ISSN 1009－3095 *Journal of Zhejiang University SCIENCE* V.3，No.4，P.489－492，Sep.－Oct.，2002
http://www.periodicals.com.cn；http://www.zju.edu.cn/English
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Effect of pretreatment with aspirin and ticlopidine on the change of platelet aggregability after radiofrequency catheter ablation

WANG Li-hong(王利宏)，CHEN Jun-zhu(陈君柱)，ZHENG Lian-rong(郑良荣)
TAO Qian-ming(陶谦民)

(*The First Affiliated Hospital，College of Medicine，Zhejiang University，Hanzhou 310003，China*)

Received Aug.6，2001；revision accepted Jan.28，2002

Abstract: Eighty-two patients with supraventricular tachycardia undergoing radiofrequency catheter ablation (RFCA) were studied to observe the inhibition effect of aspirin and ticlopidine on platelet aggregability (PAG) and thromboxane B_2 (TXB_2) of the blood samples. Patients were divided into aspirin group A，ticlopidine group B，aspirin + ticlopidine group C and control group D. PAG and TXB_2 were increased clearly after RFCA in all groups ($P<0.001$). Treatment with aspirin or ticlopidine before operation could reduce the platelet aggregability caused by RFCA and the joint effect of two drugs(change rate of group A: 52.51 ± 12.51%; group B: 54.78 ± 11.27%; group C: 30.51 ± 10.59%; group D: 91.75 ± 21.43%; $P<0.05$)was studied. The much decreased platelet aggregability after antiplatelet therapy was evidence of the potential benefit of the treatment in preventing thromboembolism after ablation. Pretreatment with aspirin and ticlopidine together is a good way to decrease palatelet aggregability after RFCA.

Key words: Catheter ablation，Platelet aggregability，Thromboxane B_2，Aspirin，Ticlopidine
Document code: A **CLC number:** R969.2

INTRODUCTION

Radiofrequency catheter ablation has become the treatment of choice for patients with symptomatic supraventricular tachycardia unresponsive to medications. However，thromboembolism occurred in 0.4% －2.0% of the subjects who underwent catheter ablation with radiofrequency energy(Zhou et al.，1999). The mechanism remains unclear. There is no unified way to prevent the occurrence of thromboembolism at present(Anfinsen et al.，1999). Pretreatment with aspirin or ticlopidine alone does not decrease the thrombogenic potential of RF ablation(Antonis et al.，1998). Only combined therapy with aspirin and ticlopidine has favorable effect，as reflected by the lower degree of D-dimer elevation serving as an index of reactive fibrinolysis(Antonis et al.，1997). Thus，the purpose of the present study was to investigate，by measuring platelet aggregability and thromboxane B_2 levels at different times，whether randomized pretreatment with either agent alone(aspirin vs ticlopidine) or combined aspirin and ticlopidine had any similar protective effect on the thrombogenicity of RF ablation. This may help to find a better way to prevent the complication of thromboembolism.

MATERIALS AND METHODS

1. Patients selection

We investigated 82 consecutive patients who underwent radiofrequency current ablation for supraventricular tachycardia from 1999 to 2000 in the First Affiliated Hospital，College of Medical Sciences，Zhejiang University and who did not have any other heart diseases and blood system diseases. All the patients' ages were under sixty-five. They hadn't taken any drugs which could interfere the function of platelet for two weeks. The underlying mechanisms of tachycardia were atrioventricular nodal reentry tachycardia in 37 subjects，accessory pathways in 45. The patients were randomized into Group A($n=19$) who received pretreatment with aspirin (300 day)for 1 day before the procedure，Group B($n=22$) who received pretreatment with ticlopidine(500 mg/d)for 1 day before the procedure，Group C($n=23$) who received pretreatment with combined aspirin and ticlopidine and Group D($n=18$) who received placebo treatment only through random number. For all patients，all anti-arrhythmic medications had been discontinued before the procedure for at least 5

half-lives of the drug. Patients were followed up one month after the ablation procedure. All patients gave informed written consent for the procedures.

2. Blood Sampling

From each patient about to undergo RFCA, five blood samples were obtained. Initially, blood was taken immediately after insertion of the venous sheaths and before introduction of the electrode catheters (baseline measurement). Then, blood samples were taken upon completion of the electrophysiologic study (EPS) and mapping, just before delivering the first RF lesion (post-EPS measurements). The third sample was taken after completion of the RF procedure (post-RF measurements) and prior to sheath removal. At about 10 minutes and 30 minutes afterward, the fourth and fifth blood samples were obtained.

3. Platelet aggregability and thromboxane B_2

Each 9 ml of whole blood was completely mixed with 1 ml 3.8% sodium citrate and then centrifuged to get platelet rich plasma and platelet poor plasma. Platelet aggregablilty was induced by the substrate ADP. The measurement of platelet aggregability was based upon the turbidity test by a photometric aggregometer. The measurement of TXB_2 was performed according to an established enzyme immunoassay method by using a kit.

