# Alterations of platelet aggregation while treating cardiac arrhythmias with radiofrequency ablation

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***Key words**: platelet aggregation, radiofrequency catheter ablation.*

***Summary.** Objective. To find out if radiofrequency ablation as method of treatment of cardiac arrhythmia influences platelet aggregation and if intensity of this process depends on the number of radiofrequency ablation episodes for one patient.*

*Material and methods. We analyzed platelet aggregation before, right after and in 24 hours after radiofrequency ablation in whole blood and platelet rich plasma in 39 cases with cardiac arrhythmias. Adenosine diphosphate and adrenaline were used for aggregation induction. Three groups of patients were formed based on the number of radiofrequency ablation episodes: A – <10, B – 10–20, C – >20 for one patient.*

*Results. We detected a decrease in spontaneous, adenosine diphosphate and adrenaline induced platelet aggregation in plasma right after radiofrequency ablation, and also the same tendency was noted in adenosine diphosphate induced aggregation in whole blood. In 24 hours after radiofrequency ablation platelet aggregation tended to return to pre-radiofrequency ablation levels. Based on the number of radiofrequency ablation episodes we detected significant changes in spontaneous and adrenaline-induced aggregation in plasma. In group A adrenaline induced aggregation after radiofrequency ablation increased by 0.4%, in group B it decreased by 15.7% and in group C it decreased by 19.4% from pre-radiofrequency ablation level ($p<0.05$, between groups A and C). Spontaneous platelet aggregation after radiofrequency ablation decreased in group A 41.9%, in group B – 20.8% and in group C – 18.4% from pre-radiofrequency ablation level ($p<0.05$ between groups A and C). The greater decrease in adenosine diphosphate induced aggregation in plasma and in whole blood was detected in the group with larger number of radiofrequency ablation episodes.*

*Conclusions. This study found that platelet aggregation decreased in plasma and in whole blood after radiofrequency ablation. And this alteration was significant in groups B and C, when the number of radiofrequency ablation episodes were >10. In 24 hours platelet aggregation increased again to pre- radiofrequency ablation level.*

## Introduction

Cardiac arrhythmias (atrial fibrillation etc.) caused by thrombus in cardiac chambers are one of the main thromboembolic complications and the cause of the stroke. Prevention of embolization with antithrombotic medications in these cases is essential.

Using modern electrophysiologic test for assessment of causes of arrhythmia and detection of topography of active focus the radiofrequency ablation (RFA) became an effective and safe method of radical treatment for various arrhythmias. However, since RFA has a mechanical and thermal effect on a relatively wide area of the tissue (endocardium, endothelium, etc.) that may lead to a clot formation, and it is being discussed if embolization prevention with coagulation system modulating (usually suppressing) medications (antiplatelet drugs and/or anticoagulants) is beneficial. Evaluating relations between thromboembolism and RFA it was established that it is important to distinguish effects on coagulation system and clot formation caused by electrophysiologic procedure and RFA itself (1).

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There are early and late post-RFA thromboembolic complications. The early complications are caused by local haemostatic disruption in the catheter zone and the late ones by endothelial damage (2). Up to 1-2% of post-RFA complications of both types have been reported (3-7), even after one month of antiplatelet drug therapy (8). The complications are more common after the left heart procedures (2).

The process of clot formation involves plasma coagulation factors and is completed by platelets. Although plasma's and platelets coagulation systems are different, the end result is mutual - thrombus/clot (9, 10). The purpose of this study is to find out if RFA affects the platelet function (i. e. aggregation) and whether the intensity of this process depends on the number of RFA episodes irrespective of medications used and the disease substrate.

**Material and methods**

In this study we examined 39 cases of cardiac arrhythmias (atrial flutter, supraventricular tachycardias and extrasystoles), in Clinic of Cardiology of Kaunas University of Medicine Hospital. The main diagnosis of a case was based on clinical and electrophysiologic test data. Patients had no meal and antiarrhythmic medications and did not smoke 12-16 hours before the RFA.

