Coagulation alterations in treating arrhythmias with radiofrequency ablation

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Key words: *platelet aggregation; fibrinogen; D-dimer; radiofrequency ablation.*

Summary. *Objective. To determine an influence of radiofrequency ablation on changes in coagulation system.*

Material and methods. We investigated 30 patients with cardiac arrhythmias. Platelet aggregation, fibrinogen and D-dimer level were analyzed before, right after, 24 and 72 h after radiofrequency ablation. Platelet aggregation was explored in whole blood and platelet-rich plasma using adenosine diphosphate (ADP), epinephrine, and collagen for induction.

Results. Platelet aggregation induced by ADP and collagen in whole blood plasma increased significantly (P<0.01) (by 45% and 43%, respectively) in 24 h after radiofrequency ablation and remained increased in 72 h after radiofrequency ablation (by 11% and 35%, respectively) (P<0.01) as compared with baseline results. Spontaneous aggregation of platelet-rich plasma as well as ADP- and collagen-induced platelet aggregation tended to decrease right after radiofrequency ablation. Epinephrine-induced platelet aggregation significantly decreased by 17.5% after radiofrequency ablation (P<0.01) and started to increase in 24 h after radiofrequency ablation. In 72 h after radiofrequency ablation, platelet aggregation induced by different agonists increased by 7–45% significantly (P<0.05), and values were higher than baseline ones. Fibrinogen level after radiofrequency ablation did not differ from that of the baseline (3.08±0.7 g/L), but D-dimer level increased significantly (from 0.39±0.3 to 1.29±2.4 mg/L, P<0.01). In 24 h after radiofrequency ablation, an increase in fibrinogen level and a decrease in D-dimer level were found. Fibrinogen level increased to 3.32±0.6 g/L significantly in 72 h after radiofrequency ablation (P<0.05). Meanwhile, D-dimer concentration decreased to 0.78±0.8 mg/L, but it was still significantly higher (P<0.05) than the baseline value.

Conclusion. Despite diminished platelet aggregation and increased D-dimer level right after radiofrequency ablation, a risk of thrombosis increased in the next few days after radiofrequency ablation.

Introduction

Radiofrequency ablation (RFA) is a relatively safe and effective treatment of cardiac arrhythmias. However, post-RFA complications were reported in less than 0.2% of children (1) and in 0.6–10.3% of adults (2–7), depending on heart chamber where RFA was applied and arrhythmias type. Post-RFA thromboembolic complications are divided into early caused by local hemostatic disorder in the ablation area and the late ones due to endothelial damage (2). An area of ablation is the zone of active impact on coagulation system. Constant local platelet activation ensues as long as the affected place of the endocardium has not been completely regenerated despite the relatively small size of the area (8).

The need of antiplatelet medications and anticoagulants for the prevention of thromboembolic complications remains a matter of discussions treating such arrhythmias as supraventricular tachycardia, extrasystole. Only few comprehensive clinical studies have been carried out.

In our previous study (9), we found that platelet aggregation (PA) right after RFA significantly decreased while in 24 h after RFA it increased again.

The objective of this study was to determine how RFA influences alterations in other links of coagulation system in early post-RFA period as well as in prolonged period, i.e. 72 h after RFA. For this purpose, PA, fibrinogen and D-dimer levels were investigated.

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Methods

Study patients

Studies of human subjects were carried out according to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients, and the study was approved by the Regional Bioethics Committee of Kaunas University of Medicine (December 21, 2004, No. 150/2004).

Thirty consecutive patients with cardiac arrhythmias undergoing RFA procedure (atrial flutter, supraventricular tachycardia, and extrasystole) were included into the study. Clinical characteristics of all patients are summarized in Table 1.

