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Efficiency of Thrombodynamics for Analysis of Hemostasis in Case of Transitory Ischemic Attack after Radio-frequency Ablation in a Patient with Paroxysmal Atrial Fibrillation

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Abstract Efficiency of thrombodynamics for analysis of hemostasis in case of transitory ischemic attack after radio-frequency ablation in a patient with paroxysmal atrial fibrillation.

Keywords: *radio-frequency ablation, rivaroxaban, transitory ischemic attack, thrombodynamics*

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1. Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmia. Within the population, the frequency thereof reaches 1-2%. Some of patients suffering from atrial fibrillation have painful symptoms aggravating the quality of life. This requires the modern medicine to develop and improve an antiarrhythmia strategy of treatment for such patients. [1]. One of the most progressive methods for treatment of AF is catheter treatment based on elimination of the potentially arrhythmogenic sites of the left atrium (in the majority of cases, this means isolation of the muscular sleeves of pulmonary veins from the left atrium myocardium) with physical action of the radio-frequency energy or cold. The advantages of this method are as follows: low invasiveness, good tolerability, short period in hospital, absence of rehabilitation necessity. At the same time, catheter-based treatment can cause thromboembolic (TE) complications: this must be taken into account when selecting patients for such kind of treatment as well as during the intra- and postsurgery treatment of such patients. The thrombogenic risk of catheter treatment can be explained by a number of reasons such as: injury of endothelium of the left atrium and liberation of tissue factor (TF), which activates the coagulation system; transseptal positioning of electrodes; effect of stunning of the left atrium with absence of mechanical systole thereof [2].

The risk of appearance of cardiovascular problems and TE complications during the catheter procedure requires prescription of antiplatelet or anticoagulant therapy. Such risks are usually assessed using the scores such as SCORE and CHA2DS2-VASc, correspondingly [2,3,4]. According to the data from different sources, the risk of TE complication development after radio-frequency ablation (RFA) may reach from 0.94% [5] to 7.4% or even 37% in case of RFA involving the use of a circular catheter PVAC [3].

This defines the key principle of carrying out of such procedures: all patients under catheter treatment must receive anticoagulant therapy during the procedure and up to 2 months after surgery, independently of TE complication risks [1,2].

In this study, the novel test of thrombodynamics was used for assessment of the hemostasis in the patient with AF along with the standard coagulation assays. This test is based on registration of spatial clot growth rate from the surface with an immobilized activator – TF. It was demonstrated that the absence of thrombotic complication risks, estimated according to the commonly used scores and the conventional coagulation tests, cannot provide a guarantee for absence of such complications. At the same time, the TD test can be used as a prognostic tool for analysis of hemostasis and monitoring of the anticoagulant therapy in such patients.

2. Materials and Methods

Patient. A male, 63 years old, admitted to the hospital of the National Research Center for Prophylactic Medicine (Ministry of Health, Moscow, Russia). Admission

diagnosis: arrhythmia – paroxysmal atrial fibrillation, frequency of episodes from 1 to 2 times per month.

Materials. An automated coagulometer ACL 8/9/10000 System (Instrumentation Laboratory, USA) with the corresponding reagents of this manufacturer were used to measure activated partial thromboplastin time (APTT), prothrombin time (PT) which was also recalculated as the International Normalized Ratio (INR), and D-dimer levels. Thrombodynamics was measured using the device «Thrombodynamics analyzer T-2» produced by HemaCore (HemaCore LLC, Moscow, Russia), with special kit of reagents manufactured by this company.

Collection of blood and preparation of samples. Blood was collected in 9 ml vacuum tubes (Vacuette) with 3,2 % (0.109 M) sodium citrate solution (volume ratio blood/sodium citrate = 9:1). Blood was centrifuged for 15 min at 1600g to obtain platelet poor plasma (PPP); a part of PPP was then centrifuged for 5 min at 10000g to obtain platelet-free plasma (PFP) [6].

Clotting tests and concentration of D-dimers. APTT, PT and D-dimers were measured in samples of PPP according to the corresponding guidelines by the manufacturer. The reference values proposed by the manufacturer were used as normal values for these tests.

Thrombodynamics. The PFP sample (120 µl) was first incubated for 15 min at 37°C with a contact activation inhibitor. Then plasma was recalcified, put into the measurement cuvette, and coagulation was activated by introducing into the cuvette of an insert-activator with immobilized TF. The video images of a growing clot were recorded for 30 min, once in every 6 sec (Figure 1A). Spatial profiles of light scattering of the sample in different moments after activation were built based on these images (Figure 1B).

