Delayed Thrombogenensis Following Radiofrequency Catheter Ablation

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The cause and duration of the thrombogenesis provoked by radiofrequency catheter ablation (RF-CA) was investigated by measuring the thrombin–antithrombin III complex (TAT) in 43 patients who underwent RF-CA and in 20 control subjects who underwent an electrophysiologic study. Blood samples were collected at 7 different times: before introducing the sheaths, during the ablation procedure and at 30 min, 6 and 24 h, and 3 and 6 days after the procedure. Hepatocyte growth factor (HGF) was simultaneously measured in the ablation group. Plasma TAT concentration exhibited a double peaked pattern in the ablation group: the first peak occurred during the ablation procedure (42.8±15.5 ng/ml), and the second peak 3 days later. Plasma TAT at 3 days after the procedure was significantly higher than that of the control group (21.3±19.0 vs 2.5±1.4, p=0.0003). The first peak significantly correlated with the procedure time prior to the administration of heparin (r=0.669), but the second peak did not (r=0.132). A subgroup with a serum HGF >0.40 ng/ml at 6 h after the procedure exhibited a significantly high second peak. The thrombogenesis caused by RF-CA has 2 phases; in the acute phase, there is hemostasis during placement of the catheters, and in the delayed phase thrombogenesis is the result of endothelial damage from the RF current. (Circ J 2002; 66: 671–676)

Key Words: Endothelium; Hepatocyte growth factor; Radiofrequency catheter ablation; Thrombogenesis

Radiofrequency catheter ablation (RF-CA) is the widely accepted treatment of cardiac tachyarrhythmias, but its limitation is the risk of thromboembolism, particularly when the ablation is on the left side of the heart. Thromboembolism is a rare, but critical complication of RF-CA, with an incidence between 0.6% to 1.3%.1–5 The embolic complications do not always occur during the procedure; some reports have described a delayed onset of thromboembolism after the ablation.1,2

The previous reports of thrombogenesis caused by RF-CA6–9 have mainly focused on the hemostasis caused by the placement of the intravascular catheters in the heart and some had concluded that the thrombogenesis disappeared immediately after removal of the catheters.6,7 However, another report reported an elevation of D-dimer 48 h after the ablation procedure8 and an experimental histological examination found thrombus formation 1 week after the procedure.10 A further study has shown that the endothelial damage induces a loss of anticoagulation function for several days11 Thus we hypothesized that thrombogenesis caused by the damage to the endothelium persists for some time and might be thought of as a delayed phase of thrombogenesis.

The purpose of this study was to investigate the existence of a delayed phase of thrombogenesis caused by RF-CA, as well as assessing the relationship between this delayed phase and changes in the serum concentration of hepatocyte growth factor (HGF), an indicator of endothelial damage.12–14

Methods

Patient Characteristics

The study group consisted of 43 patients who were referred for ablation therapy for supraventricular tachyarrhythmias: atrioventricular nodal reentrant tachycardia in 18 patients, right-sided accessory pathways in 13, and left-sided accessory pathways in 12. The control group consisted of another 20 patients who were referred for a diagnostic electrophysiologic study (EPS) for supraventricular tachycardias, but who did not undergo ablation therapy. None of the patients had malignant disease, previous embolic events, recent surgery or trauma, or a history of atrial fibrillation. No medications affecting the function of the platelets and coagulation system were administered in any of the study subjects.

EPS and RF-CA

After giving their written informed consent, each patient was studied in the postabsorptive state under light sedation with nitrazepam. Cardiac antiarrhythmic agents were discontinued for at least 5 half-lives before the study. Four or 5 introducer sheaths (7 or 8F) were positioned in the right and left femoral veins and right jugular vein. In the patients who required an arterial approach, an 8F sheath was introduced into the left femoral artery. Standard electrophysiology catheters (St Jude Medical, Daig Division, Minnetonka, MN, USA; Cordis Webster, Baldwin Park, CA, USA; EP technologies, Sunnyvale, CA, USA) were introduced into the coronary sinus, high right atrium, right ventricle, and His bundle positions.
The intracardiac electrograms were filtered at a bandpass of 30–400 Hz, and recorded using an EPlab (Quinton, Seattle, WA, USA). Each pacing stimulus was performed at twice the diastolic threshold with a programmable stimulator (Model 3F-61; NEC San-ei, Tokyo, Japan). The RF current was delivered between the distal tip electrode of the ablation catheter (EP Technologies) and a cutaneous indifferent adhesive pad attached to the left posterior side of the thorax with a target temperature of 55–60°C.