Table 1. **Clinical characteristics of patients**

Number of patients	30
Sex Female Male	 15 15
Age, years Female Male	 52±13 45±19
Using aspirin	5
Using LMWH	4
Mean total energy of RFA, J	11 968±10 250
Mean coagulation duration of RFA, min	6.48±6.29
Cardiac arrhythmias: Supraventricular tachycardia Atrial flutter Extrasystole	 11 14 5

LMWH – low-molecular-weight heparin;
RFA – radiofrequency ablation.

RFA procedure

Through the puncture of the right femoral vein or artery using the standard Seldinger method, multicontact electrodes were inserted into the heart and directed to the certain cardiac areas with an accuracy of 1–2 mm. Electric activity and the spread of the impulse were registered in the intracardiac ECG by the computer system (PRUCKA Engineering, Inc. Cardiolab 4.0; General Electrics; USA). The arrhythmogenic substrate was destroyed by using radiofrequency energy (500 kHz, 30–60 W), which produces temperature of 50–70˚C and hence irreversibly coagulates a tissue area of 2 to 4 mm^3 at the site of contact between the special destructive electrode-catheter and endocardium. Commonly treating supraventricular tachycardia and extrasystole, a catheter 4 mm in diameter is used, whereas atrial flutter needs an 8-mm-diameter catheter.

Assay scheme

Patients had no meal and did not smoke for 12–16 hours before the RFA. Patients who had been using aspirin (the mean daily dose of 150 mg) discontinued its usage 3 to 4 days prior to the procedure, while for those who had been using warfarin (INR within the range of 2 to 3), it was replaced by low-molecular-weight heparin (LMWH 7500 IU, two times per day), and the procedure was performed at INR of ≤1.5.

Blood samples of all patients were analyzed four times: before RFA, after RFA, 24 hours and 72 hours after RFA.

Preparation of blood

For testing platelet aggregation, fibrinogen and D-dimer levels, the blood was drawn from the antebrachial vein into 4.5 mL vacuum test tubes with 3.8% sodium citrate. Platelet-rich plasma (PRP) was separated from red blood cells by blood centrifuging at 111*g* (1000 rpm) for 15 min at room temperature. Platelet-poor plasma was obtained by further centrifuging the rest of the blood at 1006*g* (3000 rpm) for 30 min. It was used for evaluation of fibrinogen and D-dimer levels as well as for platelet aggregation control.

Whole blood platelet aggregation (WBA; venous blood platelet aggregation) was analyzed with a whole blood impedance aggregometer (WBA, CHRONO-LOG, USA), which measures platelet aggregation by the variation in blood impedance after six minutes, expressed in ohms (Ω). ADP (10 μmol/L) and collagen (2 μg/mL) were used for the induction of platelet aggregation (10).

Platelet aggregation of platelet-rich plasma was analyzed using an aggregometer (CHRONO-LOG, USA), which measured, in relative percentage, the variation in optical density in platelet plasma in the process of aggregation using the classical Born method (11). To induce aggregation, ADP (3.8 μmol/L), epinephrine (4.5 μmol/L), and collagen (2 μg/mL) were used. Spontaneous platelet aggregation was assessed without any inductor stimulating the aggregation.

Fibrinogen concentration (g/L) was estimated by the clotting method of Clauss (12) using a semiautomatic analyzer ST ART 4 with a Fibri-Prest Automate 2 reagent (Diagnostica Stago, France).

D-dimer level (mg/L) was assessed by the immunoturbidimetric assay (13) using an automatic coagu-

lation analyzer STA COMPACT with a STA-Liatest D-Di reagent (Diagnostica Stago, France).

Statistical analysis

Statistical calculations were carried out using Microsoft Excel and SPSS 12.0 for Windows statistical packages. Results are presented as mean ± standard deviation. Student's *t* test for dependent variables was used for comparison of data.

Results

All patients had an uneventful RFA procedure; none of them developed thromboembolic complications after the procedure during the hospital stay. The obtained data of RFA impact on platelet aggregation both in platelet-rich plasma and whole blood are presented in Table 2.

