The Incidence of Thromboembolism and the Hemocoagulative Background in Patients with Rheumatic Heart Disease

Yohichiro Fukuda, M.D., and Kazuhiko Nakamura, M.D.

We discussed the existence of a thrombotic tendency and the relationship between the high incidence of thromboembolism and the thrombotic tendency in patients with rheumatic heart disease (RHD). The augmentation of platelet function was detected in all kinds of rheumatic valvular disease from the finding of high values of plasma β-thromboglobulin (72 ng/ml, normal 29 ng/ml). The existence of hypercoagulation was also detected in patients with mitral stenosis by showing low levels of plasma antithrombin III (AT III), while fibrinolytic reaction remained normal. The degree of hypercoagulation became augmented in the order of cases of mitral stenosis (MS) complicated by both atrial fibrillation and chronic congestive heart failure, MS complicated only atrial fibrillation and MS with normal sinus rhythm (AT III: 19.6, 25.0, 26.7 mg/dl, respectively). On the contrary, hypercoagulation, the degree of which was almost the same as that in the respective MS groups, also existed in comparable controls of non-RHD, accompanied by the acceleration of fibrinolytic reaction as shown by the decrease in activity of plasma α2-plasmin inhibitor. Therefore, it was concluded that thrombotic tendency certainly existed in patients with MS compared to those with non-RHD and that it was one of the causes of the significantly high incidence of thromboembolism in comparison with non-RHD.

As has been reported in many papers, today it is considered a fact that compared to other cardiovascular diseases thromboembolism is frequently accompanied by rheumatic heart disease (RHD). But there have been only a few reports which revealed how thrombi, which are the indispensable condition of thromboembolism, are actually formed and develop.1,2 We evaluated the data on the incidence of thromboembolism and the hemocoagulative examination on 151 patients with RHD (1354.6 patient-year, (p.y)) and 109 with non-RHD (834.4 p.y) who had been followed up. Our primary concern was whether there existed a thrombotic tendency in RHD patients or whether a hemocoagulative background, which could explain the difference of the incidence of thromboembolism between RHD and non-RHD patients. Concretely speaking, the staple hemocoagulative parameters were the concentration of plasma β-thromboglobulin (β-TG) for platelet function, the concentration of plasma antithrombin III (AT III) for coagulative reaction and the activity of plasma α2-plasmin inhibitor (α2-PI) for fibrinolytic reaction. We also investigated the prophylactic effect of Warfarin and the treatment of acute thromboembolism by urokinase.

SUBJECTS AND METHODS
The clinical subjects which have been observed in our clinic were 22 cases of healthy

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Key Words:
Rheumatic heart disease
Thromboembolism
Thrombotic tendency
Antithrombin III
α2-plasmin inhibitor

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controls, 151 patients with RHD and 109 with other cardiovascular diseases excluding ischemic heart disease (non-RHD). Patients with RHD were divided hemodynamically into 3 major groups: (1) mitral stenosis (MS) or MS with aortic valve disease (AVD) (MS group, 73 cases), (2) mitral stenosis and regurgitation (MSR) or MSR with AVD (MSR group, 39 cases) and (3) mitral regurgitation (MR) and/or AVD (MR/AVD group, 39 cases). These 3 groups were subclassified respectively into the sinus rhythm (SR) group, the atrial fibrillation (AF) without chronic congestive heart failure (CHF) group (AF group) and the AF with CHF (AF-CHF) group. The 109 patients with non-RHD consisted of 22 cases with hypertensive heart disease, 15 with congenital heart disease, 35 with cardiomyopathy, 35 with lone AF and 2 with miscellaneous heart diseases. Ischemic heart disease was excluded from the non-RHD group because of its having a close relation to thrombosis. The non-RHD group was also divided into the SR, the AF and the AF-CHF groups (Fig. 1).

The incidences of thromboembolism and bleeding were calculated as number of episodes/ follow-up years (patient-year) x 100% in each period with or without the anticoagulant agent.