In the control group, we introduced 3 or 4 sheaths through the right and left femoral veins. We also introduced a 5F sheath into the left femoral artery to record the arterial blood pressure in 5 of the control group. Intracardiac catheters were introduced into the high right atrium, right ventricle and His bundle positions. An additional catheter was positioned in the coronary sinus in some of the patients. All sheaths were removed immediately after the session was completed in both groups.

Blood Sample Collection and Analysis

Blood samples were collected at 7 different times in each patient. Baseline samples were drawn before introducing the sheaths. The next sampling was performed at 5 min after the last RF current delivery (during the procedure). After the session, additional blood samples were taken at 30 min, 6 h and 24 h after removal of the sheaths, then at 3 and 6 days after the session. All samples were drawn by cubital vein puncture with a minimum of venous stasis, except for when obtained during the procedure, in which case blood was then drawn through the sheath located in the femoral vein. Care was taken to avoid activation of platelets while drawing the blood samples.

In the last 20 of the 43 patients who had ablation therapy, we measured the serum HGF concentration at baseline, and at 6 and 24 h, and 3 and 6 days after the procedure. We did not measure the HGF concentration during the procedure or 30 min after the removal of the sheaths because of possible effects from the administration of heparin.

In the control group, the blood samples were collected at 4 different times: at baseline, and 24 h, 3 and 6 days after the procedure. Because the focus was on the existence of a delayed phase of thrombogenesis, we did not obtain samples during the procedure. All samples were drawn by cubital vein puncture with a minimum of venous stasis.

The serum and citrated plasma were obtained from venous blood by centrifugation at 3,000 rpm for 15 min at 4°C. The thrombin–antithrombin III complex (TAT) was measured by enzyme immunoassay, and HGF by enzyme-linked immunosorbent assay using commercial reagents (SRL, Tokyo, Japan). The upper reference limits were TAT <3.0 ng/ml and HGF <0.40 ng/ml.

Follow-up and Anticoagulation Regimen

All patients in the ablation group received anticoagulation with heparin after the diagnostic EPS and prior to the RF applications (5,000 U by bolus injection, followed by 1,000 U/h during the rest of the procedure). Antiplatelet therapy with 81 mg of aspirin orally was begun immediately after the procedure and continued for 1 month. None of the control patients were treated with heparin or aspirin.

Statistical Analysis

All data are presented as mean±SD. Comparisons between the groups of patients were performed with the unpaired Student’s t test. Multiple comparisons were examined by one factor analysis of variance with Bonferroni’s method to adjust the p value. Simple regression analysis was used to estimate the correlation between 2 parameters. p<0.05 was considered statistically significant.

Results

RF-CA

All patients were successfully treated by RF-CA without any adverse effects. A sudden impedance rise was seen during the delivery of the RF energy in 3 of the 43 patients, but there were no cases of visible clotting at the tip of the ablation catheter. No clinical thromboembolic complications occurred in either of the study groups during the procedure or the follow-up period (median: 14 months, range: 6–21 months).

The demographic data are presented in Table 1. There were no significant differences in terms of age, gender, systolic and diastolic blood pressure, or the number of catheters between the ablation and EPS groups.

Serial Change in TAT

The serial change in plasma TAT concentration is shown in Fig 1. In the ablation group, the baseline concentration was 2.8±1.6 ng/ml, 42.8±15.5 ng/ml during the procedure, and 13.0±7.8 ng/ml at 30 min, 5.6±2.3 ng/ml at 6 h, 10.0±10.0 ng/ml at 24 h, 21.3±19.0 ng/ml at 3 days and 11.9±16.7 ng/ml at 6 days after removal of the sheaths. The TAT concentration significantly increased during the RF-CA procedure (first peak), and then decreased to baseline by 6 h after removal of the sheaths; however, it increased again by 24 h after the session, and reached a second peak by 3 days after the RF-CA. At 6 days after the session, the TAT concentration tended to diminish, but was still significantly high compared with the baseline value.