The RFA procedure was performed using a standard Seldinger method. Through the puncture of the right femoral vein or artery, multicontact electrodes were inserted into the heart and directed to the certain cardiac areas with the accuracy of 1-2 mm. Their electric activity and the spread of the impulse were registered in the intracardiac ECG by computer system (PRUCKA). Arrhythmogenic substrate was destroyed using radio-frequency 500 kHz 30-60 W energy which produces 50-70° temperature irreversibly coagulating 2-4 $mm^3$ area of tissue at the side where a special destructive electrode-catheter contacts the endocardium (11).

The blood for platelet aggregation testing was drawn from the antebrachial vein into 5 ml vacuum test-tube with 3.8% sodium citrate before, right after, and 24 hours after RFA. The platelet rich plasma was separated from red blood cells by blood centrifuging 1000/min (100 g) 15 min at the room temperature. Platelet-free plasma was obtained by further centrifuging the rest of the blood 3000/min (1000 g), 30 min.

We tested platelet aggregation in the whole blood and platelet rich plasma. Platelet aggregation in the whole blood was analyzed using a special whole blood aggregometer (WBA, Chrono-Log, USA) that measures platelet aggregation by the principle of electric resistance variation in units of resistance (ohms). Adenosine diphosphate (ADP, 10 mcmol/l) was used for induction of platelet aggregation. Platelet aggregation was analyzed using aggregometer (Chrono-Log, USA) by classic Born method (12) based on platelet plasma optical density variation in the process of aggregation, expressed in relative percents. ADP in 2 concentrations ($ADP_1$ - 3.8 mcmol/l and $ADP_2$ - 0.45 mcmol/l) and adrenaline (ADR 4.5 mcmol/l) were used for aggregation induction. Spontaneous aggregation (SP) was recorded without any inductor, only under the mechanical effect of centrifuge.

Statistic calculations were made using "Excel" and "Statistica" statistic packages.

**Results**

In order to evaluate RFA effect on platelet aggregation 3 groups of the examined patients were formed: group A - the number of RFA episodes given to the patient ≤9; group B - 10-20 RFA episodes; group C >20 RFA episodes (Table 1).

The results of platelet aggregation obtained before, right after, and in 24 hours after RFA are shown in Fig. 1.

The results revealed a significant decrease in spontaneous, $ADP_1$ and ADR induced platelet aggregation in plasma. The same tendency was noted for aggregation induced by lower ADP concentration ($ADP_2$) and in the whole blood (WBA). Platelet aggregation in 24 hours after RFA tended to return to the pre-RFA levels.

Table 2 contains data of platelet aggregation based on the number of RFA episodes. These results demonstrate a significant change in spontaneous and adrenaline-induced platelet aggregation in plasma based on the number of RFA episodes.

In group A (number of RFA episodes 1-9) there practically was no change (increase by 0.4%) in adrenaline - induced post - RFA platelet aggregation, in group B (number of RFA episodes 10-19) there was a decrease by 15.7% in platelet aggregation, in group C (number of RFA episodes ≥20) there was a decrease by 19.4% from a pre-RFA level ($p<0.05$, between group A and C). The opposite tendency was noted in a decrease in spontaneous platelet aggregation after RFA based on the number of episodes: in group A there was the most noticeable (evident) decrease - 41.9% in group B - 20.8%, and in group C - 18.4% from the pre-RFA level ($p<0.05$, between groups A and C).

***Table 1.*** **Clinical characteristic of the examined patients**

| Patients groups | Number of patients | Mean age (years) | Mean number of RFA episodes | Total RFA energy (J) | Total duration of RFA coagulation (min) |
|---|---|---|---|---|---|
| A | 14 | 49±11 | 4.4±2.7 | 2365±2248 | 1.6±0.7 |
| B | 12 | 55±9.5 | 14±2.6 | 11295±6064 | 5.7±2.07 |
| C | 13 | 44±11 | 37±11 | 26898±15236 | 14±4.0 |