4. Statistical analysis

All values are expressed as mean ± SD (standard deviation). Statistical comparison was performed using one-way analysis of variance, q test and two-way variance analysis. The P value of <0.05 was considered significant.

RESULTS

1. The clinical characteristics of the patients

The clinical characteristics of the patients in four groups are listed in Table 1. There were no differences in age, sex, underlying mechanisms of tachycardia, platelet count, bleeding time, and coagulation profiles.

Table 1 Clinical characteristics of 82 patients who underwent RFCA*

Group	n	Age	Sex (male: female)	Platelet ($\times 10^9$/L)	BT (min)	CT (min)	Procedural variables		Duration of procedure (min)
							Energy dose (w)	Duration of energy (s)	
A	19	46.42±14.69	11:8	144.91±44.71	2	2	24.53±5.46	163.00±75.74	110.05±47.44
B	22	44.96±12.81	12:10	142.61±43.57	2	2	24.12±4.98	170.14±70.54	120.47±46.71
C	23	45.17±15.02	10:13	141.82±44.33	2	2	24.01±4.81	173.08±72.35	116.39±49.48
D	18	43.89±13.08	11:7	141.50±46.85	2	2	24.44±4.69	168.22±71.28	113.72±50.01
P value		>0.05		>0.05			>0.05	>0.05	>0.05

* variance analysis; RFCA = radiofrequency catheter ablation

2. The evolution of platelet aggregability (PAG) and thromboxane B_2 (TXB_2)

After RF ablation, PAG and TXB_2 levels rose significantly in all groups when compared to post-EPS levels. Ten minutes later, PAG and TXB_2 levels had decreased compared with post-RF levels. Thirty minutes later, PAG and TXB2 levels were lower than before but did not return to baseline levels ($P<0.05$). PAG and TXB_2 degree measured at post-EPS rose to higher levels compared with baseline levels ($P<0.05$). (Table 2 and Table 3)

From Table 4, we can get the increased percentage of PAG and TXB_2 levels in all groups immediately after RF ablation compared with just before RF ablation procedure. The increased percentage of PAG level in group D was the highest in all groups ($P<0.001$). The data obtained in this study indicated that the subclinical thrombogenicity induced by RF ablation was effectively decreased by the combined effect of aspirin and ticlopidine. The two agents appeared to have a synergistic effect on PAG ($P<0.05$). There were no differences between the aspirin group's and the ticlopidine group's effect on PAG ($P>0.05$). The results of TXB_2 were different. Compared with the control group, the change of TXB_2 after RF ablation was slighter in the aspirin group ($P<0.001$), but was nodifferent in the ticlopidine group ($P>0.05$). Compared with use of aspirin only, use of ticlopidine

trended to have more potent effect ($P>0.05$) on TXB_2. Combined use of the two agents appeared to have no synergistic effect on TXB_2.

Table 2 PAG(%)levels at different times in four groups*

Group	n	Pre-RFCA		Post-RFCA			F value	P value
		Baseline	Post-EPS	Immediate	10 min	30 min		
A	19	33.69±16.26	36.56±15.37④	54.47±19.75①	43.32±17.93②	39.00±15.08③	4.34	0.003
B	22	34.83±10.89	37.31±10.51④	57.50±15.73①	47.40±11.10②	40.86±10.76③	12.74	0.000
C	23	30.34±10.41	37.96±13.87④	49.11±16.78①	42.26±18.18②	35.33±16.89③	4.86	0.001
D	18	38.12±12.19	41.99±11.12④	79.31±16.85①	65.46±17.15②	49.82±9.62③	27.42	0.000

* q test; ①Compared with post-EPS levels, $P<0.001$; ②Compared with immediate post-RFCA levels, $P<0.001$; ③Compared with baseline levels, $P<0.01$; ④Compared with baseline levels, $P<0.05$

PAG=platelet aggregability; RFCA=radiofrequency catheter ablation; EPS=electrophysiologic study

Table 3 TXB_2(ng/L)levels on different times in four groups*

Group	n	Pre-RFCA		Post-RFCA			F value	P value
		Baseline	Pre-EPS	Immediate	10 min	30 min		
A	19	65.73±16.21	67.83±18.54④	90.28±20.92①	76.12±16.07②	69.85±13.81③	6.25	0.000
B	22	69.08±14.43	71.27±15.36④	101.69±19.57①	86.46±20.34②	75.65±17.22③	12.94	0.000
C	23	65.37±16.56	66.73±18.31④	85.59±18.92①	74.08±18.36②	68.67±17.50③	4.85	0.001
D	18	70.09±13.79	74.77±11.78④	110.24±15.41①	91.31±11.78②	75.61±11.77③	29.08	0.000

* q test; ①Compared with post-EPS levels, $P<0.001$; ②Compared with immediate post-RFCA levels, $P<0.001$; ③Compared with baseline levels, $P<0.01$; ④Compared with baseline levels, $P<0.05$

