Fever Associated With Acute Aortic Dissection

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Background Although fever is a common accompanying feature of acute aortic dissection, few reports have been published concerning the duration and character of this fever.

Methods and Results The mean duration of fever was calculated for a total of 57 patients with acute aortic dissection, who were then divided into 2 groups: those with duration of fever shorter than the mean (Group A) and those with duration of fever equal to or longer than the mean (Group B). The reduction in false lumen size and hematological parameters were compared between groups. The mean duration of fever was 15.9±11 days. The false lumen reduction ratio was significantly higher in Group A (18.3±5.0%) than in Group B (2.0±5.3%). There was a significant negative correlation between the false lumen reduction ratio and duration of fever. Hematological parameters did not differ significantly between the 2 groups except for fibrin degradation product, although the white blood cell count and platelet counts and C-reactive protein concentration tended to be higher in Group B.

Conclusions Checking for fever is important in assessing the status of individual cases of acute aortic dissection. (Circ J 2007; 71: 766–771)

Key Words: Aortic dissection; Fever; Thrombus

Acute aortic dissection presents with various symptoms; that is, pain, nausea, vomiting, hematemesis, cold sweat, syncope, cerebrovascular accident, ischemic peripheral neuropathy, hypertension, congestive heart failure, shock, cardiac arrest, and sudden death. In addition, fever is often associated with acute aortic dissection and in rare cases is persistent so that it becomes difficult to determine whether or not it is associated with acute aortic dissection. A number of such cases have been reported1-4 as well as those in which aortic dissection was identified as the cause of an initially unexplained fever5-10 However, the duration of fever associated with acute aortic dissection is not well known, so the present study was undertaken to investigate the duration of fever associated with acute aortic dissection and to examine the relationship between duration and hematological parameters and reduction in false lumen size.

Methods

Subjects During the 26-year period from January 1978 to December 2003, 336 patients with acute aortic dissection were admitted to Kinki University Hospital. Of these 57 meeting the following requirements were selected: (1) hospitalization within 1 week after disease onset, (2) treated medically rather than surgically, (3) judged free of infection, ileus, acute renal failure, malignant tumor, collagen disease, drug allergy, etc and (4) followed for 1 month after disease onset.

Diagnosis of Dissection Contrast-enhanced computed tomography (CT) scans were used to make a definitive diagnosis of aortic dissection.

Fever Axillary body temperatures were measured and the highest temperature during the day was considered the body temperature for that day. A diagnosis of fever was made if body temperature was over 37°C. The mean duration of fever was calculated for the entire study population. The patients were then divided into 2 groups: those with duration of fever shorter than the mean (Group A; brief fever group) and those with duration of fever equal to or longer than the mean (Group B; extended fever group). Hematological parameters and reduction in false lumen size were compared between these groups.

Reduction in False Lumen Size Contrast-enhanced CT images, obtained at admission and 1 month later, were fed into a computer to determine the false lumen reduction ratio, as shown in Fig 1.

Hematology White blood cell (WBC) and platelet counts, and C-reactive protein (CRP), fibrinogen, fibrin degradation product (FDP), D-dimer, and thrombin–antithrombin III complex (TAT) concentrations were compared between groups. Mean values for the WBC and platelet counts and CRP concentration were calculated for each week, and changes were analyzed at 1, 2, 3 and 4 weeks after admission. For fibrinogen, FDP, D-dimer, and TAT, the means weeks 1–2 and weeks 3–4 were analyzed.
Fever and Acute Aortic Dissection

Statistical Analysis
Student’s t-test (unpaired) was used for statistical analysis of age, fibrinogen, FDP, TAT, and D-dimer levels. The chi-square test was used for statistical testing of the male-to-female ratio. ANOVA for repeated measures (Scheffe’s F) was used for analysis of WBC and platelet counts, and CRP concentration. Correlation analysis, regression analysis, and Student’s t-test were used to analyze the false lumen reduction ratio.

Results
Duration of Fever
The duration of fever was 15.9±11 days (mean±SD), and ranged from 0 days (absence of fever) to 56 days. It was ≤1 week in 15 cases, >1 week but ≤2 weeks in 14 cases, >2 weeks but ≤3 weeks in 10 cases, >3 weeks but ≤4 weeks in 11 cases, >4 weeks in 7 cases.