Samples for hemocoagulative examinations were obtained as citrate plasma in the early morning before breakfast, and frozen below.
TABLE I INCIDENCE OF THROMBOEMBOLISM

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>AF</th>
<th>AF-CHF</th>
<th>AF'</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P.Y</td>
<td>TE(%)</td>
<td>P.Y</td>
<td>TE(%)</td>
<td></td>
</tr>
<tr>
<td>non RHD</td>
<td>466</td>
<td>0.43</td>
<td>264.8</td>
<td>2.64</td>
<td>103.6</td>
</tr>
<tr>
<td></td>
<td>466.2</td>
<td>0.64*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHD</td>
<td>262.6</td>
<td>1.52</td>
<td>663.7</td>
<td>5.27</td>
<td>428.3</td>
</tr>
<tr>
<td></td>
<td>265.6</td>
<td>2.64*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>136</td>
<td>2.21</td>
<td>403.8</td>
<td>6.44</td>
<td>146.5</td>
</tr>
<tr>
<td>MS/MSR</td>
<td>143.6</td>
<td>2.09</td>
<td>626.3</td>
<td>5.59</td>
<td>334.3</td>
</tr>
<tr>
<td>MR/AVD</td>
<td>119</td>
<td>0.84</td>
<td>37.4</td>
<td>0</td>
<td>96.0</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>3.28*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AF' = both the af and the af-CHF groups; RHD = rheumatic heart disease; MS = mitral stenosis; MSR = mitral stenosis and regurgitation; MR = mitral regurgitation; AVD = aortic valve disease; P.Y = patient-year; * = if including cases complicated with infective endocarditis

TABLE II DATA OF COAGULATION & FIBRINOLYSIS

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>MS/nonRHD-SR</th>
<th>MS/nonRHD-af</th>
<th>MS/nonRHD-af-CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>263±47 (20)</td>
<td>291±87 (18)</td>
<td>280±71 (43)</td>
<td>260±54 (40)</td>
</tr>
<tr>
<td>Antithrombin III (mg/dl)</td>
<td>29.6±1.4 (22)</td>
<td>26.7±2.3* (20)</td>
<td>25.6±3.2* (46)</td>
<td>25.0±3.4* (44)</td>
</tr>
<tr>
<td>Plasminogen (mg/dl)</td>
<td>12.6±1.8 (22)</td>
<td>11.2±1.8 (20)</td>
<td>10.7±2.0* (46)</td>
<td>10.8±1.9* (44)</td>
</tr>
<tr>
<td>α2-plasmin inhibitor (%)</td>
<td>99±11 (21)</td>
<td>105±15 (17)</td>
<td>96±17 (37)</td>
<td>97±15 (41)</td>
</tr>
<tr>
<td>α2-macroglobulin (mg/dl)</td>
<td>179±42 (22)</td>
<td>203±47 (20)</td>
<td>188±53 (46)</td>
<td>206±41 (44)</td>
</tr>
</tbody>
</table>

mean ± S.D (No. of cases)
MS = mitral stenosis; nonRHD = heart diseases except rheumatic heart disease and ischemic heart disease; SR = sinus rhythm; af = atrial fibrillation; CHF = chronic congestive failure; * = significant, p < 0.05 (vs healthy controls)

-20°C until measurement. Concentration of fibrinogen in the plasma was measured using Clauss' method. Concentrations of AT III, plasminogen and α2-macroglobulin in the plasma were measured using the single radial immunodiffusion method and the activities of α2-PI were measured using the chromogenic substrate method using the substrate of S-2251. Concentration of plasma β-TG measured using the radioimmunoassay kit. Concentration of fibrinogen/fibrin degradation products (FPD) in serum were measured using the latex agglutination method.

The stastical method was dealt with as follows: Comparisons of incidences among multiple groups were made by the χ²-test, comparisons of hemocoagulative parameters among multiple groups by the unpaired t-test and changes of the parameters before and after the treatments by the paired t-test.

RESULTS

I. INCIDENCE OF THROMBOEMBOLISM

The number of the episodes in the observed periods was 53 in the RHD and 11 in the non-RHD group. The site of thromboembolic lesion was the cerebral arteries in 38 cases (72%), the lower extremities in 10 (19%), the upper extremities in 2 and the coronary arteries in 2, and

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the intra-abdominal arteries in 1 for RHD group, while the cerebral arteries in 6 (54%), the upper extremities in 4 (36%) and the upper extremities in 1 for the non-RHD group (Fig. 2). The incidence of thromboembolism in the non-RHD group was 1.32% and showed 1.42% if the cases complicated with acute infective endocarditis are included. In the non-RHD group, the incidences in the SR, the AF and the AF-CHF subgroup were 0.43, 2.64, 1.93%, respectively. The incidence in all cases with AF was 2.39% and it was significantly higher than that in the SR group (Fig. 3).

