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Original Research
Journal of Atrial Fibrillation

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Paroxysmal Atrial Fibrillation: An Independent Risk Factor for Prothrombotic Conditions

Mariya Negreva[1]; Krasimira Prodanova[2]; Ana Zarkova[3]

[1]Associate professor at Department of Cardiology, Medical University of Varna, First clinic of cardiology, Varna University Hospital "St. Marina", Varna, Bulgaria.
[2]Professor at Faculty of applied mathematics and informatics, Technical University of Sofia, Sofia, Bulgaria.
[3]Doctor at National Specialized Hospital for Active Treatment of Hematologic Diseases, Sofia, Bulgaria.

Abstract

Objective It remains unclear whether atrial fibrillation (AF) alone determines systemic changes in hemocoagulation. Our aim was to examine the prothrombin fragment F1+2 and fibrinopeptide A (FPA) as early markers of coagulation activity still in the first twenty-four hours of paroxysmal AF (PAF) and to correlate them with the arrhythmia onset.

Methods 51 non-anticoagulated patients (26 men, 25 women, aged 59.84±1.6 years) and 52 controls (26 men, 26 women, aged 59.50±1.46 years) were sequentially selected. F1+2 and FPA plasma levels were measured by enzyme-linked immunoassays.

Results F1+2 was significantly higher in patients (292.61pmol/L±14.03pmol/L vs 183.40pmol/L±8.38pmol/L; p<0.001). FPA was also substantially higher (4.47ng/mL±0.25 ng/mL vs 3.09ng/mL±0.15ng/mL, p<0.001). Among the potential predictors for these deviations: age, gender, BMI, PAF duration and CHA_2DS_2-VASc score, it was established that higher F1+2 and FPA plasma levels were independently associated only with PAF duration (p<0.05). Moreover, longer episodes were associated with higher values of F1+2 (Adjusted R^2 = 0.68) and FPA (Adjusted R^2 = 0.70).

Conclusion Increased coagulation activity was present still in the first twenty-four hours of PAF clinical presentation. The disease itself was associated with increasing hypercoagulability over time, suggesting its importance as an independent risk factor for thromboembolic events.

Introduction

Atrial fibrillation (AF) remains the most common rhythm disorder diagnosed in clinical practice [1]. The observed trend for increasing incidence is thought to persist in the coming decades, and is therefore often considered epidemic [2]. The most significant and debilitating complications associated with AF are thromboembolic events. AF increases the risk of ischemic stroke from three to five fold and significantly worsens its prognosis [3].

A number of studies on thrombus formation in AF identified it as a good example fulfilling the Virchow's triad [4,5]. However, AF-related embolic events have been diagnosed in the absence of stasis and/or anatomical and structural changes in the left atrium. In this sense, the significant systemic changes in haemostasis and coagulation in AF patients established over the past two decades are defined as being key factors for embolic incidents observed in AF [4,5]. The question is whether they are closely associated with the rhythmic disorder itself or result from comorbidities. A clearly defined answer to this question would be of great clinical importance, especially to determine the anticoagulant approach in AF patients. At present, risk scales defining precisely anticoagulant therapy in AF integrate factors (diseases) with an established procoagulant effect [6]. They do not take into account the clinical presentation of the arrhythmia itself, which is somewhat paradoxical. In this regard, recently published data by Christiensen et al. are of interest [7]. They performed analysis of the Danish registers, involving over 3 million patients over 50 years old, and found that AF expression was associated with an increased risk of ischemic stroke, transient ischemic attack or systemic thromboembolism in the absence of CHA_2DS_2-VASc risk factors. The authors believe that the disease itself has the embologenic significance of one CHA_2DS_2-VASc risk factor. Moreover, Go et al. have shown a relationship between the burden (total amount of time in AF) of the arrhythmia and the risk of ischemic stroke [8]. Even paroxysmal AF (PAF), often considered as having a lower risk, compared to non-paroxysmal AF, has a risk of ischemic stroke, independent of known embologenic risk factors, that increases with the duration of the arrhythmia. Studies have shown increased embologenic risk even in device-detected AF, independent of