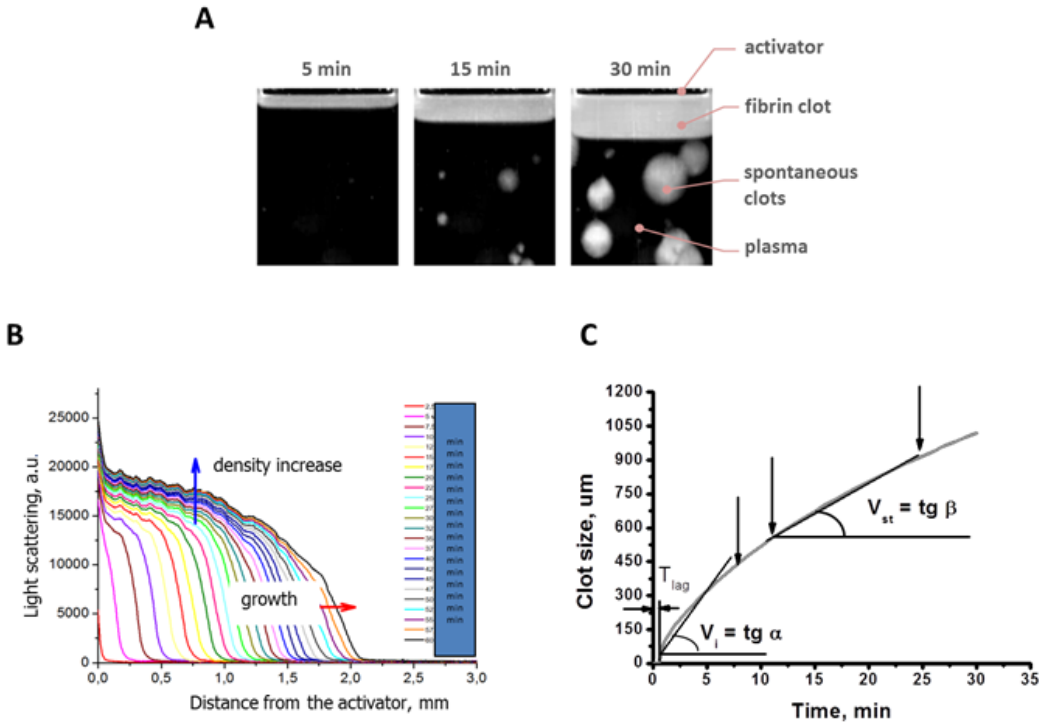

Figure 1. A principle of the thrombodynamics test work, and calculation of TD parameters. (A) – typical images of clots in plasma samples at different moments (5, 15 and 30 min) after coagulation activation. (B) – profiles of light scattering built on the base of a series of consequent images of a growing clot. (C) –Dependence of the clot size on time. The following measured parameters are registered: Tlag – delay of clot growth, Vi (tg α) – initial clot growth rate, Vst (tg β) – stationary clot growth rate

Clot size at each moment was calculated as a coordinate position of the corresponding profile at a point where the intensity of light scattering was 50% of the maximum (Figure 1B) [7,8,9]. The parameters of TD test were as follows: delay in clot growth (Tlag) – time between the contact of plasma with the activator and the start of clot formation; initial (Vi) and stationary (Vst) rates of clot growth representing the slopes of tangents to the curve clot size/time on time intervals 2-6 min and 15-25 min after Tlag, correspondingly (Figure 1C); clot size at 30 min after clotting activation (CS). Another parameter used in TD is formation of spontaneous clots. These are the clots formed within the volume of the sample and not connected directly with the activator surface. Spontaneous coagulation is absent is case of normal coagulation but present in some pathologies related with development of a hypercoagulation state.

For parameters of the thrombodynamics test, reference values defined by the manufacturer were used (see Table 1).

3. Description of the Clinical Case

Admission of the patient

Patient is 63 years old, suffers from paroxysmal AF for about 3 years, frequency of episodes - 1-2 per month, episodes are not longer than 3 hours with spontaneous sinus rhythm restoration.

The cardiologic assessment revealed the following:

- Negative hereditary history;
- Absence of medical history data confirming the presence of arterial hypertension;
- No clinical signs of ischemic heart disease, negative treadmill test;

- According to the results of echocardiography (ECHO-CG), no signs of structural pathology of the myocardium, including the valves; dimension of the left atrium along the longer axis - 3.8 cm; left atrium ejection fraction - 63% (according to Simpson);

- Laboratory analyses revealed no pathological changes in the general and biochemical blood analyses; no thyroid or carbohydrate metabolism dysfunction (thyroid stimulating hormone (TSH) 1.8 IU/l (reference values 0.4-4.0 IU/l), glucose of the venous blood in the fasted state 4.8 mmol/l (reference values 3.9-6.4 mmol/l));

- Conventional coagulation tests (APTT, PT, INR, D-dimers) – normal coagulation.