The incidence of thromboembolic episodes in the RHD group was 3.91%, which was significantly high compared to that in the non-RHD group and showed 4.12% if infective endocarditis is included. In the RHD group, the MS group and the MSR group showed a very high incidence of 5.83 and 5.16%, respectively, while the MR/AVD group showed a low incidence of 0.40% and 1.57% if infective endocarditis is included (Table I). In the MS group, the incidences in the SR, the AF, the AF-CHF and both the AF and AF-CHF subgroup were 2.21, 6.44, 7.51 and 6.72%, respectively. These were significantly higher than the incidences in the corresponding subgroups of non-RHD patients. The incidence in both the AF and the AF-CHF group showed also a significantly high value compared to that in the SR group (Fig. 3).

The 112 cases with MS and MSR were divided into 2 groups. In one group, the left atrial thrombus was clearly detected on echocardiograms or angiograms or found during open heart surgery (the LA (+) group) and in the other it was not detected clinically or not found during surgery (the LA (−) group). The incidences in the LA (−) group were 2.89% in the SR, 3.54% in the AF, 2.29% in the AF-CHF subgroup and 2.98% in both the AF and the AF-CHF group, respectively. That is, there were no significant differences among them. On the other hand, the LA (+) group revealed a markedly high incidence of 7.91% in the AF, 7.62% in the AF-CHF subgroup and 7.84% in both AF and AF-CHF subgroup, which were significantly higher than those in the corresponding subgroup of the LA (−) group. No cases in the non-RHD group were thought to have thrombi in the left atrium according echocardiograms or angiograms (Fig. 3).

*Fig.3. Incidence of thromboembolism.
The MS groups showed a significantly high incidence compared to the respective groups of non-RHD. In the cases with MS/MSR, the LA thrombus (+) groups showed very high incidences compared to the LA (−) groups.

*Fig.4. Values of serum FDP.

*Fig.5. Incidence of thromboembolism and bleeding in cases with MS/MSR using Warfarin.
II. HEMOCOAGULATIVE FINDINGS

The concentration of β-TG in the plasma was 29.4 ± 15.1 (18) ng/ml (mean ± standard deviation (no. of cases)) in the healthy controls, 72.0 ± 51.7 (40) ng/ml in the RHD group without prosthetic valves and 120.9 ± 56.2 (14) ng/ml in the RHD group with prosthetic valves. There were significant differences between the level in the healthy controls (29.4 ± 15.1 (18) ng/ml) and that in the RHD group without prosthetic valves, and between the RHD groups with and without prosthetic valves. The concentration in cases having mitral lesions, aortic lesions and/or both in the RHD without prosthetic valves were 78.5 ± 58.1 (27), 56.4 ± 36.6 (7) and 61.0 ± 30.8 (6) ng/ml, respectively. There were no significant differences among them.

The concentrations of AT III, α₂-PI, fibrinogen, plasminogen and α₂-macroglobulin in the plasma are shown in Table II. The level of plasma AT III was lower in the non-RHD group than that in the healthy controls. The level in the non-RHD group was lower in the order of the AF-CHF, the AF and the SR group. The plasma AT III levels in the MS-SR, the MS-AF and the MS-AF-CHF group were as low as those in the corresponding groups of the non-RHD. On the other hand, the level of plasma α₂-PI activity differed among the groups. Namely, the level in the non-RHD group was significantly lower in the AF-CHF and the AF than in the SR group or the healthy controls while the level in the corresponding groups in MS patients remained normal (Table II). Concentration of the plasma plasminogen was low in both the non-RHD and MS group, and that in the MS subgroups was as the same as that in each group in non-RHD. There were no significant differences in either plasma fibrinogen or α₂-macroglobulin concentration among the healthy controls, the non-RHD and the MS group. Abnormally high levels more than 20 µg/ml of serum FDP were detected in 4 cases out of the 101 in the non-RHD groups and 4 out of the 62 in the MS groups (Fig. 4). Finally, no hemocoagulative differences were detected between MS/MSR patients with the left atrial thrombus and those without it.