Key Words

Paroxysmal Atrial Fibrillation, Risk Factor, Prothrombin Fragment 1+2, Fibrinopeptide A, Hypercoagulability

Corresponding Author
Mariya Negreva, MD, PhD
First Clinic of Cardiology, Varna University Hospital "St. Marina"
Hr. Smirneneski bulv. 1, Varna 9000, Bulgaria

other risk factors [9,10,11]. This has led some authors to suggest a possibility of improving stroke risk stratification by combining the rating scale with AF presence/duration or burden [11]. In this respect, it is appropriate to emphasize that the duration of PAF, defined as embologenic in studies, is too short. In recent years, data on AF have been presented, establishing it as an independently associated risk factor for stroke events. It remains unclear whether this fact is related to systemic changes in hemocoagulation and to what extent AF expression itself is associated with systemic activation of coagulation. This determined the aim of our study: to investigate the early markers of coagulation activity prothrombin fragment 1+2 (F1+2) and fibrinopeptide A (FPA) in the first hours of PAF (up to the 24th hour), and to seek connection between them and the manifestation of the rhythmic disturbance.

Material and methods

Study design

The clinical study was conducted at the First Cardiology Clinic of the University Hospital in Varna, Bulgaria after approval by the local ethics committee (9/14.10.2010). The study was carried out in accordance with the Declaration of Helsinki for the period October 2010 – May 2012 [12]. Patients with PAF episode duration <24 hours, persistent at hospitalization, were screened using the exclusion criteria below: diseases and conditions associated with changes in hemocoagulation. The participants were selected sequentially. Diagnosis was accepted after electrocardiography.

A control group of outpatient volunteers without anamnestic or electrocardiographic AF data at the time of screening was also formed. Controls were selected on the basis of the exclusion criteria.

The patient and control groups were matched by gender, age, body mass index (BMI), deleterious habits, comorbidities and treatment. This was incorporated into the study design in order to eliminate the possible influence of these factors on the hemostatic profile.

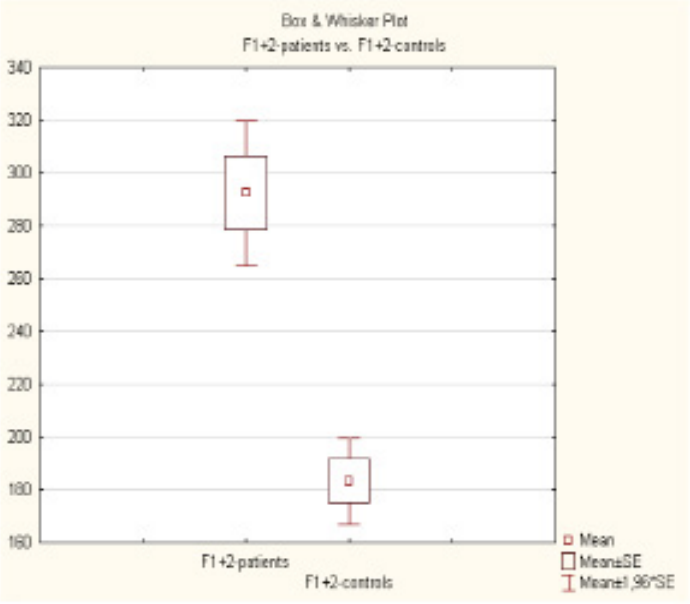

Figure 1: Plasma level of prothrombin fragment F1+2 (F1+2) measured in pmol/L in control and patient groups.