In whole blood, platelet aggregation induced by ADP and collagen significantly increased 24 h after RFA (by 45% and 43%, respectively; $P<0.01$) and remained increased at 72 h after RFA (by 11% [NS] and 35% [$P<0.01$]) as compared with the baseline results.

Spontaneous aggregation of platelet-rich plasma as well as platelet aggregation induced by ADP and collagen tended to decrease by 9%, 4.7%, and 6.8%, respectively, right after RFA as compared with the baseline values. Epinephrine-induced platelet aggregation significantly decreased by 17.5% right after RFA ($P<0.01$, *t* test for dependent variables). In 24 h after RFA, we observed an increasing level of platelet aggregation induced by different agonists. In 72 h after RFA, we found significantly increased platelet aggregation: spontaneous PA by 45% ($P<0.001$); induced by ADP, 7% ($P<0.05$); by collagen, 12.3% ($P<0.01$); and by epinephrine, 29.4% ($P=0.001$) comparing with post-RFA levels, and they were higher than the baseline values.

We also studied the influence of RFA on changes of fibrinogen and D-dimer concentration in platelet-poor plasma. The results are presented in Fig.

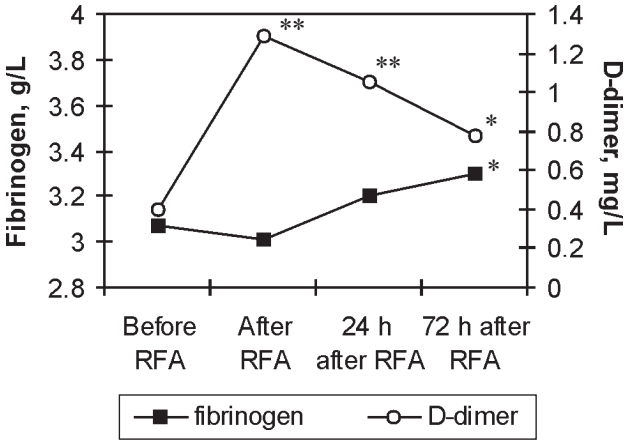

Fig. **Influence of radiofrequency ablation (RFA) on fibrinogen and D-dimer levels**

*$P<0.05$, **$P<0.01$ comparing with pre-RFA values (*t* test for dependent variables).

Fibrinogen level did not differ from that of the baseline (3.08±0.7 g/L to 3.02±0.7 g/L) right after RFA, but D-dimer concentration was increased significantly (0.39±0.3 mg/L to 1.29±2.4 mg/L, $P<0.01$). After 24 h following RFA, we observed increased fibrinogen level and decreased D-dimer level ($P<0.01$). In 72 h after RFA, a significant increase in fibrinogen level to 3.32±0.6 g/L was seen ($P<0.05$ comparing with the results of baseline and post-RFA). Simultaneously, D-dimer concentration further decreased to 0.78±0.8 mg/L, but it was still significantly higher ($P<0.05$) as compared with the baseline value.

Discussion

In the normal body state or in the presence of minor tissue injury, a declining hemostatic physiologic function does not manifest clinically, and dynamic balance is preserved between activating and suppressing

Table 2. **Influence of radiofrequency ablation on platelet aggregation**

Platelet aggregation (inductor)	Before RFA	After RFA	24 h after RFA	72 h after RFA
WB (ADP)	4.7±2.9	4.24±3.6	6.8±4.1**	5.2±4.2
WB (collagen)	10.6±5.9	11.1±3.85	15.2±5.3**	14.3±4.7**
PRP (ADP)	75.1±11.7	71.6±15.7	74.6±13.8	$76.5±11.7^{+}$
PRP (epinephrine)	68.0±19.4	56.1±27.2**	$66.3±20.0^{+}$	$72.6±17.5*^{+++}$
PRP (collagen)	75.3±17.1	70.2±21.1*	72.4±20.8	$78.8±11.4^{++}$
Spontaneous PA	5.24±2.9	4.76±3.4	$6.8±4.7*^{++}$	$6.9±4.1**^{+++}$