Table 1  Clinical Characteristics of the Patients and Control Group

<table>
<thead>
<tr>
<th></th>
<th>EPS group (n=20)</th>
<th>Ablation group (n=43)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>70±16</td>
<td>68±17</td>
<td>0.31</td>
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<tr>
<td>Male gender</td>
<td>10 (50%)</td>
<td>25 (58%)</td>
<td>0.59</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>125±15</td>
<td>130±14</td>
<td>0.24</td>
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<td>Diastolic blood pressure (mmHg)</td>
<td>71±11</td>
<td>75±10</td>
<td>0.21</td>
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<td>No. of catheters</td>
<td>3.3±0.5</td>
<td>3.7±1.0</td>
<td>0.06</td>
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<tr>
<td>Total RF energy (joules)</td>
<td>17,270±17,314</td>
<td>8.62±6.1</td>
<td></td>
</tr>
<tr>
<td>No. of RF application</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure time prior to heparin administration (min)</td>
<td>67.0±24.0</td>
<td>80.3±36.3</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Data are mean±SD or number (%) of patients. There was no significant variation between both groups. EPS, electrophysiologic study; RF, radiofrequency.
In the EPS group, the baseline plasma TAT concentration was 2.7±1.5 ng/ml, and 4.5±5.2 ng/ml at 24 h, 2.5±1.4 ng/ml at 3 days and 2.6±1.3 ng/ml at 6 days after the session. None of these values was significantly different to the baseline value. However, the difference between the 2 groups was statistically significant at 24 h and 3 and 6 days after the procedure.

The plasma TAT concentration was not significant different between right-sided and left-sided ablation. The total energy of the RF current did not correlate with either the first or second peak of TAT. In both the ablation and EPS groups, the TAT concentration was not significantly different between the patients who had the catheters introduced through the artery and the other patients.

Serial Change in HGF
In the last 20 cases of the ablation group, the serum HGF concentration was 0.22±0.07 ng/ml at baseline, 0.41±0.17 ng/ml at 6 h, 0.43±0.17 ng/ml at 24 h, 0.32±0.02 ng/ml at 3 days and 0.24±0.05 ng/ml at 6 days after the ablation procedure. There was a significant increase until 24 h after the ablation and then a gradual decline (Fig 2) to the baseline level by 3 days after the session.

Correlation Between TAT and Procedure Time Prior to Heparin Administration
The procedure time prior to the administration of heparin was compared with the first and second peaks in plasma TAT concentration. The first peak significantly correlated with the procedure time, not the second peak (Fig 3). Neither the number of RF applications nor the total energy had a relationship to TAT concentration at any given time instance.

Correlation Between TAT and HGF
There was no significant correlation between plasma TAT concentration and the simultaneously obtained HGF concentration. We focused on the serum HGF concentration obtained 6h after the procedure in relation to the first and second peak of TAT. The first peak of TAT did not have a statistically significant correlation with serum HGF concentration (r=0.346, p=0.27), but the second peak of TAT exhibited a weak but not statistically significant correlation (r=0.473, p=0.10). For further analysis, we dichotomized the patients at an HGF concentration of 0.40 ng/ml.
Both subgroups showed a first peak followed by a re-
duction in the plasma TAT concentration. The HGF high
group exhibited the double-peaked pattern with the second
peak at 3 days after the procedure, but the HGF low group
did not show a significant second elevation in TAT.

**Discussion**

This study demonstrated that the thrombogenesis caused
by RF-CA has 2 phases: an acute phase peaking during the
procedure and a delayed phase peaking 3 days after the
procedure. Because the EPS group did not show a second
elevation in the TAT concentration, the delayed phase of
thrombogenesis is caused by the RF current and not by the
placement of catheters.

**Thrombogenesis Caused by Radiofrequency Current**

The thrombogenesis associated with RF-CA has 3 fac-
tors: hemostasis caused by the placement of the catheters,
a direct heating effect triggering the platelet and coagulation
system, and endothelial damage caused by the RF current.
The hemostasis that occurs with the placement of cath-
eters has been described by Manolis et al with some investiga-
tors correlating it with the duration of the pre-heparin pro-
cedure, as was seen in the present study. Another report
showed that platelet aggregability increased during RF
current delivery and Manolis et al showed that RF-CA
provoked an elevation in the D-dimer concentration by 48 h
after the procedure. These previous studies have not fully
elucidated the influence of the RF current on thrombus
formation nor have they observed the delayed phase of
thrombogenesis. Previous experimental studies have shown
histological changes in association with RF-CA, one of
which is thrombus formation 7 days after the proce-
dure. Thus, it is also unclear how long the thromboem-
bole risk continues after RF-CA.

To the best of our knowledge, this is the first report to
clearly demonstrate the acute and delayed phase of the
thrombogenesis caused by RF current application and may
explain the discrepancy in the previous studies. According
to our results, the elevation of the D-dimer concentration
reported by Manolis et al might represent the delayed phase
of thrombogenesis. Previous experimental studies have shown
histological changes in association with RF-CA, one of
which is thrombus formation 7 days after the proce-
dure. Thus, it is also unclear how long the thromboem-
bole risk continues after RF-CA.