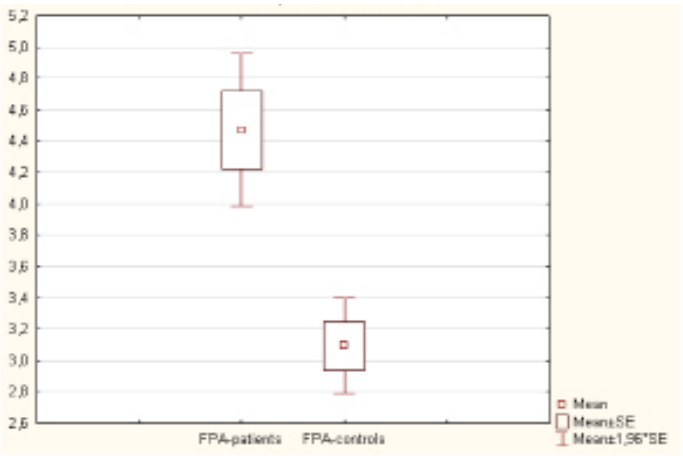

Figure 2: Plasma level of fibrinopeptide A (FPA) measured in ng/mL in control and patient groups.

Peripheral venous blood was collected once from each study participant to study plasma levels of F1+2 and FPA. In patients, this was done immediately after hospitalization and diagnosis, and in controls during outpatient examination.

Exclusion criteria:

1. cardiovascular diseases: ischemic heart disease, heart failure, high-grade and/or uncontrolled hypertension, moderate or severe acquired valve defects, cardiomyopathy, implanted device for the treatment of rhythm-conduction disorders, inflammatory heart disease, congenital heart diseases;
2. other diseases: kidney or liver failure, inflammatory and/or infectious diseases, neoplastic and autoimmune diseases, chronic pulmonary insufficiency, endocrine disorders (except for non-insulin dependent, well-controlled DM type 2); previous thromboembolic incidents, bleeding diathesis, miscarriages (for women);
3. intake of hormone replacement therapy, contraceptives, oral anticoagulants or antiplatelet drugs, pregnancy, systemic intake of analgesics (incl. NSAIDs), obesity with BMI >35;
4. unsuccessful restoration of sinus rhythm with drugs (propafenone) (for the patient group)

Study population

A total of 338 patients were screened, from which 51 (26 men and 25 women) with a mean age of 59.84±1.60 years (31-77 years) were sequentially selected. 287 patients were dropped due to exclusion criteria. The control group was formed as a result of screening 169 outpatients who visited their GP for annual check-up. 52 (26 males, 26 females) were sequentially selected. Their mean age was 59.50±1.46 years (30-76 years).

Patients and controls were selected for the study after the study design was explained in advance and after signing informed consent.

Laboratory procedures

Blood samples were collected in a coagulation 3.2% sodium citrate tube (VACUETTE, Greiner Bio-One North America, Inc.) and a heparin tube (VACUETTE, Greiner Bio-One North America, Li Hep). Subsequently they were centrifuged and the resulting plasma was separated and stored strictly according to the manufacturer

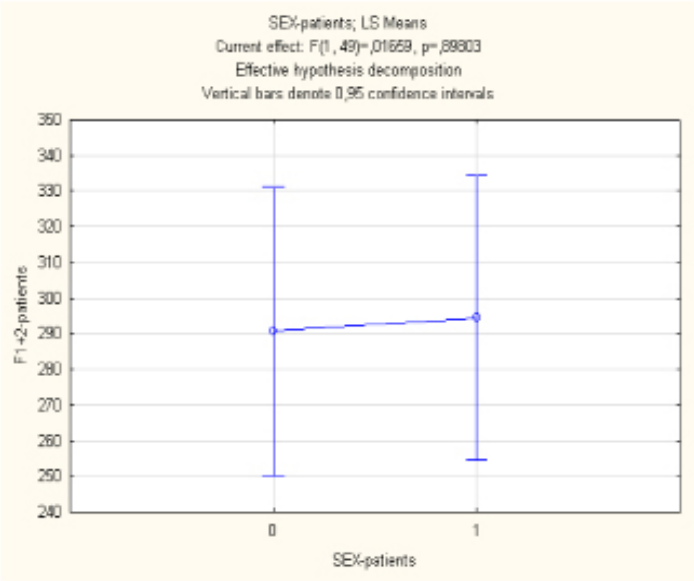

Figure 3: The mean values and 95% confidence limits of F1+2 plasma levels in women and men with PAF (0-values in women; 1- values in men)

