

THE PHARMA INNOVATION - JOURNAL

Status of Coagulation and Platelet Hemostasis Parameters in Patients with Permanent Atrial Fibrillation on the Background of Metabolic Syndrome

Mariya A. Orynychak ^{1*}, Maryana M. Vasylechko ¹

1. Department of internal medicine of stomatological faculty, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, 76000, Ukraine
[E-mail: mariyaorynychak@gmail.com; Tel: +3800667845464]

To study peculiarities of the coagulation and platelet hemostasis parameters in hypertensives with permanent form of atrial fibrillation (AF) background of metabolic syndrome (MS).

Materials and Methods: The study included 70 hypertensives (25 male, 45 female), mean age: 70±9 years with permanent form of AF and MS by ATP III (2001). Blood pressure (BP) monitoring, electrocardiography (ECG) and coagulation hemostasis parameters for prothrombin index (PtI), fibrinogen, soluble fibrin-monomer complexes (SFMC), D-dimers and platelet aggregative activity (PAA) such as the beginning of aggregation, the degree of aggregation rate and speed aggregation and platelet von Willebrandt factor (vWF) accordingly to body mass index (BMI) by standard biochemical and immunoassay procedures were measured. The control group consisted of 20 healthy individuals.

Results and Discussion: Basal BP levels were ranged 140/90 ± 10/7 mm Hg. By clinic and ECG symptoms AF permanent form was diagnosed in all cases. Abdominal obesity (AO) with increasing BMI over 30 kg/m² in 57 (81.00%) and overweight with BMI 27.50±2.05 kg/m² in 13 (19.00%) cases were found. Among them in 32 (56.00%) cases II degree obesity with BMI equal to 34.90 ± 3.92 kg/m² and in 25 (44.00%) cases III degree obesity with BMI equal to 43.41 ± 2.25 kg/m² were diagnosed. In all patients MS was diagnosed that's why low risk of thromboembolism by CHADS₂ and CHA₂DS₂-VASc indicators panel was not found. Basal blood activation of aggregative function and fibrinolysis levels with increasing PtI; fibrinogen and SFMC parameters by 11.85%; 78.28% and 91.05% vs. 98.11±3.68%; 3.04±0.52 g/L and 3.80±0.8 mg/ml accordingly in the control group (p<0.05) in all patients were revealed. In patients with AO hypercoagulable status with plasma positive D-dimers in 20 (35.00%) and increased PAA levels in 37 (65.00%) cases in patients with overweight in 3 (25.00%) and 10 (75.00%) cases accordingly were found. In all patients the platelets number ranged 280.14±11.52×10⁹/l vs. 284.21±8.32×10⁹/l in the control group (p>0.05).

Conclusions: Atrial fibrillation complicated by increased levels aggregation and coagulation disorders of hemostasis under MS. Assessment of hemostasis disorders severity solely on the basis of PtI and fibrinogen is insufficient because it does not take into account other parameters of coagulation and platelet hemostasis, in particular, the level of circulating SFMC, D-dimers and PAA parameters according to the aggregation start parameters, the degree and rate of aggregation and vWF that are predictors of acute cardio-vascular events and the definition of a high risk of thromboembolism by CHADS₂ and CHA₂DS₂-VASc scales.

Keyword: Atrial Fibrillation, Metabolic Syndrome, Coagulation, Platelet Hemostasis, Diagnoses.

1. Introduction

In the world 1 – 2% of the population suffer from AF. The prevalence of AF increases with age, increasing from <0.5% among those aged 40 – 50

years old to 5 – 15% among persons who are 80 years old [2, 5]. Atrial fibrillation is often not diagnosed and treated disorder that cause acute ischemic stroke and myocardial infarction (MI),

especially in patients with arterial hypertension (AH) [5].

Among the main branches of AF pathogenesis a loss of antithrombotic properties of endothelium and increase the capacity of blood coagulation with the formation of stable hypercoagulation are observed [2].

It is known that one of the components of the MS is hypercoagulation with activation of blood coagulation, fibrinolysis and platelet activation [1, 2, 5]. Basic mechanisms of prothrombotic states are associated with atheromatous and atherothrombotic risks in particular, the components of MS such as AO, AH, impaired glucose tolerance, insulin resistance and dyslipidemia [1].