Taking into consideration the patient's arrhythmia, the risk of thromboembolic complications was assessed according to the CHA2DS2-VASc score: this risk was found to be of 0 points which did not require prescription of anticoagulant therapy. The risk of cardiovascular complications according to SCORE was of 3-4% which also did not require prescription of antiplatelet therapy. Nevertheless, the patient showed bad personal tolerance of the episodes: weakness, feeling of rapid arrhythmic heartbeat leading to restriction of physical activity – grade II-III according to the scale of the European Heart Rhythm Association (EHRA). This is why the adjustment of the antiarrhythmia therapy was executed in the outpatient setting. The following medications were tested: sotalol in a dose of up to 160 mg/24h, allapinin in a dose of up to 75 mg/24h, bisoprolol 5 mg/24h. Due to impossibility to reach a clinically significant efficiency, the RFA procedure was recommended. Taking into account the high risk of TE complications within 2-3 months after RFA and the absence of experience of administration of the anticoagulants, the patient started taking rivaroxaban – an anticoagulant, factor Xa inhibitor – in a dose of 20 mg once a day, with food, 14 days before the RFA procedure. While testing the medication, no hemorrhagic complications were registered; the assessment of thrombotic complications was not executed.

The administration of rivaroxaban was stopped 24 hours before RFA; the patient was put on conversion therapy with enoxaparin (1 mg/kg twice a day). Before RFA (16 hours before the procedure), the administration of enoxaparin was also stopped.

The parameters of hemostasis obtained before RFA (12 hours after withdrawal of all anticoagulants) are given in Table 1. The standard tests showed normal coagulation. The thrombodynamics test revealed slight tendency to hypercoagulation, Vst was exceeding the reference values – 29.5 μm/min.

Table 1. Parameters of patient's hemostasis monitored by different tests

Parameter	Reference values	Before RFA*)	After RFA	
			3 days	14 days
Standard tests				
APTT, sec	24.3-35	25.8	26.3	29.7
PT, sec	9.1-12.1	11	11.2	13.3
INR	0.8-1.2	0.95	0.97	1.14
D-dimers, ng/ml	0-255	134	**1370**	252
Thrombodynamics				
Tlag, min	0.6-1.5	0.9	0.8	1.1
Vi, μm/min	38-56	52.6	**64.6**	**58**
Vst, μm/min	20-29	**29.5**	**44.7**	**30.6**
CS, μm	800-1200	1168	**1592**	**1235**
Spontaneous clots**)	-	-	+	-

*) RFA – radio-frequency ablation

***) Absence (-) or presence (+) of spontaneous clots formation.

RFA procedure

Within the frame of presurgery assessment, a multi-layer spiral contrast-enhanced computer tomography (CAT) of the myocardium was executed: according to it, the volume of the left atrium was of 75 ml; no structural pathology of the myocardium was detected.

The RFA procedure was executed on the background of administration of the unfractionated heparin (UFH). In total, 6500 IU UFH was administered during the procedure. APTT during RFA was of 300-350 sec. The procedure was executed using a non-fluoroscopic mapping (CARTO XP Biosense Webster), a diagnostic electrode Lasso Biosense Webster, and an irrigation ablation electrode NaviStar Biosense Webster. No technical complications were encountered: common femoral vein and subclavian vein puncturing were without complications; interatrial septum puncturing under X-ray control was without complications; positioning of the electrodes and application of the radio-frequency effect were also without complications.

Early postsurgery period

The therapy with rivaroxaban was resumed 4 h after RFA.

After 24 hours, the patient presented disposable claims for dizziness and vision disorder. Taking into account the assumption of thromboembolic complications, a magnetic resonance imaging (MRI) of his brain was executed. No focal lesions of the brain were detected. Repeated ECHO CG showed absence of thrombosis of the heart cavities.

However, 5 days after the procedure, the patient resumed his claims for increased dizziness and vision disorder. After examination by a neurologist, the following diagnosis was established: acute cerebrovascular insufficiency/ transitory ischemic attack (ACVI/TIA) within the vertebrobasilar system in spite of rivaroxaban treatment.

After nootropic therapy (mexidol, pyracetam) for 3 days, a repeated medical examination by the neurologist was executed. The neurological symptoms regressed completely leaving no residual neurological impairment. The repeated MRI showed no dynamics of the TIA. The patient was still taking rivaroxaban (20 mg once a day).