**Endothelial Damage and Thrombogenesis**

Endothelial cells are highly sensitive to injury, so select-
tive tissue damage by ablation results in damage or loss
which leads to platelet adhesion, activation, aggregation,
and fibrin generation, and thus to thrombus formation at the

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**Table 2 Characteristics of the HGF-High and HGF-Low Groups**

<table>
<thead>
<tr>
<th></th>
<th>HGF-high</th>
<th>HGF-low</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46±21</td>
<td>55±19</td>
<td>0.42</td>
</tr>
<tr>
<td>Male gender</td>
<td>2 (40%)</td>
<td>4 (27%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>123±18</td>
<td>129±11</td>
<td>0.37</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71±8</td>
<td>74±8</td>
<td>0.43</td>
</tr>
<tr>
<td>No. of catheters</td>
<td>2.8±0.5</td>
<td>3.1±0.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Total RF energy (joules)</td>
<td>21.506±19.986</td>
<td>20.940±26.978</td>
<td>0.97</td>
</tr>
<tr>
<td>No. of RF application</td>
<td>14±5.5</td>
<td>8.9±6.6</td>
<td>0.25</td>
</tr>
<tr>
<td>Procedure time prior to heparin administration (min)</td>
<td>67.0±38.5</td>
<td>61.2±29.8</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Data from the hepatocyte growth factor (HGF) high and low groups are presented as mean±SD or number (%). There was no significant variation between both groups. RF, radiofrequency.
Delayed Thrombogenesis by RF-CA

HGF and Endothelial Damage

HGF is an endothelium-specific growth factor and because the proliferation and cell motility involved in the repair of mechanically wounded endothelial cell monolayers is induced by HGF,21 increased local HGF production would enhance re-endothelialization after injury from RF current application.

Studies have shown that serum HGF is a marker for endothelial damage. A recent experimental study showed that serum HGF was an early marker for arterial thrombi induced by mechanical endothelial damage22 and another report showed that high serum HGF concentrations might predict adverse events in cases of acute coronary syndrome.14 In the present study, a significantly high second peak in TAT concentration was seen in the group in which the serum HGF concentration was greater than 0.40 ng/ml at 6 h after RF-CA, which suggests that the serum HGF concentration at that time may predict the degree of delayed thrombogenesis.

Thus we consider that the HGF high group had greater endothelial damage, although it was difficult to precisely evaluate it. The HGF high group included cases of multiple accessory pathways and the group overall had more applications of RF current. Therefore, the HGF high group included cases that were more difficult to treat and thus evoked greater endothelial damage.

A previous study established that heparin was a potent enhancer of HGF synthesis in various types of cells23 and administration of heparin increased the serum concentration of HGF for 1 h after the infusion, an effect that disappeared 3 h later.15 We measured the serum HGF concentration at least 6 h after the infusion of heparin, so the influence of the heparin would have been completely diminished.

Study Limitations

This study has the principle limitation that the elevation of the biochemical markers did not directly correlate with the clinical thromboembolic risk. No clinical thromboembolic event was seen in this study. In addition, we could not directly correlate the endothelial damage and thrombus formation with the pathological examination.

The second peak in TAT concentration depends on the regimen of anticoagulation, and we might not have observed the precise peak of the thrombogenesis caused by the endothelial damage. However, the control group, which had an EPS but no ablation therapy, did not have an elevation in the TAT concentration in the delayed phase. Thus, we believe the delayed phase of thrombogenesis was clearly caused by the RF current itself.

As previously described, sampling through intravascular sheaths causes error,24 but we obtained all the samples by a cubital vein puncture with minimum venous stasis, except for 1 sample obtained during the procedure.

HGF is a known pleiotropic agent acting under various conditions, and thus the serum HGF concentration might not indicate only endothelial damage. We compared the prognostic significance of serum HGF concentration in a small number of cases, but a much larger series of patients is required to determine this.

Clinical Implications

The present study indicated that subclinical thrombogenesis continued for 6 days after RF-CA and that endothelial damage might be the cause. Although we have not directly revealed the presence of clinical thromboembolism, the results indicate a possible risk of delayed thrombosis in a limited situation. Oral administration of aspirin at a dose of 81 mg did not completely prevent the delayed phase of thrombogenesis.

Conclusions

Thrombogenesis provoked by RF-CA has been considered to be caused by hemostasis from the placement of the intravascular catheters, and that it disappears immediately after removal of the catheters and introducer sheaths. However, the present study clearly showed that the thrombogenesis has 2 phases: an acute phase during the procedure, and a delayed phase that peaked at 3 days after the procedure. The delayed phase of thrombogenesis is provoked by endothelial damage caused by application of the RF current.

Acknowledgment

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References