WB – whole blood; PRP – platelet-rich plasma; PA – platelet aggregation; RFA – radiofrequency ablation.
*$P<0.05$; **$P<0.01$ comparing with results pre-RFA, $^{+}P<0.05$, $^{++}P<0.01$, $^{+++}P<0.001$ comparing with PA after RFA (*t* test for dependent variables).

hemostatic mechanisms. Antithrombogenic properties of blood vessels (factors excreted from endothelium, increased blood flow, etc.) inhibit platelet adhesion to the intact wall. Therefore, failure to detect thrombi in the ablation area might be not only due to minor injuries, but also due to increased blood flow through that area (14), though a spontaneous post-RFA echogenicity during the procedure of RFA has been documented by transesophageal echocardioscopy (15–17). Otherwise thrombus formation on the transseptal catheter sheath while performing RFA in the left atrium (LA) for treating atrial fibrillation (AF) or LA macroreentrant tachycardia was observed in 10.3% of all patients despite the treatment with anticoagulants had been applied (6).

Our results demonstrate that the spontaneous and ADP-, epinephrine-, and collagen- induced PA decreased after RFA comparing with pre-RFA results. PA was increased 24 h after RFA and exceeded initial values 72 h after RFA. Significant maximal values of PA in WB were found at 24 h after RFA, and it slightly decreased in 72 h after RFA. However, it remained higher than pre-RFA value.

The increases in PA induced by ADP, collagen, and thromboxane B_2 in blood taken from the ascending aorta and pulmonary artery after 10 min following RFA were reported, and these parameters returned to the baseline levels after 30 min following RFA (18). It shows that strong antithrombotic mechanisms integrate, and their outcomes might be observed later than 30 min after and also more distally from the area of RFA procedure where the information about injury is transmitted by fast blood flow. Our data confirm it by demonstrating the decrease in PA after RFA. Other authors note that the increased activity of platelets remained for 48 h after RFA; however, this increase was insignificant (19). There are also data about significantly increased spontaneous aggregation after RFA, which returned to the baseline level 24 h after RFA (3).

The increase of von Willebrand factor (vWf) as the marker of endothelial damage, which actively assists in processes of platelet aggregation and adhesion, was found after RFA (20) and 24 h after RFA (21). As other data imply, there was no significant difference in the levels of plasma endothelin and vWf before and after RFA. Therefore, the authors concluded that RFA procedure did not damage the endothelium significantly. However, it might increase expression of glucoproteins of platelet membranes and thromboxane (22); thereby, platelet activation is stimulated.

Other links of coagulation system same as platelets are activated during endothelial damage by RFA, especially fibrinolysis. There are no data about influence of RFA on the changes in fibrinogen concentration. Our results demonstrated an increase in fibrinogen concentration 24 h after RFA, and it continued to rise in 72 h after RFA. A significant increase in D-dimer level in plasma after RFA represents an activation of fibrinolysis process, which continued in 24 h after RFA and subsided only in 72 h after RFA. An increase in D-dimer level represents the fact that fibrinogen level increases practically after RFA, and it cannot increase significantly in time due to activation of fibrinolysis. However, we observed an increase in fibrinogen concentration when fibrinolytic potential was exhausted after 24 h and 72 h following RFA. Other data in literature confirm such course of events. It has been found that tissue plasminogen activator (t-PA) and D-dimer levels were increasing after RFA (3, 21, 23) and in 24 h after RFA when D-dimer level achieved the greatest level (3, 21, 24). Activation of D-dimer even administering antiaggregants, aspirin or ticlopidine, 3 days before RFA (25) was increased, while using anticoagulants, D-dimer concentration was significantly lower (25, 26). Plasminogen activator inhibitor 1 (PAI-1) as an active inhibitor of fibrinolysis process was found to be decreased after RFA; however, it returned to initial level after 24 h following RFA (21).