Fig. 1. False lumen reduction ratio = \left( \sum_{i=1}^{N} A_i + A_{1} + A_{2} + A_{3} + \ldots + A_{N} \right) \times P \times 100 \div \left( \sum_{i=1}^{N} B_i + B_{1} + B_{2} + B_{3} + B_{4} + \ldots + B_{N} \right) \times P. Reduction ratio = \left( \text{False lumen ratio at entry} - \text{False lumen ratio after 1 month} \right) \times 100 \div \text{False lumen ratio of entry.}

Fig. 2. Duration of fever. (a) Mean duration of fever was 15.9±11 days (mean±SD). (b) ≤1 week, (c) >1 week but ≤2 weeks, (d) >2 weeks but ≤3 weeks, (e) >3 weeks but ≤4 weeks, (f) >4 weeks.
weeks but ≤3 weeks in 10 cases, >3 weeks but ≤4 weeks in 11 cases, and >4 weeks in 7 cases (Fig 2a). Among those in whom fever lasted for more than 2 weeks, a small number had fever every day, though many had intermittent fever (with periods of fever alternating with a few fever-free days) (Figs 2b–f).

Because the mean duration of fever was 15.9 days, the patients were divided by duration of fever into 2 groups with the cutoff point at 15 days: Group A (fever lasting ≤15 days: n=32) and Group B (fever lasting ≥16 days: n=25).

### Table 1  Fever and Age, Sex, and DeBakey Classification in Patients With Acute Aortic Dissection

<table>
<thead>
<tr>
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<tr>
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<td>Group B ≥16 days</td>
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<td>64</td>
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<tr>
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<tr>
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**Age, Sex, and DeBakey Classification**

Mean age did not differ significantly between Group A (63 years) and Group B (64 years). Analysis of the male-to-female ratio revealed that the percentage of females was

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Fig 3. Fever and the false lumen reduction ratio. (a) False lumen reduction ratio (mean±SE). Duration of fever: Group A ≤15 days, 16 days ≤Group B. (b) Correlation and regression analysis of false lumen reduction ratio and duration of fever.

Fig 4. Fever and inflammation. Duration of fever: Group A ≤15 days, 16 days ≤Group B. White blood cell (WBC), platelet count and C-reactive protein (CRP) concentration did not differ significantly between the 2 groups.
higher in Group B (male/female = 11/14) than in Group A (24/8). There was no significant difference between Group A and Group B in the DeBakey classification. In both groups, the percentage of patients rated class IIIb was high (Table 1).

**False Lumen Reduction Ratio**

The false lumen reduction ratio (mean ± SE) was significantly higher in Group A (18.3±5.0%) than in Group B (2.0±5.3%) (Fig 3a). There was a significant negative correlation between the false lumen reduction ratio and duration of fever (Fig 3b).

**WBC and Platelet Counts and CRP Concentration**

In both groups, WBC peaked at 1 week after admission and decreased thereafter, returning to within the normal range within 4 weeks of admission. The overall time course of changes in WBC did not differ significantly between the 2 groups, although WBC tended to be higher in Group B (Fig 4). Similar to WBC, CRP peaked at 1 week after admission and decreased thereafter in both groups, returning to within the normal range within 4 weeks of admission. The overall time course of changes in CRP did not differ between the 2 groups, although CRP tended to be higher in Group B (Fig 4).

Platelet counts peaked at 3 weeks after admission and decreased thereafter. The overall time course of changes in the platelet count did not differ significantly between the 2 groups, although this parameter tended to be higher in Group B (Fig 4).

**Fibrinogen, TAT, FDP, and D-Dimer**

There were no significant differences between the groups in fibrinogen, TAT, or D-dimer levels. FDP level was significantly higher in Group B than in Group A (mean ± SE). TAT, thrombin–antithrombin III complex; FDP, fibrin degradation product.

**Discussion**

Fever is one of the symptoms of acute aortic dissection. Hirst et al reported that it occurred in one-third of all patients with this condition.11 A number of reports have been published concerning cases in which aortic dissection was identified as the cause of an initially unexplained fever,5–10 but few studies of the mean duration of fever associated with acute aortic dissection have been published. In Japan, Komatsu et al reported that in most cases fever lasted for 2–3 weeks and subsided thereafter, but that slight fever subsequently appeared intermittently in many cases, and that fever was noted in approximately half of all cases, even 30 days after disease onset.12 In the present study involving 57 patients who underwent medical follow-up for 1 month, only 2 patients were free of fever during the follow-up period. The mean duration of fever was 15.9 days. Fever lasting for 30 days or longer occurred in 7 cases. In many of the patients with long-lasting fever, fever appeared intermittently. It was not able to be proven in this study, but expansion of the dissection, recurrent dissection or exposure of thrombi were considered to be the cause of intermittent fever. Our findings indicate that fever is one of the major symptoms of acute aortic dissection, and that acute aortic dissection should be considered one of the conditions possibly responsible for unexplained fever even in patients free of typical symptoms such as chest pain.