In prospective study Northwick Park Heart Study (1993) the role of coagulation factors in the development of atherosclerosis and its complications such as stroke and MI were revealed. There was established that fibrinogen levels closely and independently associated with mortality from cardio-vascular diseases [7].

Fibrin degradation products such as SFMC and D-dimers are formed in the body during activation of fibrinolysis. On the other hand, increased SFMC and D-dimer in blood plasma are typical for blood coagulation activity. Moreover, the greater concentration of fibrin degradation products (FDP) provokes the highest risk of intra-vascular thrombus formation with thrombophilia, thrombosis. Therefore, the presence of FDP in blood plasma is an indicator of haemostatic balance violation. The levels of FDP in blood plasma is a very important indicator to confirm the state of activation or inhibition blood system coagulation and anticoagulative properties. However, the state of haemostatic balance in patients with AF on the background of MS remains poorly understood [1, 3, 6].

According to recommendations of European Society Cardiology (ESC, 2010; 2012) stratification of the thromboembolism or stroke risks formation in patients with AF is carried out by the CHADS₂ and CHA₂DS₂-VASc scales [5].

Actuality question is the assessment of hemostasis in AF patients on the background of MS that caused the purpose of our study.

Purpose – to study peculiarities of the coagulation and platelet hemostasis parameters in hypertensives with permanent form of AF background of MS.

2. Materials and Methods

The study included 70 hypertensives (25 male, 45 female), mean age: 70±9 years with permanent form AF and MS by ATP III (2001) criteria [1]. Overweight with BMI ranged 25-29 kg/m² was revealed in 13 (19.00%) cases. Abdominal obesity (AO) with increasing BMI over 30 kg/m² in 57 (81.00%) cases. Among them in 32 (56.00%) cases II degree obesity with BMI equal to 34.90 ± 3.92 kg/m² and in 25 (44.00%) cases III degree obesity with BMI equal to 43.41 ± 2.25 kg/m² were diagnosed.

Stratification for stroke and thromboembolism risks in patients with AF and MS was performed using the CHADS₂ and CHA₂DS₂-VASc scales (ESC, 2010; 2012). Estimation model according to these scales is based on point system where 2 points are awarded for a stroke in anamnesis or transient ischemic attack, age >75 years and 1 point for the presence of AH, diabetes mellitus, heart failure, vascular disease, female gender. According to CHADS₂ and CHA₂DS₂-VASc scale 0 point was classified as low risk, 1-2 points - as moderate risk, and >2 points - as high risk of thromboembolism [5].

In addition to the basic general clinical investigation of the patient weight, height, BMI, waist circumference were measured.

To characterize the state of coagulation part of hemostasis parameters plasma fibrinogen concentration was determined gravimetric method (RA Rutberg, 1961); Ptl by the method of AJ Quick (1935); SFMC by orthophenantroline test using kit "Technology-Standard" (Russia). The plasma D-dimers concentration was determined by immunoenzyme method using a kit of «D-dimer Latex Agglutination Kit» company (Dialab, Austria).

Platelet link of hemostasis parameters evaluated in terms of PAA through the device aggregometer AR 2110 "Solar" (Belarus) using adenosine diphosphate (ADP) 2.5 mmol/l. Registration of

aggregatogramme allows to get quantitative measures: the degree of aggregation (%), the rate of aggregation (%/s), aggregation time (s), platelet count (thousands/ml) and vWF (%).

Statistical analysis of the results carried out using the software package «Statistika for Windows 7.0» (Statsoft, USA).

3. Results and Discussion

Basal BP levels were ranged $140/90 \pm 10/7$ mm Hg. By clinic and ECG symptoms AF permanent form was diagnosed in all cases. It is known that MS is characterized by the presence of AO or overweight [1]. Among our patients in 13 (19.00%) cases overweight with increasing waist circumference >102 cm in men and >88 cm in women were found. Abdominal obesity with increasing BMI over 30 kg/m^2 was found in 57 (81.00%) cases. Among them in 32 (56.00%) cases II degree obesity with BMI equal to $34.90 \pm 3.92 \text{ kg/m}^2$ and in 25 (44.00%) cases III degree obesity with BMI equal to $43.41 \pm 2.25 \text{ kg/m}^2$ were diagnosed.