requirements in plastic tubes at -20˚C for up to 1 month. Quantitative determination of F 1+2 in plasma was performed by an enzyme-linked immunoassay technique (F1+2 enzyme (monoclonal) Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). A competitive enzyme-linked immunosorbent assay was used to determine plasma FPA levels (ELISA FPA, USCN Life Science, Wuhan, China).

Each indicator was examined twice and the arithmetic mean was taken into account.

Statistical analysis

All analyses were conducted using STATISTICA 13.3.0, StatSoft Inc, USA.

Continuous variables were expressed as mean ± standard error of the

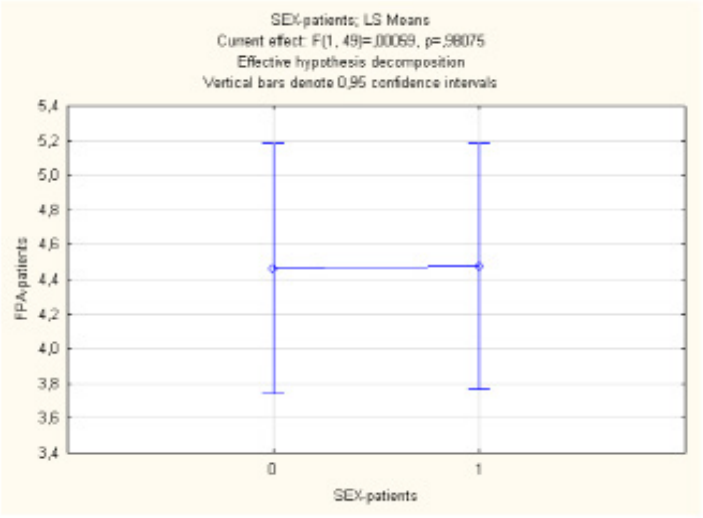

Figure 4: The mean values and 95% confidence limits of FPA plasma levels in women and men with PAF (0-values in women; 1- values in men).

Table 1: Clinical characteristics of the participants.

	Patients with PAF	Control group	P values
Number of participants	51	52	p=0.89
Mean age (years)	59.84±1.60	59.50±1.46	p=0.87
Men/Women	26/25	26/26	p=1/p=0.93
Accompanying diseases			
Hypertension	37 (72.54%)	34 (65.38%)	p=0.44
Diabetes mellitus type 2	3 (5.88%)	2 (3.84%)	p=0.62
Dyslipidemia	4 (7.84%)	3 (5.77%)	p=0.69
Medicaments for Hypertension and Dyslipidemia			
Beta blockers	19 (37.25%)	17 (32.69%)	p=0.62
ACE inhibitors	15 (29.41%)	14 (26.92%)	p=0.78
Sartans	11 (21.57%)	9 (17.31%)	p=0.58
Statins	4 (7.84%)	3 (5.77%)	p=0.69
Deleterious habits			
Smoking	8(15.69%)	7(13.46%)	p=0.75
Alcohol intake	7(13.72%)	6(11.53%)	p=0.74
BMI (kg/m²)	23.85±0.46	24.95±0.45	p=0.09
CHA_2DS_2 –VASc score		No score	
Number of patients with score < 2	25		
Number of patients with score ≥ 2	26		

mean (SE) and categorical variables were expressed as percentage of the total group. Normality of distribution was assessed by the Kolmogorov-Smirnoff test. Two-tailed Student's t-test for independent samples was used to compare quantitative variables. Fisher's exact or Pearson's chi-square tests were used to compare categorical variables and occurrence frequency. Values $p<0.05$ were adopted for statistically significant.