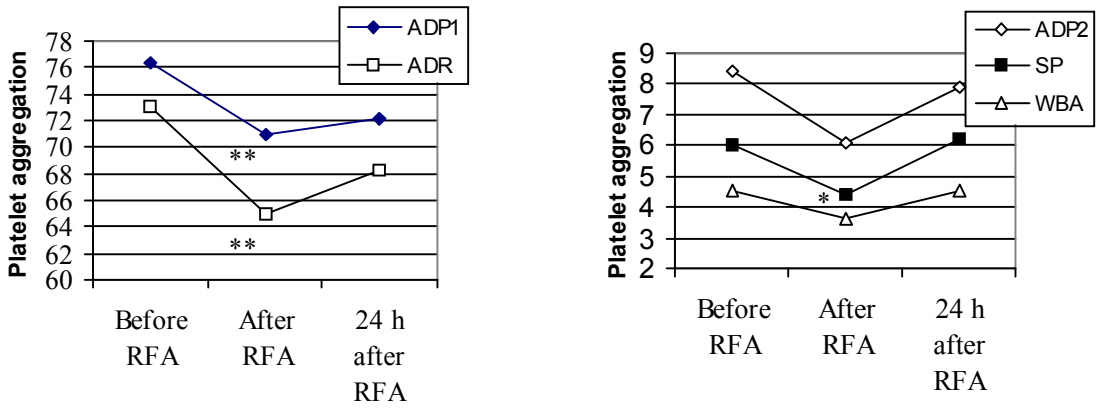


***Fig.*** **The effect of RFA on platelet aggregation**

* p<0.05, ** p<0.001, comparing with intensity of pre-RFA platelet aggregation (t-test for dependent values).

***Table 2.*** **The dependence of the intensity of platelet aggregation on the number of RFA episodes**

| Aggregation inductor | Number of RFA episodes | Platelet aggregation (X±SD) | | |
|---|---|---|---|---|
| | | Before RFA | After RFA | 24 h after RFA |
| WBA<br>ADP (ohms) | <10<br>10–20<br>>20 | 4.3±2.2<br>4.3±3.3<br>4.8±3.5 | 3.5±3.0<br>3.6±3.3<br>3.6±2.8 | 4.1±2.7<br>4.3±2.7<br>5.2±2.9 |
| Spontaneous (%) | <10<br>10–20<br>>20 | 6.2±4.4<br>5.3±4.0<br>7.6±6.4 | 3.6±2.5 **<br>4.2±2.8<br>6.2±3.4 | 7.7±9.4<br>6.2±4.1<br>5.2±3.0 |
| $ADP_2$ (%) | <10<br>10–20<br>>20 | 8.0±6.5<br>11.9±21.1<br>7.0±5.7 | 7.2±8.5<br>7.0±8.4<br>4.9±3.3 * | 6.9±6.6<br>12.1±18.9<br>6.5±5.8 |
| $ADP_1$ (%) | <10<br>10–20<br>>20 | 77.9±10.5<br>77.6±8.1<br>73.5±14.8 | 75.5±11.0<br>70.2±8.4 **<br>67.8±15.4 * | 69.8±15.2<br>79.6±13.6<br>68.7±17.8 |
| ADR (%) | <10<br>10–20<br>>20 | 72.0±17.4<br>81.3±6.3<br>67.1±17.9 | 72.3±15.4<br>68.5±16.2 *<br>54.1±24.5 *** | 66.7±18.8<br>74.3±20.4<br>64.5±23.9 |

* p<0.005; ** p<0.001; *** p<0.0001 comparing with pre-RFA platelet aggregation (t-test for dependent values). WBA - whole blood aggregation, ADP - adenosine diphosphate, $ADP_1$ $ADP_2$ - adenosine diphosphate of different concentration for rich platelet plasma, ADR - adrenaline.

ADP-induced platelet aggregation in plasma and in whole blood also tended to demonstrate a greater decrease with a higher number of RFA episodes. Although these 2 parameters demonstrated similar changes, correlation between whole blood and plasma platelet aggregation in the examined patients is very low (r=0.004-0.28) and not reliable.

**Discussion**

All 39 patients had an uneventful RFA procedure. Testing platelet activity it was not taken account of a disease substrate as well as patients taking antiplatelet drugs and anticoagulants. In this study we tried to detect if RFA influences platelet aggregation and whether the number of RFA episodes may affect the intensity of aggregation.