Since all patients MS was diagnosed, so low risk for thromboembolism according to CHADS₂ and CHA₂DS₂-VASc scales was not found. In 52 (74.29%) cases moderate risk and in 18 (25.71%) high risk of tromboembolism were revealed.

Subendothelium containing collagen significantly affects on hemostasis. Owing to dilatation, overdistension, degenerative changes of endocardium at AF subendothelium is bared in contact and blood coagulation activity. Abnormal physical or biochemical integrity of the endothelial area leads to the transformation of athrombogenic endocardium with platelet aggregation and additional portions of the thrombin formation [1].

Indicators of coagulation ability of blood proved controversial in patients with AF depending on the availability of obesity. In patients with overweight and with obesity PtI levels were increased by 10.41% and 11.95% accordingly vs. the control group ($p < 0.05$) (Table 1).

It is known that under the thrombin action a polymerous fibrin of soluble plasma proteins fibrinogen is formed. The final product of the process blood clotting is fibrin, which is also a

substrate for plasmin – the main enzyme of fibrinolysis [1]. Increased levels of fibrinogen, fibrin and its degradation products SFMC and D-dimer are regarded as activation status of coagulation blood system and fibrinolysis [4].

The levels of fibrinogen in patients with AF with overweight and obesity was significantly higher by 61.51% and 78.28% vs. the control group ($p < 0.05$). Moreover, in 12 (21.05%) patients with obesity III degree increasing fibrinogen level reached >8 g/L. Therefore, upon availability of permanent forms of AF and severe obesity a hypercoagulable state is formed.

It is proved that the rapid increase in the concentration of thrombin leads to activation of fibrinolysis and fibrinogenolysis, resulting in accumulation of FDP including SFMC and D-dimers in the blood flow [1, 4, 6].

Accumulation of SFMC >4 mg/ml was found in 9 (69.23%) cases in patients with overweight and in 45 (78.94%) cases under obesity. Moreover, the SFMC levels were higher by 72.36% and 38.68% in patients with overweight and obesity accordingly vs. the control group ($p < 0.05$).

It is known that high levels of circulating D-dimer indicates the fibrinolytic activity of blood which occurs after a previous activation of coagulation hemostasis parameters and fibrin formation. So, it can be a sign of hypercoagulability [4]. Plasma D-dimer levels >200 ng/mL were detected in 5 (38.46%) and 18 (31.58%) cases in patients with overweight and obesity accordingly vs. the control group ($p < 0.05$). Accumulation of D-dimers is more observed in patients with obesity III grade, which may indicate the activation of thrombosis in patients with AF on the background of severe obesity.

Equally important in the blood flow development changes in microvessels is the functional state of platelets. Although the mechanical properties of platelets due to their small size have little effect on the state of the microcirculation, PAA and their sensitivity to proreagents can have a significant impact on blood flow state [1, 6]. This can be explained by the fact that platelet aggregates in vessels hardly dissolve and reduce the blood flow through the capillary occlusion

and subsequent activation of the coagulation process [3, 6].

When studying ADP-induced platelet aggregation disturbances of disaggregation we found in 4 (30.76%) and 23(40.35%) cases among AF patients with overweight and obesity accordingly. We found shortening the aggregation start, increasing the degree and rate of aggregation. Established, the reduction of the aggregation time by 1.63 and 1.75 times in patients with overweight and obesity vs. the control ($p<0.05$) was compared. In patients with overweight degree and rate of aggregation were increased by 12.27% and 13.48% ($p<0.05$). Degree and rate of aggregation were higher than the rate in the control by 13.96% and 17.30% respectively in patients with permanent form of AF and obesity characterized by increased levels of PAA with shortening the aggregation start rate compared to patients with overweight and control group. Modern studies [2, 5] proved that at atherosclerotic changes in the coronary arteries the greatest role in PAA plays vWF. It allowed to consider the

vWF along with increased concentration of fibrinogen as a primary predictor of a hypercoagulable state, and thus the destabilization of cardiovascular system (coronary heart disease, AF, AH) [6]. In patients with AF and MS we found a significant increasing of vWF rate by 25.30% and 27.52% compared with the rate in the control ($p<0.05$) that is consonant with the literature data [2]. Although the exact mechanism of increasing the vWF levels at AF is not completely clarified [2].

Despite the activation of hemostasis aggregation link the significant changes in the number of platelets in the blood of examined patients were not found ($p>0.05$).

