A Case of Acute Myocardial Infarction With Repetitive Stent Thrombosis During Emergent Percutaneous Coronary Intervention

Transient Decrease in Antithrombin III Activity and Heparin Resistance

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SUMMARY

A 59-year-old woman was admitted to our hospital for the treatment of an acute anterior myocardial infarction. She had a history of uncontrolled diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking. Coronary angiography revealed 90% stenosis with spontaneous dissection in the proximal portion of the left anterior descending artery. At this time, heparin was initiated for the first time. Although direct stenting (Be-stent, 3.0-18 mm) was performed for the culprit lesion, coronary dissection occurred at the left main trunk and additional stenting (Multi Link ZETA stent 3.5-15mm) was performed for the left main trunk. Soon after stenting, repetitive stent thrombosis occurred. Aspiration of the thrombus using an aspiration catheter was ineffective and repetitive angioplasty and intraaortic balloon pumping were required. Although we used 17,000 units of unfractionated heparin during the intervention, the activated coagulation time (ACT) was not prolonged (157 seconds). In the coronary care unit, the ACT and activated partial prothrombin time (aPTT) were not prolonged despite the use of large amounts of heparin (69,000 units in 2 days). Protein-S, protein-C, and heparinase testing were within normal limits and heparin-platelet factor IV complex antibody was not detected. In the acute phase, a decrease in the antithrombin III activity (65%) was noted and with administration of argatroban, prolongation of the aPTT was achieved. In the chronic phase, the decrease in antithrombin III activity and heparin resistance had improved spontaneously. It is important to recognize the existence of transient decreases in antithrombin III activity in the acute phase of myocardial infarction. (Int Heart J 2009; 50: 111-119)

Key words: Heparin resistance, Acute coronary syndrome, Antithrombin III

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PERCUTANEOUS coronary intervention (PCI) using coronary stents is widely performed for the treatment of coronary atherosclerosis, and its usefulness has been confirmed by several investigators.^{1,2)} Even in the treatment of acute coronary syndrome (ACS), coronary stenting is used commonly with good results.³⁾ However, stent thrombosis is a significant complication and sometimes results in patient death.⁴⁾

Unfractionated heparin is generally used for anticoagulation therapy for patients with ACS and it plays an important role in the treatment of ACS.⁵⁻⁷⁾ Thus, PCI with coronary stenting in the setting in which heparin fails to suppress the coagulation system makes for unfavorable results.

We describe a case in which a transient decrease in antithrombin III (AT-III) activity and repetitive stent thrombosis occurred in the acute phase of ACS and the decrease in AT-III activity improved spontaneously in the chronic phase.

CASE REPORT

A 59-year-old woman was admitted with acute anterior myocardial infarction. Two days before the onset of acute myocardial infarction, she had frequent episodes of angina pectoris. She had uncontrolled diabetes mellitus, hypertension, hyperlipidemia, obesity (body weight: 85 kg, body mass index: 32.4 kg/m²) and tobacco use (50 cigarettes/day for about 40 years). She had no previous episodes of thrombosis before this event.

Figure 1. An electrocardiogram performed on admission showed ST segment elevations in leads V1-5 and reciprocal ST depressions in leads II, III, and aVf.

Figure 2. Emergent coronary angiography revealed severe stenosis and spontaneous coronary dissection in the proximal portion of the left descending coronary artery (white arrows).

Figure 3. Direct stenting (Be-stent 3.0-18 mm) was performed for the culprit lesion, coronary dissection occurred in the left main trunk (white arrow). To repair the new dissection of the left main trunk, additional stenting (Multi Link ZETA-stent 3.5-15 mm) was performed.

Her blood pressure was 178/92 mmHg and pulse rate was regular and 115/minute on admission. No murmurs, rales or bruits were observed and the Killip class was grade I. An electrocardiogram on admission showed ST segment elevations in leads V1-5 and reciprocal ST depressions in leads II, III, and aVf (Figure 1). Her white blood cell count was increased to $16,000/\text{mm}^3$ and the hemoglobin A1c content was 11.1%. The total cholesterol concentration was 281 mg/dL and the triglyceride concentration was 305 mg/dL on admission. After admission, we also evaluated various markers of thrombosis. However, the protein S (94%), protein C (118%) and hepaplastin tests (76%) were within normal ranges and heparin-platelet factor IV complex antibody was not detected.

Emergent coronary angiography revealed spontaneous coronary dissection and severe stenosis at the proximal portion of the left anterior descending coronary artery (LAD) (Figure 2). At this time, heparin was used for the first time. Although direct stenting (Be-stent 3.0-18 mm) was performed for the culprit lesion with 10 atm, coronary dissection occurred at the left main trunk (LMT). To repair the new dissection of the LMT, additional stenting (Multi Link ZETA stent 3.5-15 mm) was performed with 10 atm (Figure 3). Soon after bail out stenting, stent thrombosis occurred in the Be-stent. Therefore, additional ballooning was performed with 14 atm using a 3.0 mm balloon. Stent thrombosis then occurred in the ZETA stent, which was implanted in the LMT. We per-

Figure 4. Soon after bail-out stenting, stent thrombosis appeared in the Be-stent (white arrows). Stent thrombosis then occurred in the ZETA stent, which was implanted at the left main trunk (black arrows). After additional balloon angioplasty, distal embolization occurred in a branch of the left circumflex artery (arrow head).