III. PROPHYLAXIS BY THE ANTICOAGULANT

The incidence of thromboembolism during Warfarin therapy (91.0 p.y) was examined in patients with MS/MSR. The incidence was 0 in the SR, 3.50% in the AF, 0 in the AF-CHF and 2.29% in both the AF and AF-CHF groups, while the incidence of thromboembolism in MS/MSR
patients not treated with Warfarin was 5.62%. On the contrary, 2 patients in the AF-CHF group suffered from cerebral bleeding during Warfarin therapy. The incidences of bleeding were 0 in the SR and the AF, 5.97% in the AF-CHF and 2.29% in both the AF and the AF-CHF group (Fig. 5).

Plasma AT III levels were compared between patients with MS taking Warfarin and those not taking it. The AT III levels in MS-AF patients were 26.5 mg/dl for the former and 25.0 mg/dl for the latter group, and in MS-AF-CHF patients 25.3 mg/dl for the former and 19.6 mg/dl for the latter group. The significant increase in plasma AT III was detected in the AF-CHF group treated with Warfarin but not in the AF group. In addition, the comparison of the change of plasma AT III before and after Warfarin therapy was made using 65 samples in 22 patients and the result revealed a significant increase of 1.73 ± 4.00 mg/dl after the treatment while the mean prothrombin time after the treatment decreased to 39 ± 17.4% (Fig. 6).

IV. THROMBOLYTIC TREATMENT IN ACUTE THROMBOEMBOLISM

Five patients with acute thromboembolism in the extremities were treated with urokinase: 24,000 IU intravenously in acute phase, followed by 550,000–600,000 IU drip infusion for 3 hours. Clinical manifestations, such as loss of pulsation or decrease in the skin temperature, improved in all the cases. Hemocoagulative examinations under the urokinase therapy revealed a significant lowering of plasma α2-PI from 94 to 39% and plasma plasminogen from 10.4 to 7.6 mg/dl. The concentration of plasma fibrinogen had a tendency to decrease after the treatment but was not statistically significant. There were no significant changes in plasma AT III and α2-macroglobulin and serum FDP (Fig. 7).

DISCUSSION

The incidence of thromboembolism in natural history that has been reported to date was from 1 to 4% per patient year in RHD8 In this study it was 3.91% per p.y, and slightly higher than previously reported. This may be due to our selection of the patients.

In our present study thromboembolism occurred more frequently in cases with RHD, especially MS compared to non-RHD, in cases complicated with AF and in cases having left atrial thrombus. A higher incidence of thromboembolism in AF cases was noted not only in MS but also in non-RHD group. Though hypercoagulability, which was clearly detected in AF in comparison with SR cases, was thought to be one of the major reasons why AF cases showed high incidence, the hemorroeological effect of AF should be taken into account. With regard to this, the following example may be informative. The female patient experienced transient rapid AF. With digoxin therapy her rhythm was slowed but later developed into an atrioventricular junctional rhythm, in which the blood flow in the left atrium would be impaired due to the lack of atrial kick. Two days later, at the moment when the rhythm was restored to normal sinus rhythm, she had an episode of cerebral embolism and right hemiplegia.

The fact that thromboembolism occurred frequently in cases having a left atrial thrombus suggests that thromboembolism is prone to occur in cases with a thrombotic tendency or at least having had it formerly. Accordingly, we have to investigate whether patients with MS have a thrombotic tendency or not. In the present study, the thrombotic tendency was evaluated from the thrombocytic and coagulofibrinolytic points of view. Concentration of plasma β-TG, which increases during platelet aggregation, was examined for the thrombocytic response9 and concentrations of plasma AT III, which is the most important one among the antithrombins10 and α2-PI, which plays the most important role among antiplasmins11 were for the coagulofibrinolytic response.12 Antithrombin III reacts on thrombin and Factor Xa10 which activates coagulation factors, leading to actual fibrin formation, and thus a decrease in plasma AT III may bring about a thrombotic state, so-called hypercoagulability, because of its reduced inhibitory effect against the activated coagulation factors. On the other hand, α2-PI reacts on the activated fibrinolytic factor of plasmin, which causes actual thrombolysis, and thus the increase or the decrease in plasma α2-PI promotes or inhibits the growth of thrombi, respectively.11