Simple linear regressions were used to determine the associations between the values of the coagulation activity markers F1+2 and FPA in AF (dependent continuous variables) and the explanatory continuous variables age, BMI and PAF duration (time spent in AF until hospitalization) (independent variables). The relationships were analyzed using the linear equations:

$$Yi=a+b*Xj,\ i=1,2 \text{ and } j=1,2,3,$$

where Yi were the values of dependent variables, Xj – independent variables, a and b – parameters of the regression equation.

Associations between F1+2 and FPA plasma levels in AF and the categorical independent variables sex and CHA_2DS_2 – VASc score were determined by an analysis of variance (ANOVA). Variables showing a

Table 2: Echocardiographic parameters of the participants.

	Patients with PAF	Control group	P values
Echocardiographic indicators			
LVEDD (mm)	52.57±0.58	52.29±0.57	p=0.73
LVESD (mm)	34.43±0.56	34.73±0.48	p=0.69
EF (%)	62.98±0.70	61.54±0.58	p=0.12
IVS (mm)	10.37±0.23	9.92±0.26	p=0.20
PW (mm)	10.24±0.21	9.73±0.28	p=0.16
LA volume (ml/m²)	22.81±0.45	23.82±0.48	p=0.13
RVEDD (mm)	30.54±1.58	29.17±1.52	p=0.18

Table 3: Univariate analysis showing the association between F1+2 plasma level in AF and independent variables age, BMI and PAF duration.

Xj	a* p-value	B* p-value	R**	R2 ***
Age (years)	260,59 0,05	0,53 0,67	0,06	0,001
BMI (kg/m²)	259,42 0,05	1,39 0,75	0,05	0,002
PAF duration (hours)	167,68 <0,001	15,31 <0,001	0,83	0,68

*a and b – estimated parameters of the regression equation; ** - values of the correlation coefficient R; *** - value of the coefficient of determination R2 (as an overall measure of model goodness-of-fits) for variable F1+2)

level of association p<0.05 were considered as prognostic.

Results

Study participants

No statistically significant difference was found between the two groups in terms of age, gender, accompanying diseases, treatment, deleterious habits and BMI (p> 0.05) (Table 1).

No difference was also found in transthoracic echocardiography indicators (p> 0.05) (Table 2).

The statistical analysis showed that patients were hospitalized between the 2nd and the 24th hour of the onset of the arrhythmia, most often at the 5th hour. The mean duration of episodes before hospitalization was 8.14±0.76 hours.

Atrial fibrillation and blood coagulation activity markers

Plasma levels of F1+2 were significantly higher in the patient group compared to controls (292.61 pmol/L±14.03 pmol/L vs 183.40 pmol/L ± 8.38 pmol/L; p<0.001) (Fig. 1). Substantially higher were FPA levels in AF group (4.47 ng/mL ± 0.25 ng/mL vs 3.09 ng/mL±0.15 ng/mL, p <0.001) (Fig 2).

As we can see from Table 3, the higher F1 + 2 levels found in PAF patients were independent of patients' age (p>0.05) and BMI (p>0.05). The duration of PAF (time spent in AF) was a significant predictor of coagulation indicator values (p <0.001). Based on R_2, 68.14% of the F1 + 2 variation could be predicted by the duration of the PAF.

Also, no correlation was found between FPA values and age (p> 0.05) and BMI (p> 0.05) of patients (Table 4). A correlation was found between coagulation indicator levels and PAF duration (p <0.001)

Table 4: Univariate analysis showing the association between FPA plasma level in AF and independent variables age, BMI and PAF duration.