The patients with AF and MS have disorders of platelet and coagulation hemostasis parameters. In particular, high PAA, increase SFMC, fibrinogen and D-dimer should be regarded as a marker of atherothrombogenicity and thrombinemia [1, 3, 4, 6], which is a high risk factor for cardio-vascular events.

Table 1: Characteristic of coagulation and platelet hemostasis parameters in patients with permanent form atrial fibrillation and metabolic syndrome

Parameter, unit of measure	Protrombin index, %	Fibrinogen, g/L	SFMC, mg/ml	D - dimer, ng/ml	Aggregation time, s	The rate of aggregation, %/s	The degree of aggregation, %	Platelet count, thousands/ml	von Willebrand factor, %
Control, n=20	98.11±3.68	3.04±0.52	3.80±0.8	105±2.02	15.60±1.93	14.18±0.50	23.06±0.76	284.21±8.32	194.32±5.21
Patients with AF and overweight (n=13)	108.32±1.31 $p<0.05$	4.91±0.54 $p<0.05$	5.27±0.92 $p<0.05$	268.6±10.41 $p<0.05$	9.57±1.49 $p<0.05$	15.92±0.73 $p<0.05$	26.17±0.54 $p<0.05$	280.84±7.32 $p<0.05$	243.6±1.62 $p<0.05$
Patients with AF and AO (n=57)	109.83±2.26 $p<0.05$	5.42±0.84 $p<0.05$	6.55±0.76 $p<0.05$	285.3±11.72 $p<0.05$	8.92±1.24 $p<0.05$	16.16±0.36 $p<0.05$	27.05±0.54 $p<0.05$	282.73±5.47 $p<0.05$	247.8±2.35 $p<0.05$

Note: $p <$ probability of difference compared with the control;

1. Assessment of hemostasis disorders severity solely on the basis of protrombin index and fibrinogen is insufficient because it does not take into account other parameters of coagulation and platelet hemostasis, in particular, the levels of circulating SFMC, D-dimers and PAA parameters according to the aggregation start parameters, the

degree and rate of aggregation and vWF that are predictors of acute cardio-vascular events and the definition of a high risk of thromboembolism by CHADS₂ and CHA₂DS₂-VASc scales.

2. Prothrombotic disorders of coagulation hemostasis links are manifested by increased levels of Ptl, fibrinogen and FDP.

3. Prothrombotic disorders of platelet hemostasis parameters are manifested by increased PAA with shortening the start of aggregation, increasing the degree and rate of aggregation and vWF in patients with AF and MS.

Northwick Park Heart Study // T.W. Meade, V. Ruddock, Y. Stirling / Lancet. 1993. 342: 1076 – 1079.

6. Perspectives for further Research

Further scientific research should direct on the study coagulation and platelet hemostasis parameters changes in hypertensives with permanent form of AF background of MS under complex treatment.

7. References

1. Alessi M.C. Metabolic syndrome, haemostasis and thrombosis. *Thromb. Haemost.* 2008; 99: 995 – 1000.
2. Atrial fibrillation in heart failure is associated with an increased risk of death only in patients with ischaemic heart disease / J. Raunso, O.D. Pedersen, H. Dominguez, M.L. Hansen, J.E. Moller // *European Journal of Heart Failure.* 2010; 12; 7: 692 – 697.
3. Association of fibrin monomer polymerization function, cerebrovascular risk factors and ischemic cerebrovascular disease in old people / M. Hong., W. Wei, H. Li // *J. Huazhong. Univ. Sci. Technolog. Med. Sci.* 2003. 23: 131 – 133.
4. Characteristics and prognostic impact of plasma fibrin monomer (soluble fibrin) in patients with coronary artery disease / Hetland O., Knudsen A., Dickstein K. // *Blood Coagul. Fibrinolysis.* 2002. 13. 4: 301 – 308.
5. Guidelines for the management of atrial fibrillation. The task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) / A.J. Camm, P. Kichhof, G.Y.H. Lip // *European Heart Journal.* 2010. 31: 2369-2429.
6. Pathophysiology of the proatherothrombotic state in the metabolic syndrome / I. Palomo, R. Moore-Carrasco, M. Alarcon // *Front. Biosci. (Schol. Ed).* 2010. 2: 194 – 208.
7. Fibrinolytic activity, clotting factors and long-term incidence of ischemic heart disease in