Discussing these problems, we should address to multiple effects of RFA: hemocoagulation changes inserting the catheters, direct thermal effect on surrounding tissues, and endothelial damage in all stages of the procedure. Authors who studied these problems emphasize the activation of platelet and coagulation system in the early and late post - RFA stages. The increase in blood thrombogenicity was confirmed by definite markers. The increase in concentrations of prothrombin fragments $F_{1+2}$ D - dimmers and thrombin - antithrombin complex was noted (13-16). Anfinsen A.G. (17) who detected an increase of concentration of intracellular platelet component beta-thromboglobulin in plasma, related it to platelet degranulation and increase in their activation.

Our study demonstrated a post-RFA decrease in platelet aggregation in blood and plasma and this change was statistically significant in group B and C, where the number of RFA episodes >10. In 24 hours platelet aggregation returned to pre-RFA level.

The mechanism of post-RFA thromboembolism remains unclear. Increase (18) in both platelet aggregation and thromboxane B2 concentration is noted 10 min after RFA. These parameters returned to the previous levels 30 min after RFA. Mean values (17) of beta-thromboglobulin were somewhat higher at the end of RFA procedure and returned to normal in 24 hours. There was no change in beta-thromboglobulin concentration 10 min after RFA. Also, there was no correlation between beta-thromboglobulin concentration and the duration and number of RFA episodes.

Using RFA procedure, fibrinolytic activity measured by D-dimers concentration was higher after RFA (19) in patients who did not take antiplatelet drugs. In 24 hours D-dimers' quantity went down but their concentration was increased up to 48 hours and it did not correlate with the duration and number of RFA episodes.

Michelucci A. and others (3) surveyed spontaneous platelet aggregation in the blood, increase in coagulation activation markers (prothrombin 1+2 fragments, thrombin - antithrombin complex) and activation of fibrinolytic system (inhibitor of plasminogen activator and D-dimers). A significant post-RFA increase in spontaneous platelet aggregation in blood returned to the previous level in 24 hours. A marked hypercoagulation (prothrombin 1+2 fragments) was detected in patients in whom RFA duration exceeded 23.5 s.

There was no correlation noted between clot formation and total RFA energy in experiments with dogs (20) when in 20% of cases post-RFA thrombosis at the ablation sites was documented macro- and microscopically.

In the normal state of organism or in the presence of minor tissue injury declining hemostatic physiologic function does not manifest clinically and dynamic balance is preserved between activating and suppressing hemostatic mechanisms. Platelet adhesion to the intact blood vessel wall is inhibited by antithrombogenic factors of the endothelium (endothelium - derived factors, increased blood flow, etc.)

More serious damage of the endothelium results in 2 different types of platelet reaction: a) morphologic structure changes stimulating clot formation, and b) biochemical changes leading to antithrombotic substance expression in the endothelium. Numerous factors that stimulate or inhibit platelet function appear at the site of endothelial damage: strong agonist - collagen (exposed in endothelial damage), thrombin (produced under influence of thromboplastin and tissue factor), weak agonist - ADP (present in each cell), adrenaline (in the endothelial damage) and others, antagonists - prostacyclin $PGI_2$, NO (endothelial relaxation factor). Activated platelets release active substances (serotonin, adrenaline, platelet factors 3 and 4, beta - thromboglobulin, etc.) (9, 10).

Under the influence of weak stimulus platelet activation terminates at the stage of their shape changes. In the case of a strong stimulus the process proceeds to adhesion, aggregation, and final secretion stages. However, fibrinolysis activation is a parallel process to hemostasis activation.

The experiments with pigs revealed that endocardial endothelium has a stronger antiplatelet action than the endothelium of coronary arteries. Endocardial cells inhibit

platelet aggregation though PG $I_2$ more than it does through the endothelial relaxation factor (EDRF) (21).