Xj	a* p-value	b* p-value	R**	R2 ***
Age (years)	3,93 0,005	0,009 0,69	0,06	0,003
BMI (kg/m²)	3,71 0,05	0,03 0,68	0,06	0,003
PAF duration (hours)	2,22 <0,001	0,28 <0,001	0,84	0,70

*a and b – estimated parameters of the regression equation; ** - values of the correlation coefficient R; *** - value of the coefficient of determination R2 (as an overall measure of model goodness-of-fits) for variable FPA)

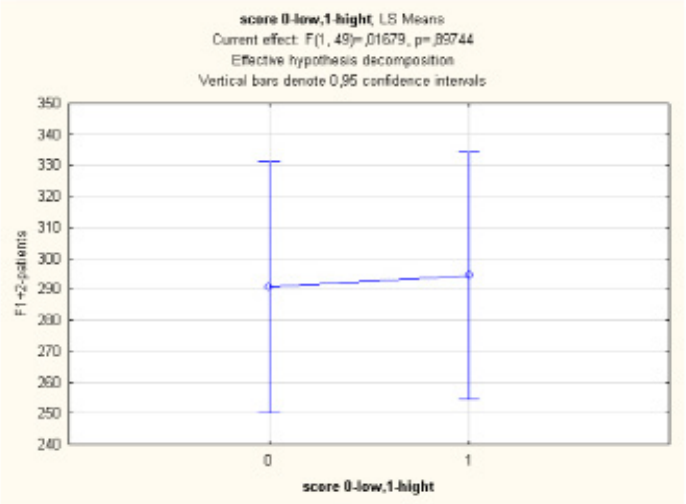

Figure 5: The mean values and 95% confidence limits of F1+2 plasma levels for CHA_2 DS_2 – VASc values in PAF patients (0 – coded low risk patients with score<2; 1- coded high risk patients with score≥2).

(Table 4). Based on R2, 70.32% of the variation in FPA values were explained by the PAF duration values.

ANOVA analysis showed no differences between men and women with PAF with respect to plasma F1+2 levels (290.70 pmol/L±21.76 pmol/L vs 294.35 pmol/L±18.30 pmol/L; F-statistics p>0.05) and FPA (4.46 ng/mL ± 0.39 ng/mL vs 4.48 ng/mL±0.32 ng/mL; F-statistic p>0.05) (Figure 3 and Figure 4).

Results concerning CHA_2DS_2 – VASc score as a predictor for F1+2 and FPA values in PAF are shown in Figure 5 and Figure 6. There was no difference in F1+2 values between patients with CHA_2DS_2 – VASc<2 and CHA_2DS_2 – VASc≥2 (290.69 pmol/L±18.66 pmol/L vs 294.37 pmol/L±21.22 pmol/L; F-statistic > 0.05) as well as in FPA values (4.42 ng/mL±0.33 ng/mL vs 4.52 ng/mL±0.38 ng/mL; F-statistic p>0.05).

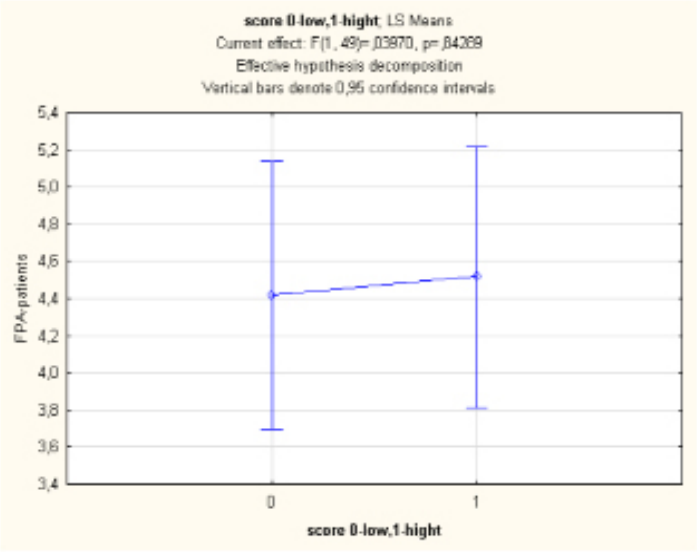

Figure 6: The mean values and 95% confidence limits of FPA plasma levels for CHA_2 DS_2 – VASc values in PAF patients (0 – coded low risk patients with score<2; 1- coded high risk patients with score≥2).