Factors generally responsible for fever include (1) thrombi, (2) destroyed tissue, and (3) cytokines, free radicals, oxygen radicals etc induced by thrombi or destroyed tissue, each of which appears to be associated with aortic dissection. To test the correctness of this view, we considered it necessary to demonstrate a correlation between duration of fever and reduction in the size of the false lumen created by aortic dissection. As shown in Fig 3, the false lumen reduc-
tion ratio was significantly lower in the extended fever group than in the brief fever group. There was a negative correlation between duration of fever and the false lumen reduction ratio, with less reduction in false lumen size seen in patients with fever for longer periods of time. The length of contrasted false lumen and the full length of the false lumen did not differ between the 2 groups, although it tended to be longer in Group B (data not shown). The main cause of fever is destroyed tissue or thrombus. However, the end of fever, namely reduction of the false lumen, is considered the end of the inflammation reaction to destroyed tissue and thrombus. So if inflammation itself is a factor in the individual’s duration of fever, we would not obtain a significant difference in fever duration by only analyzing the length of the false lumen. These findings suggest that the presence of a false lumen created by aortic dissection is responsible for the fever, and also that the presence/absence of persistent fever may be an indicator of a reduction in the size of the false lumen in cases of aortic dissection.

We then examined changes in hematological parameters. Because fever typically involves an inflammatory reaction, we examined the time course of changes for 3 indicators of the inflammatory reaction (WBC and platelet counts, and CRP level). There was no significant difference in the time course of changes in any of these indicators between the brief and extended fever groups. However, all 3 parameters tended to be higher in the extended fever group at 2 weeks and later after admission, which clearly indicates that fever reflects the inflammatory reaction in cases of acute aortic dissection. The peak platelet count was recorded at 3 weeks after admission and in the present patients the time courses of changes in WBC counts and CRP concentration were identical to those reported by Komatsu et al.12

Regarding the relationship between fever and the false lumen reduction ratio, we suspected that thrombi and tissue destruction associated with aortic dissection were responsible for triggering fever. We therefore examined the relationship between duration of fever and indicators of clotting and fibrinolysis to evaluate the relationship between fever and thrombus formation, although the number of patients available for the investigation was limited. During the 1-month follow-up period, the fibrinogen level remained high irrespective of the duration of fever. TAT is a complex of thrombin and its protease inhibitor antithrombin III and its level reflects the amount of thrombin formed, which can be viewed as an indicator of the pre-thrombotic state. In the present study, the TAT level was high at 1 week after onset but had decreased by the end of the 1-month follow-up period, irrespective of the duration of fever. FDP and D-dimer are indicators of fibrinolysis system activity. FDP is a product of the degradation of fibrinogen and fibrin and is an indicator of enhanced primary and secondary fibrinolysis. D-dimer is a product of fibrin degradation and an indicator of enhancement of only secondary fibrinolysis system activity, unlike FDP. In the present study, soon after onset, FDP was significantly higher in the extended fever group than in the brief fever group, and tended to be higher in the former in the later stages of disease. These findings suggest that thrombus formation plays a major role in inducing fever. Furthermore, because the false lumen reduction ratio correlated with fever, the time course of changes in the FDP level should reflect the reduction in false lumen size. According to a recent report, the D-dimer level had a useful auxiliary means of diagnosing acute aortic dissection.13-15 In the present study, the D-dimer level had decreased by the end of the 1-month follow-up period, irrespective of the duration of fever.

It has been reported that during the course of aortic dissection, some abnormalities of the coagulation system, such as disseminated intravascular coagulation (DIC), can develop.16-18 None of the present patients developed DIC during the follow-up period, but some patients in the extended fever group exhibited marked enhancement of clotting and fibrinolysis system activity, suggesting that there is a risk for DIC in patients who undergo aortic dissection, depending on the balance between the supply and demand of each clotting and fibrinolysis system component.

Study Limitations

The present study was carried out retrospectively. Although the number of patients examined varied among the individual indicators, we know of no previous studies of fever in cases of acute aortic dissection similar to the present study. Our findings indicate that tissue destruction and thrombi associated with the false lumen induce an inflammatory reaction. It seems likely that as long as there is an unstable false lumen, in communication with the true lumen, the inflammatory reaction will not subside and fever will persist. Several questions remain: which substance is the major cause of fever in patients with acute aortic dissection? Should fever be suppressed in such patients? Should inflammation be suppressed in the acute phase? Should the clotting and fibrinolysis system activity be controlled? In any event, the present study demonstrated that in cases of acute aortic dissection (a condition with diverse complications that necessitate various tests during patient care), checking for fever (the most basic vital sign) is important in assessing the status of individual patients.

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References