During the procedure of RFA transesophageal echocardioscopy documented a spontaneous post-RFA echogenicity (22-24) however failure to detect thrombi at the site of ablation may be due to minor RFA damages and massive blood flow at this site (21). Perhaps therefore platelets do not remain in activated form for a prolonged period of time as the largest platelet aggregation and clot formation is observed 10 min after the injury.

Results provided in the literature about RFA effects on hemostatic markers are ambiguous. Data we obtained demonstrated a decrease in platelet aggregation right after RFA procedure. In the presence of marked tissue damage this change could be explained by intensive mobilization of anticoagulation system factors or a certain remaining effect of used antiplatelet drugs and anticoagulants. Further tests are needed to disclose the mechanism of post-RFA thromboembolism and to assess the necessity for its prophylaxis with antiplatelet drugs and anticoagulants. Although the number of post-RFA thromboembolism cases is not high it does not prevent some patients from suffering from it and therefore the question about preventive measures should not be neglected.

**Conclusions**

Decrease in spontaneous and in natural platelet aggregation (induced by two aggregates (adenosine diphosphate and adrenaline)) was detected in vitro in the whole blood and platelet rich plasma right after the procedure in patients in whom arrhythmias were treated with radiofrequency ablation. These parameters almost returned to pre-RFA levels in 24 hours. The intensity of platelet aggregation right after RFA was decreasing depending on the number of episodes used for treatment.

## Trombocitų agregacijos pokyčiai gydant širdies aritmijas radiodažnine abliacija

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**Raktažodžiai:** trombocitų agregacija, radiodažninė abliacija.

**Santrauka.** Darbo tikslas. Ištirti, ar aritmijų gydymui taikoma radiodažninė abliacija turi įtakos trombocitų agregacijai, ar šio proceso intensyvumas priklauso nuo radiodažninės abliacijos epizodų skaičiaus.

Medžiaga ir metodai. Ištyrėme 39 ligonių, sergančių širdies ritmo sutrikimais, trombocitų agregaciją prieš radiodažninę abliaciją ir praėjus 24 val. po jos kraujyje ir plazmoje, indukuotą adenozino difosfatu ir adrenalinu. Ligonius suskirstėme į tris grupes pagal radiodažninės abliacijos epizodų skaičių: A – <10, B – 10–20, C – >20 epizodų ligoniui.

Rezultatai. Iškart po radiodažninės abliacijos pastebėta sumažėjusi spontaninė, indukuota adenozino difosfato ir adrenalino sužadinta trombocitų agregacija plazmoje. Tokią pačią tendenciją nustatėme sužadinę agregaciją kraujyje adenozino difosfatu. Kitą parą po radiodažninės abliacijos trombocitų agregacija turėjo normalizuotis iki reikšmių, buvusių iki radiodažninės abliacijos. Priklausomai nuo radiodažninės abliacijos epizodų skaičiaus, reikšmingai pakito spontaninė ir adrenalino indukuota trombocitų agregacija plazmoje. A grupėje adrenalino indukuota agregacija po radiodažninės abliacijos padidėjo 0,4 proc.; B grupėje sumažėjo 15,7 proc.; C grupėje sumažėjo 19,4 proc. nuo pradinės agregacijos reikšmės iki radiodažninės abliacijos ($p<0,05$ tarp grupių A ir C). Spontaninė trombocitų agregacija sumažėjo A grupėje 41,9 proc., B grupėje – 20,8 proc. ir C grupėje – 18,4 proc. nuo pradinės reikšmės iki radiodažninės abliacijos ($p<0,05$ tarp grupių A ir C). Adenozino difosfato indukuota trombocitų agregacija plazmoje ir kraujyje po radiodažninės abliacijos taip pat mažėjo daugiau, kai radiodažninės abliacijos epizodų skaičius didesnis.

Išvada. Tyrimas parodė, kad trombocitų agregacija kraujyje ir plazmoje po radiodažninės abliacijos sumažėjo ir kad šis pokytis buvo statistiškai reikšmingas tiriant B ir C grupių ligonius, kai radiodažninės abliacijos epizodų skaičius daugiau nei 10. Po 24 val. trombocitų agregacija vėl padidėjo iki pradinių reikšmių.

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