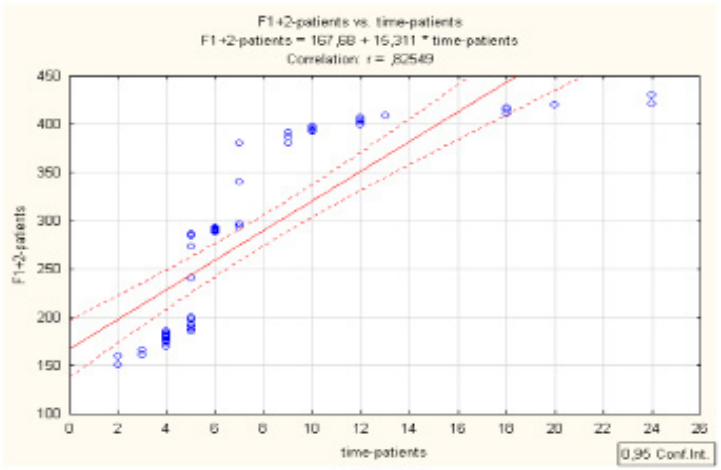

Figure 7: **Correlation between F1+2 plasma levels and time spent in PAF (hours).**

Linear regression results showed a relationship between the plasma levels of studied indicators and the duration of the PAF episode. When the duration of the rhythm disorder increased, the values of F1+2 (R square = 0.83; p <0.001) and FPA (R square = 0.84; p <0.001) also increased (Figure 7, Figure 8).

Discussion

The conversion of prothrombin (prothrombin, FII) into its active thrombin form (thrombin, FIIa) is an essential step in the common terminal pathway of the coagulation cascade, in which the prothrombin fragment F1+2 is released. This is due to the fact that thrombin is a key molecule in the thrombus formation process [13]. Its main effect is related to proteolytic cleavage from the fibrinopetide A (FPA) and fibrinopeptide B fibrinogen molecule and production of fibrin monomers, which then polymerize and form a stable clot. Thrombin is further involved in stabilizing the fibrin clot by activating factor XIII [14]. It also activates the extrinsic and intrinsic coagulation pathway by directly activating coagulation factors V, VII, VIII and IX, enhances receptor-mediated platelet adhesion and aggregation, as well as the thrombin-activated fibrinolysis inhibitor [14]. All these effects

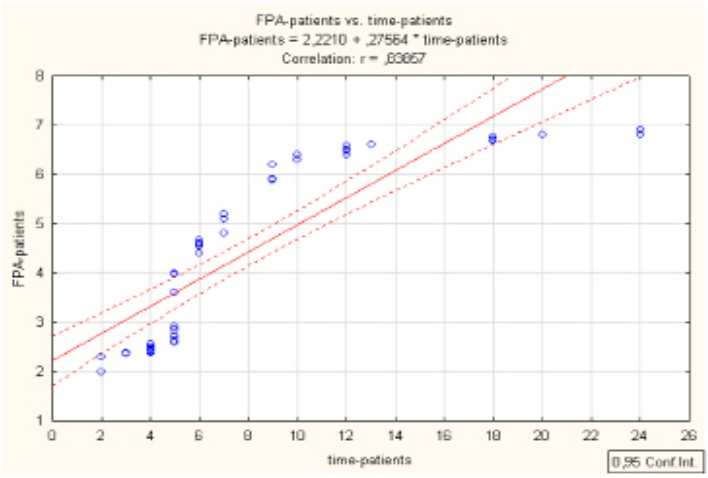

Figure 8: **Correlation between FPA plasma levels and time spent in PAF (hours).**