The hemostasiological parameters for the early postsurgery period (3 days after RFA) are given in Table 1. The standard tests showed normal coagulation and increase of D-dimer's concentration (up to 1370 ng/ml). The parameters of TD showed massive hypercoagulation with foci of spontaneous clot formation within the sample volume (Figure 2).

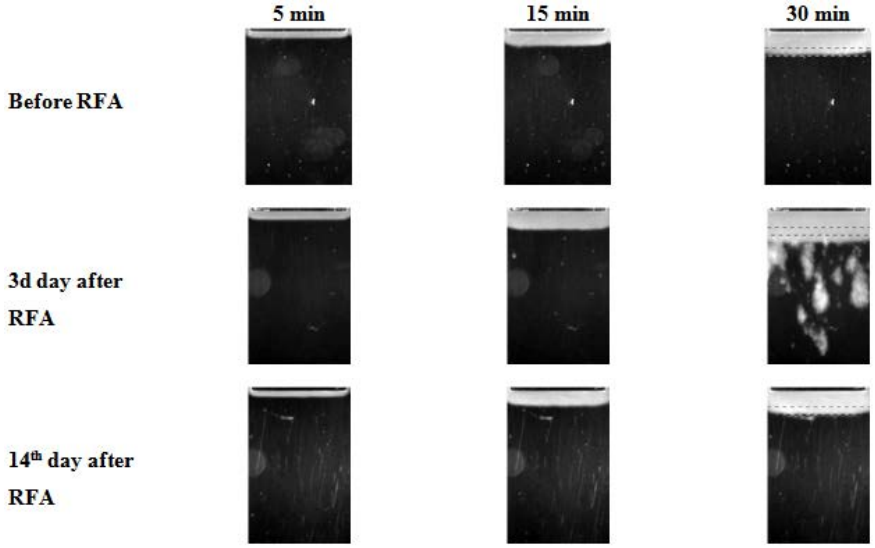

Figure 2. Images of patient clot growth before RFA, as well as on the 3[d] and 14[th] day after the procedure

Control within the postponed postsurgery period after the RFA procedure

The parameters of hemostasis obtained 14 days after RFA are given in Table 1. The standard coagulologic tests showed normal coagulation. The parameters of TD showed hypercoagulation and absence of spontaneous clot formation.

Experimental images showing clot growth within the TD test before RFA, as well as 3 and 14 days after the procedure are given in Figure 2.

4. Discussion

In this paper, the state of the patient with paroxysmal AF was investigated before and after the radio-frequency ablation procedure using standard instrumental and coagulologic methods as well as a new test for analysis of hemostasis, the TD test. The patient received an anticoagulant medication (rivaroxaban) before and after RFA. This medication is a specific inhibitor of factor Xa of the blood coagulation inhibiting not only the free factor Xa, but also the factor Xa being a part of a procoagulant prothrombinase complex [10]. Nevertheless, 3 days after RFA, the patient developed a transitory ischemic attack.

The values of different hemostasis parameters observed during investigation were ambiguous. Thus, APTT, PT and INR always registered normal coagulation in spite of alteration of the patient clinical state. On the day when the patient developed an ischemic attack, the concentration of D-dimers was increased but it returned to normal level 14 days after RFA (Table 1). None of these tests predicted a possible risk of development for TE complication before RFA. The same assessment was made using the commonly used scores CHA2DS2-VASc and SCORE.

At the same time, even before the procedure, the TD test demonstrated the hemostasis tendency to hypercoagulation. This hypercoagulation increased considerably 3 days after RFA, exactly when TIA started in the vertebrobasilar system of the brain. Thus, the TD test showed (before RFA) a risk of possible TE complication and confirmed development of such complication in the patient (after RFA). The images of clot growth (Figure 2) showed presence of spontaneous clotting 3 days after the procedure, giving evidence of high hypercoagulation. The hypercoagulation persisted even 14 days after procedure in spite of rivaroxaban administration: this means that the risk of repeated TE complications still existed.

This clinical case confirmed that the absence of indications of TE complications risk estimated by the scores CHA2DS2-VASc and SCORE, as well as according to the data of conventional coagulation tests cannot guarantee the absence of such complications.

The cumulative analysis of the results showed that the TD test allowed not only adequate estimate the risk of thrombosis in a patient before RFA (in spite of total absence of data confirming the possibility of such risk obtained from all other tests and assessment scales); but unlike APTT, PT or INR, it also revealed presence of pronounced hypercoagulation after RFA, in situation of development of a clinically significant thromboembolic complication. Thus, the results of the TD test correspond to the clinical presentation in a patient with AF; consequently, the following conclusion can be made: TD test can be useful in analysis of the coagulation status in such patients.

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