In this study the acceleration of platelet function, expressed as high plasma β-TG levels, was noted not only in MS patients but also in other rheumatic patients, and there were no significant differences in the degree of the advance among the mitral, aortic and both
valvular patients. It was also found based on the plasma AT III levels that MS patients were in a hypercoagulable state. The hypercoagulability in the MS subgroups was almost the same as in the corresponding non-RHD subgroups. Accordingly it is reasonable to consider that hypercoagulation results from AF or CHF and it is not specific to MS patient. The fibrinolytic reaction in MS patients was thought to have remained normal based on the small difference in plasma α2-PI levels between healthy controls and the respective MS subgroups. But the fibrinolytic reaction in the non-RHD patients, especially AF and AF-CHF ones, was accelerated, which led to its playing a negative role in thrombi formation.

From the above discussion, it was concluded that MS patients were in a hypercoagulable state with normal fibrinolytic response along with the augmented platelet function, which greatly contributed to the actual formation or growth of thrombi. On the contrary, the non-RHD patients had not only hypercoagulation but also the augmented fibrinolytic response, that is, they were be in a well-balanced state of coagulation and fibrinolysis. Therefore, it would not always be the cases that the hemocoagulative state in the non-RHD patients contributes actively to actual thrombi formation, even if hypercoagulation exists. Also it was considered that the difference in the fibrinolytic reaction between the MS and non-RHD patients supported the following findings: Thrombi in the heart were frequently detected in MS patients in comparison with non-RHD ones and the incidence of thromboembolism in MS was higher than in non-RHD.

The prophylactic effect of Warfarin against thromboembolism was also evaluated in this study. The incidence of thromboembolism in the patient group treated with Warfarin was less than half of the group not treated with Warfarin. This result was obtained from relatively short period of observation, and we cannot conclude at the present time that Warfarin therapy is beneficial for these patients. The effects of Warfarin on the coagulofibrinolytic factors, especially on plasma AT III, were also investigated. In severe cases complicated with both AF and CHF, the concentration of plasma AT III in cases using Warfarin was significantly higher than those not using it, while this was not the cases complicated with AF alone. This finding apparently shows the improvement of hypercoagulation by means of the administration of Warfarin in severe cases, but almost all of them had had valve replacement surgery and therefore the improvement of their congestive hemodynamics was to be expected, and thus it was inconclusive whether or not the administration of Warfarin or the improvement of hemodynamics brought about the increase in plasma AT III levels, especially noting the result that a clear improvement was not found in the AF group. It was also found that there was a significant increase in plasma AT III levels during the period of taking Warfarin compared to that before taking it, and most of the cases had had cardiac surgery. Therefore, it was difficult to conclude that there was a suppressive effect on hypercoagulation through the administration of Warfarin.

Finally, we discussed the treatment of acute thromboembolism by urokinase. The urokinase treatment was indicated for 5 patients with acute thromboembolism in the extremities. The method of administration was a 3 hour-drip infusion of 550,000-600,000 IU of urokinase following acute intravenous injection of 24,000 IU of urokinase, expecting the activation of fibrinolysis which produces the actual thrombolytic effect. Clinical manifestations disappeared during the drip infusion in all cases. On the other hand, it was found that the manner of the treatment brought about a marked fibrinolytic reaction, which would be certainly expected for its actual thrombolytic effect, in accordance with the decrease in plasma α2-PI level after urokinase infusion (from 94 to 39%). The existence of the acceleration of fibrinolysis was also supported by the decrease in the level of plasma plasminogen which was converted to plasmin by urokinase. It could not be determined whether the extreme fibrinolytic acceleration that could cause fibrinogen degradation occurred due to the manner of the treatment or not, because the decrease in plasma fibrinogen levels was not significantly detected. Therefore, it was confirmed not only clinically but also hemocoagulatively that the dose and method of the urokinase treatment were effective.

REFERENCES


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