered immediately after hospitalization of patients (after the collection of blood samples) in the prescribed for it scheme for a total duration of 24 hours.[19,20] The remaining 287 patients were excluded due to exclusion criteria.

The control group was formed only by volunteers with no previous history and electrocardiographic evidence of AF. From 169 screened controls, 52 were selected (26 men, 26 women; mean age 59.50 ± 1.46 years).

The same exclusion criteria (see below) were used for the selection of the patient and the control group.

The health status of the participants in the study was determined based on medical history, medical records, physical examination, laboratory tests, and numerous conducted electrocardiograms and transthoracic echocardiography.

The exclusion criteria included multiple diseases, conditions, and medications related to the hemostasis profile. They were identical for the patient and control groups:

1. Cardiovascular diseases, namely: ischemic heart disease; heart failure; uncontrollable hypertension; implanted device for the treatment of rhythm-conducive disorders; inflammatory and congenital heart diseases; moderate or severe valve diseases.
2. Other diseases—renal, liver, or pulmonary diseases; diseases of the central nervous system; inflammatory and/or infectious diseases for the previous 3 months; neoplastic and autoimmune diseases; diseases of the endocrine nervous system (except for diabetes mellitus type 2, noninsulin dependent, well controlled).
3. Intake of hormone-replacement therapy or contraceptives; pregnancy; systemic intake of analgesics, including nonsteroidal anti-inflammatory drugs; intake of antiplatelet drugs and anticoagulants; obesity (BMI > 35).

3.3. Collection and storage of blood samples

Blood samples were collected from the antecubital vein into coagulation tubes with 3.2% sodium citrate (VACUETTE, Greiner Bio-One North America, Inc.).

After centrifuging at 2500g for 15 minutes, the obtained plasma was separated and stored in plastic tubes at −20°C for up to 1 month.

Each indicator was determined twice, taking the average of the 2 measurements into consideration.

Re-freezing of samples was not allowed.

3.4. Laboratory procedures

Plasminogen activity in plasma was measured by a colorimetric assay (Stachrom Plasminogen, Diagnostica Stago, France). An enzyme-linked immunosorbent assay technique was applied to measure t-PA antigen level (Asserachrom t-PA, Diagnostica Stago, France). The activity of PAI-1 and α2-antiplasmin were determined by a colorimetric method (Stachrom PAI, Diagnostica Stago, France; Stachrom Antiplasmin, Diagnostica Stago, France). Quantitative measurement of vitronectin level was performed by an enzyme-linked immunosorbent assay (Imubind vitronectin, American Diagnostica GmbH). D-Dimer level was studied with an enzyme-linked immunosorbent technique (Imuclone D-dimer, American Dagnostica GmbH).

The intra-assay coefficient of variation was <6%, except for PAI-1 activity (7.9%). The interassay coefficient of variation was <6%, except for PAI-1 activity (6.6%).

3.5. Statistical analysis

Descriptive statistics was used to calculate the mean values, standard error of the mean (SEM), relative shares, and central tendency (Mo = mode). The testing of the hypotheses for the equality of means and indicators share was done using Student’s 2-tailed t-test for unpaired data for normal distributions.
result was presented as mean ± SEM or n (%). Values of P < 0.05 were considered statistically significant.

4. Results

4.1. Patient and control characteristics

Table 1 presents the patient and control group characteristics. In terms of age, clinical characteristics, deleterious habits, and body mass index (BMI), there were no statistically significant differences between the 2 groups (Table 1) (P > 0.05).

Standard transthoracic echocardiography found no significant differences between the patient and control groups (Table 2) (P > 0.05).

Statistical analysis showed that most often the patients were hospitalized during the fifth hour (M = 5; 10 of all 51 patients). The mean duration of AF episodes until hospitalization was 8.14 ± 7.66 hours.

4.2. Hemostatic markers

Plasminogen (159.40 ± 4.81 vs 100.2 ± 2.88%, P < 0.001; Fig. 1) and t-PA levels (11.25 ± 0.35 vs 6.05 ± 0.31 ng/mL, P < 0.001; Fig. 2) were significantly higher in the patient group. PAI-1 activity (7.53 ± 0.37 vs 15.15 ± 0.52 AU/mL, P < 0.001; Fig. 3) and α2-AP (112.9 ± 2.80 vs 125.60 ± 3.74%, P < 0.05; Fig. 4) as well as vitronectin plasma levels (134.7 ± 5.83 vs 287.3 ± 10.44 mg/mL, P < 0.001; Fig. 5) were lower in the PAF group. Conversely, D-dimer levels were significantly higher in patients (0.53 ± 0.07 vs 0.33 ± 0.02 mg/mL, P < 0.05, Fig. 6).