The data in literature regarding the RFA influence on markers of hemostasis, particularly on platelet activity, are not homogeneous. The data we obtained demonstrate the intensive mobilization of antithrombotic system factors right after RFA due to the marked tissue damage; therefore, the decrease of PA was observed, but platelet activity increased in 72 h after RFA. Increasing concentration of D-dimer (which is a degradation product of fibrin and represents the activity of fibrinolytic system) right after RFA demonstrates certain activation of coagulation system, which later manifests as an increase in fibrinogen level when fibrinolytic activity decreases after several days.

Conclusion

Despite diminished platelet aggregation and increased fibrinolytic activity right after RFA, the risk of thrombosis increased in the next few days after RFA. Therefore, we consider anticoagulants or antiplatelet medications to be administered for prophylaxis of thromboembolic complications.

Krešėjimo sistemos pokyčiai gydant aritmijas radiodažnine abliacija

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Raktažodžiai: trombocitų agregacija, fibrinogenas, D-dimerai, radiodažninė abliacija.

Santrauka. *Tyrimo tikslas.* Nustatyti, kokį poveikį krešėjimo sistemai turi radiodažninė abliacija.

Medžiaga ir metodai. Ištyrėme 30 ligonių, sergančių širdies ritmo sutrikimais, kuriems atlikta radiodažninė abliacija. Trombocitų agregacijos, fibrinogeno ir D-dimerų pokyčius nustatėme prieš, iškart po procedūros, 24 val. ir 72 val. po radiodažninės abliacijos. Trombocitų agregaciją tyrėme kraujyje ir trombocitais turtingoje plazmoje, naudodami induktorius: adenozino difosfatą, adrenaliną ir kolageną.

Rezultatai. Trombocitų agregacija indukuota adenozino difosfatu ir kolagenu kraujyje reikšmingai padidėjo ($p<0,01$) (atitinkamai – 45 ir 43 proc.) 24 val. po radiodažninės abliacijos ir išliko didesnė 72 val. po jos (atitinkamai – 11 ir 35 proc. ($p<0,01$)) lyginant su pradiniais rodmenimis. Spontaninė agregacija trombocitais turtingoje plazmoje, kaip adenozino difosfatu ir kolagenu indukuota trombocitų agregacija turėjo tendenciją mažėti iškart po radiodažninės abliacijos. Adrenalinu indukuota trombocitų agregacija reikšmingai sumažėjo 17,5 proc. iškart po radiodažninės abliacijos ($p<0,01$), o praėjus 24 val. pradėjo didėti. Įvairiais induktoriais indukuota trombocitų agregacija 72 val. po radiodažninės abliacijos reikšmingai padidėjo 7–45 proc. ($p<0,05$), o apskaičiuoti duomenys buvo didesni už pradinius. Fibrinogeno koncentracija nekito po radiodažninės abliacijos (3,08±0,7 g/l), bet D-dimerų koncentracija reikšmingai padidėjo (nuo 0,39±0,3 iki 1,29±2,4 mg/l, $p<0,01$) nuo pradinės reikšmės. Po 24 val. fibrinogeno koncentracija padidėjo, o D-dimerų sumažėjo. Fibrinogeno koncentracija reikšmingai padidėjo 3,32±0,6 g/l ($p<0,05$) ir praėjus 72 val. po radiodažninės abliacijos. Tuo tarpu D-dimerų koncentracija sumažėjo iki 0,78±0,8 mg/l, bet išliko reikšmingai didesnė ($p<0,05$) už pradinę reikšmę.

Išvada. Nepaisant sumažėjusios trombocitų agregacijos ir padidėjusios D-dimerų koncentracijos, iškart po radiodažninės abliacijos trombozės rizika padidėjo.

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