TXB_2=thromboxane B_2; RFCA=radiofrequency catheter ablation; EPS=electrophysiologic study

Table 4 The increased percentage(%) of PAG and TXB2 levels in all groups immediately after RFCA compared with just before RFCA procedure*

	Group A($n=19$)	Group B($n=22$)	Group C($n=23$)	Group D($n=18$)
PAG	52.51±12.51①	54.78±11.27②	30.51 ±10.59③	91.75±21.43
TXB_2	34.96±12.45④	43.70±11.37⑤	30.23 ±10.77⑥	48.47±14.03

* F test; ①F value=101.22, compared with Group D, $P<0.001$; ②F value=87.28, compared with Group D, $P<0.001$; ③F value=5.63, synergistic effect of two drugs, $P<0.05$; ④F value=25.25, compared with Group D, $P<0.001$; ⑤F value=3.14, compared with Group D, $P>0.05$; ⑥F value=0.00, synergistic effect of two drugs, $P>0.05$

PAG=platelet aggregability; TXB_2=thromboxane B_2; RFCA=radiofrequency catheter ablation

3. Safety of antithrombotic treatment

With regards to the safety of pretreatment, no excessive bleeding occurred during the procedures, nor was there any other side effect(i.e., skin rash, leukopenia) observed. On the other hand, no intracardiac thrombi were detected upon echocardiographic examination routinely performed after RF procedures. No patient in any group suffered any thromboembolic events during hospitalization or during later follow-up. There were no differences in complications between the treatment group and the control group.

DISCUSSION

1. Effect of RF on platelet aggregability

Our study showed that platelet aggregability increased significantly during and 10 minutes after ablation in patients who accepted placebo treatment. Because the sampling "during ablation" began almost immediately after radiofrequency energy was applied to target sites, the mechanism of the energy on platelet aggregability should be based upon its immediate effect instead of "late-phase" or "cumulative" effect. The PAG and TXB_2 of blood samples which were taken upon completion of the electrophysiologic study(EPS)and mapping, and just before delivering of the first RF lesion(post-EPS measurements) were higher than baseline levels. This indicated that the thrombus formation may be related to exposure to collagenous fibril derived from endothelial disruption during insertion of electrode catheters and turbulent blood flow induced by prolonged catheter placement. Moreover, the stress on the body (increased catecholamine combined with α_2-recepter on platelet

member) when symptomatic supraventricular tachycardia occurred induced by the electrophysiologic study and mapping may enhance platelet activation(Wang et al., 2000). The underlying principles of the effect of RF on platelet aggregability need further investigation.

2. The role of antiplatelet therapy

Aspirin inactivates cyclooxygenase by irreversibly acetylating it and thus blocks the conversion of arachidonic acid to prostaglandin(i.e., PGG_2, PGH_2) and thromboxane A_2, a potent stimulator of platelet degranulation. Low concentrations of aspirin are relatively effective for inhibition of platelet thromboxane formation. Ticlopidine blocks the binding of fibrinogen to platelets and thus further inhibits platelet aggregation. The mechanism may be blocking the activation of glycoprotein Ⅱb/Ⅲa receptor on platelet members which can interfere with the interaction between platelet member and fibrinogen (Harder et al., 2000).

The data provided by this study indicated that pretreatment with aspirin brought about lower values of PAG compared with control group. The levels of TXB_2 also revealed comparable results. This indicates that antiplatelet therapy has the potential benefit of preventing thromboembolism after catheter ablation. Pretreatment with ticlopidine could also prevent the precipitous increase of PAG levels noted in these patients and there were no differences between the aspirin group and the ticlopidine group. Aspirin had stronger effect than ticlopidine in preventing the precipitous increase of TXB_2. It further confirms that ticlopidine inhibition of palatelet aggregability is not effected through inactivating cyclooxygenase. Pretreatment with combination of aspirin and ticlopidine decreased the changes of PAG incurred by RF ablation more effectively compared with either agent alone. The two agents appeared to have a synergistic effect. So, pretreatment with a combination of aspirin and ticlopidine before radiofrequency catheter ablation procedure is a relatively better way to decrease the activation of palatelet after RFCA. It provides evidence of the potential benefit of the treatment in preventing thromboembolism after ablation. But it will be necessary to perform a long-term, double-blind clinical trial of antiplatelet agent in order to establish its favorable effect in preventing the complication of thromboembolism after ablation.

CONCLUSIONS

We conclude that platelet aggregability increases significantly during catheter ablation because of possible systemic effects of radiofrequency energy. The flat response of platelet aggregability after antiplatelet therapy provides evidence of the potential benefit of the treatment in preventing thromboembolism after ablation. Aspirin and ticlopidine both have favorable effect in preventing the platelet activation after RFCA. Pretreatment with a combination of aspirin and ticlopidine before radiofrequency catheter ablation procedure is a relatively better way to decrease the changes of PAG after RFCA.

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