The study of the indicators in relevance with individual patients’ risk for manifestation of stroke found statistically significant differences between the patients with high risk (CHADS2-VASc score > 2) and those with low to moderate risk (CHADS2-VASc score ≤ 2) during the first day of the manifestation of disease only in one of the studied indicators (Table 3).

5. Discussion

Fibrinolytic activity in AF is subject of research in numerous studies to date, the results being quite controversial on the changes in the activity of the system. To date, however, mainly the persistent and permanent forms of the rhythm disorder have been studied, which, as it is known, are qualitatively different forms of the disease. Studies on the activity of the fibrinolytic system in the clinical expression of PAF are scarce and present only single system indicators. Freynhofer et al.[21] measured elevated t-PA levels during the rhythm disorder, which lead them to suggest a state of hyperfibrinolysis in the course of the disease. The same study established their predictive value for the manifestation of major adverse cardiovascular incidents. The results presented by Feinberg et al.[22] according to which the manifestation of PAF is characterized by high levels of the plasmin-antiplasmin complex, also show an increased activity of the system. Drabik et al.[23] showed elevated PAI-1 antigen levels and a tendency to form denser and poorly lysable clots. There is no data on the state of the fibrinolytic system during the first 24 hours of PAF.

Fibrinolysis is a complex and finely regulated enzyme process which protects the body from excessive accumulation of intravascular fibrin and enables the removal of thrombi.[24] As a major source of plasma proteins and principal place of plasma protein clearance, the liver performs a significant role in regulating the functions of the fibrinolytic system.[25] It is responsible for plasminogen synthesis and has the ability to affect the fibrinolytic cascade at its very beginning. As is apparent from Fig. 1, the plasma levels of plasminogen in PAF patients are

### Table 1

| Clinical characteristics of patient and control group. | Patients with PAF | Control group | P |
|-------------------------------------------------------|-------------------|---------------|---|
| Number of participants in the group                   | 51                | 52            | 0.89 |
| Mean age, y                                           | 59.84 ± 1.60      | 59.50 ± 1.46  | 0.87 |
| Men/women                                            | 26/25             | 26/26         | 1.03 |
| Accompanying diseases                                 |                   |               |     |
| Hypertension                                         | 37 (72.54%)       | 34 (65.38%)   | 0.44 |
| Diabetes mellitus type 2                              | 3 (5.88%)         | 2 (3.84%)     | 0.62 |
| Dyslipidemia                                         | 4 (7.84%)         | 3 (5.77%)     | 0.69 |
| Medicaments for hypertension and dyslipidemia         |                   |               |     |
| Beta blockers                                         | 19 (37.25%)       | 17 (32.69%)   | 0.62 |
| ACE inhibitors                                       | 15 (29.41%)       | 14 (26.92%)   | 0.78 |
| Sartans                                              | 11 (21.57%)       | 9 (17.31%)    | 0.58 |
| Statins                                               | 4(7.84%)          | 3(5.77%)      | 0.69 |
| Deleterious habits                                    |                   |               |     |
| Smoking†                                              | 8 (15.69%)        | 7 (13.46%)    | 0.75 |
| Alcohol intake†                                       | 7 (13.72%)        | 6 (11.53%)    | 0.74 |
| BMI (kg/m²)                                          | 23.85 ± 0.46      | 24.95 ± 0.45  | 0.09 |

*N* more than half a pack of cigarettes weekly. The hospitalized patients had not smoked for at least 48 hours before the beginning of arrhythmia. The controls were examined after a 48 hour nonsmoking period.

†No more than 2 drinks weekly. The hospitalized patients had not consumed alcohol for at least 48 hours before the beginning of arrhythmia. The controls were examined after a 48 hour alcohol-free period.