are unidirectional and lead to increased hemocoagulation activity. Therefore, thrombin is identified as one of the main catalysts for the coagulation process and its increased activity is a serious prerequisite for enhanced coagulation and thrombus formation. However, it is difficult to measure thrombin levels directly [15]. Upon activation of the coagulation system in pathological conditions, a very small fraction (<1%) of circulating prothrombin is activated to thrombin, which in turn is rapidly neutralized by antithrombin. In contrast, the quantitative measurement of the stable molecule of the prothrombin fragment F1+2 obtained from the conversion of prothrombin to thrombin is considered to be a specific marker of thrombin generation in vivo [16, 17]. It allows for good monitoring of thrombin synthesis and coagulation activity. In turn, FPA plasma levels are a good marker of thrombin activity and an assessment of the last step of the coagulation cascade, namely the conversion of fibrinogen to fibrin [15].

F1+2 and FPA are early markers of activated coagulation and may predict the onset of thromboembolic events [18]. As a good diagnostic marker in thrombotic conditions, they are significantly elevated in deep vein thrombosis, peripheral vascular disease, acute coronary vascular thrombosis and others. [18, 19, 20]. Retention of high F1+2 levels for months after an acute coronary incident is associated with recurrent angina episodes and higher incidence of subsequent cardiac events [21]. In patients with malignancies, the indicator is an independent deep vein thrombosis predictor [22]. High F1+2 and FPA plasma levels have also been found in AF patients [23, 24, 25, 26]. Studies so far, however, could not confirm whether the changes were associated with the arrhythmia itself or were provoked by the comorbidities of the studied populations. This was a major prerequisite for us to include the study of the comorbidities. As can be seen from the results obtained (Fig. 1 and Fig. 2), plasma levels of both indicators were higher in PAF patients compared to controls (p <0.001). The established deviations are of systemic nature that predetermines changes in coagulation at systemic level. There was increased thrombin generation and increased thrombin plasma activity, which was indicative of increased coagulation activity in the first twenty-four hours of the clinical manifestation of the arrhythmia. This leads us to accept that the early manifestation of PAF is associated with a tendency for hypercoagulability. Simple linear regression and ANOVA statistics showed that the observed difference in coagulation activity between patients and controls was independent of age, gender, BMI (p> 0.05; Table 3, Figs 3 and 4), and patients' embologenic risk (Figs. 5 and 6). There was no significant difference in coagulation activity between patients with low embologenic risk (CHA_2DS_2 -VASc score < 2) and high risk of thromboembolic events (CHA_2DS_2 -VASc score ≥ 2). Plasma F1+2 and PFA levels depended on the duration of the PAF episode (Figs. 7 and 8). Longer episodes gave higher indicator values. The results led us to suggest that the rhythmic disturbance was itself a risk factor for the development of a prothrombotic condition, regardless of patient's age, gender or BMI. The clinical manifestation of PAF itself determines a state of hypercoagulability. This is a prerequisite to accept the independent embologenic potential of the disease, which increases with the duration of its clinical manifestation. Longer episodes were associated with more significant changes in coagulation. The obtained results provide a good basis for finding the place of AF itself in the embologenic risk scales, associated with its clinical expression. This would probably also change the anticoagulant approach to AF patients.

Limitations

Coagulation activity was examined only during the rhythm disturbance. F1+2 and PFA plasma levels have not been investigated after sinus rhythm recovery, which was predetermined by the study design itself.

Acknowledgements

The second author Krasimira Prodanova is totally supported by project DN12/11/20.dec.2017 of the Ministry of Education and Science of Bulgaria for statistical analysis of data

Conclusion

Increased coagulation activity was present even in the early hours of PAF clinical presentation (up to the 24th hour). The disease itself was associated with increasing hypercoagulability over time, suggesting its importance as an independent risk factor for the occurrence of thromboembolic events.

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