### Table 2

| Echocardiographic evaluation of patient and control group. | Patients with PAF | Control group | P |
|----------------------------------------------------------|-------------------|---------------|---|
| LVEDD, mm                                                | 52.57 ± 0.58      | 52.29 ± 0.57  | 0.73 |
| LVESD, mm                                                | 34.43 ± 0.56      | 34.73 ± 0.48  | 0.69 |
| EF, %                                                    | 62.98 ± 0.70      | 61.54 ± 0.58  | 0.12 |
| IVS, mm                                                  | 10.37 ± 0.23      | 9.02 ± 0.26   | 0.20 |
| PW, mm                                                   | 10.24 ± 0.21      | 9.73 ± 0.28   | 0.16 |
| LA volume, mL/m²                                         | 22.81 ± 0.45      | 23.62 ± 0.48  | 0.13 |
| RVEDD, mm                                                | 30.54 ± 1.58      | 29.17 ± 1.52  | 0.18 |

EF = ejection fraction, IVS = interventricular septum, LA = left atrium, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, PAF = paroxysmal atrial fibrillation, PW = posterior wall, RVEDD = right ventricular end-diastolic volume.
The fibrinolytic process depends to a significant degree on the delicate balance between proteases and their inhibitors. PAI-1 and α2-AP activity determines the degree of inhibition of t-PA and plasmin proteases, essential for the cleavage of the fibrin network in thrombi.\textsuperscript{11} In this sense, the simultaneous study of t-PA and α2-AP activity is an integral part of the assessment of the fibrinolytic system. Similar to PAI-1, α2-AP exhibited lower activity in the patient group compared to controls (P < 0.001, Fig. 3; P < 0.05, Fig. 4, respectively). These data have important clinical significance. They complement the already presented results and provide accurate information about the intimate regulatory mechanisms of the fibrinolytic cascade in our PAF study group. The activity of both main pathways of fibrinolysis inhibition, namely PAI-1 and α2-AP, was reduced.

In this sense, we should examine the decreased vitronectin levels in the patient group (P < 0.001, Fig. 5). As it is well known, it is an indirect noncatalytic inhibitor of plasminogen proteolysis to active plasmin.\textsuperscript{12,29} Vitronectin stabilizes the active PAI-1, prolongs, and enhances its inhibitory effect on t-PA.\textsuperscript{30} Its low values in the PAF group might explain the PAI-1 reduced activity. Moreover, they supplement the already examined indicators and along with them give grounds to assume that there is an increased conversion of plasminogen to plasmin, and as a result increased fibrinolytic activity in plasma in the early hours of the clinical manifestation of the rhythm disorder.

This assumption is also directly confirmed by the results obtained in the study of D-dimer (p < 0.05; Fig. 6). As is well known, D-dimer is a direct product of the formation and subsequent lysis of cross-linked fibrin in the thrombus and its plasma levels reflect the degree of activation of the coagulation
In this sense, we believe that the established by us expediently under the protection of i.v. unfractionated heparin allows for an immediate cardioversion attempt, performed due to hypercoagulation.

According to the 2010 European Society of Cardiology guidelines, the low embologenic potential in the acute attempt for this result requires further studies. The presented results provide information exclusively about the plasma fibrinolytic activity in the acute attempt for the early changes in the hemostasis profile of PAF patients have important clinical contribution. They show that heparin is not only relevant, but a must. This involves conducting larger clinical studies in this field and proposition of stricter rules for the use of unfractionated heparin in the acute attempt for cardioversion.

CHADS2-VASc-score is an accepted clinical model for risk stratification of AF patients according to their individual risk for brinolysis. Therefore, we believe that the established by us significant early changes in the hemostasis profile of PAF patients have important clinical contribution. They show that heparin is not only relevant, but a must. This involves conducting larger clinical studies in this field and proposition of stricter rules for the use of unfractionated heparin in the acute attempt for cardioversion.

6. Conclusion

Early changes in the fibrinolytic system occur in PAF, suggesting their close relationship with the manifestation of the disease. We established high plasma fibrinolytic activity during the very first 24 hours of the disease (high plasminogen and t-PA level, reduced PAI-1 and α2-AP activity, reduced vitronectin levels), which is most likely a pathophysiologic response to the intensified procoagulatory state (high D-dimer level).

7. Study limitations

The aim of our study was to investigate the plasma fibrinolytic activity in the early hours of the clinical manifestation of PAF, namely the first 24 hours from the onset of the disease. Therefore, we studied only patients who clearly specified that the arrhythmia started < 24 hours prior to hospitalization. In this sense the presented results provide information exclusively about the plasma fibrinolytic activity in the early hours of clinical manifestation of PAF. They cannot in any way show or predict the fibrinolytic activity in the later hours of the disease. We also believe that these limitations are a ground for new studies, which could examine the dynamics of the system.

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