Figure 5. Stent thrombosis did not improve despite additional balloon angioplasty and thrombus aspiration using an aspiration catheter (white and black arrows). Insertion of an intraaortic balloon pump (IABP) and balloon angioplasty by the kissing balloon technique was performed. Stent thrombosis gradually improved after insertion of the IABP.

formed additional balloon angioplasty at the LMT with 14 atm using a 3.5 mm balloon. After ballooning, distal embolization occurred at a branch of the left circumflex artery (LCX) (Figure 4). Despite repetitive ballooning, stent thrombosis did not improve and we attempted to aspirate the in-stent thrombus using an aspiration catheter. However, aspiration of the thrombus was not effective. Therefore, intraaortic balloon pumping (IABP) was initiated and balloon angioplasty using the kissing balloon technique (3.5 mm balloon for LMT to LAD and 2.5 mm balloon for LMT to LCX with each 10 atm) was performed. Stent thrombosis gradually improved after insertion of the IABP and PCI was completed (Figure 5).

In this case, we used 17,000 units of unfractionated heparin during PCI. However, the activated coagulation time (ACT) just after PCI was only 157 seconds. Despite the use of a large amount of heparin, the ACT was not prolonged in this patient. After PCI, in the coronary care unit we monitored the ACT frequently (Figure 6). However, these values were not prolonged, despite the use of large amounts of additional heparin (first day: 33,000 units/day, second day: 36,000 units/day) in the coronary care unit. On the second day after admission, we measured the AT-III activity by the synthetic chromogenic substrate method

Figure 6. Frequent measurements of activated coagulation time (ACT) were performed after transfer to the coronary care unit. Despite the use of large amounts of heparin, the ACT was not prolonged in this patient. PCI indicates percutaneous coronary artery intervention.

because of the presence of heparin resistance and we found that the AT-III activity was severely decreased to 65% (normal range: 80-120%). We started argatroban (60 mg/day), which is a selective thrombin inhibitor with anticoagulation activities independent of AT-III. With the administration of argatroban, prolongation of aPTT was obtained (from 39 to 57 seconds, normal range: 29-45 seconds). About 1 to 2 weeks after the onset of acute myocardial infarction, we performed follow-up studies of AT-III activity and the decrease in AT-III activity improved spontaneously (96%, 98%, respectively). After the improvement in AT-III activity, we investigated the effect of heparin. After 5,000 units of unfractionated heparin was infused intravenously, the ACT increased from 122 to 217 seconds, and unfractionated heparin prolonged the ACT effectively.

DISCUSSION

A decrease in AT-III activity generally occurs in the state of disseminated intravascular coagulation, liver cirrhosis, nephrotic syndrome, and congenital AT-III deficiency. Specifically, a decrease in AT-III activity and vascular thrombosis occurs in AT-III deficiency. On the other hand, the relationship between AT-III activity and coronary artery disease is complicated. Callas, *et al* reported that the AT-III activity in patients with ACS is higher than in healthy individu-

als.⁸⁾ In contrast, Thompson, *et al* reported that lower AT-III activities are associated with the highest risk for progression from angina to myocardial infarction.⁹⁾ Meade, *et al* reported that an increased risk for ischemic events occurs in both the lowest and highest tertiles of AT-III values compared to the middle tertile.¹⁰⁾ In patients with ACS, AT-III activity decreases after treatment with heparin.^{10,11)} However, the degree of this decrease is usually not significant in most patients, and AT-III activity is in the normal range 24 hours after heparin therapy.¹¹⁾

Commonly, the anticoagulation ability of heparin is diminished when AT-III activity is less than 80% and disappears when AT-III activity is less than 70%. In this patient, during emergent PCI, despite the intravenous administration of large amounts of unfractionated heparin (17,000 units; 200 units/kg), the ACT was not prolonged. Even after PCI, additional use of large amounts of heparin failed to prolong the ACT. On the day of admission, we were not aware of the decrease in AT-III activity. Therefore, we could not achieve appropriate anticoagulation therapy in this patient. On the second day of admission, we found a severe decrease in AT-III activity and started argatroban administration, which is a selective thrombin inhibitor with anticoagulation activity independent of AT-III.

On the other hand, stent underexpansion is an important factor in stent thrombosis.¹²⁾ In our case, we did not use intravascular ultrasound during PCI. Thus, we were unable to verify the presence of stent underexpansion. However, we implanted both the Be-stent and Multi Link ZETA stent with 10 atm and postdilation was performed with 14 atm which was more than nominal pressure (8 atm). Furthermore, underexpansion of both stents was not detected by coronary angiography. Thus, acute stent thrombosis related to stent underexpansion may not have existed in this case.

At first, we considered that the acute myocardial infarction was associated with AT-III deficiency. However, 1 week after the onset of AMI, AT-III activity improved spontaneously. One month after the onset of AMI, we attempted to determine the effect of heparin and 5,000 units of unfractionated heparin prolonged the ACT from 122 to 217 seconds. Therefore, this patient demonstrated a transient decrease in AT-III activity in the acute phase of ACS. When treating patients with ACS, not only antiplatelet therapy but also anticoagulation therapy is important.⁵⁻⁷⁾ Atherosclerotic plaque contains tissue factor and tissue factor is believed to be highly expressed in vulnerable plaque and if the plaque is ruptured, and tissue factor strongly accelerates the extrinsic pathway, creating a hypercoagulated state.^{13,14)} In the acute phase of myocardial infarction, the ruptured plaque expresses a great amount of tissue factor and it activates the extrinsic pathway. Therefore, the coagulation system is accelerated and anticoagulation system factors such as AT-III may be consumed to suppress this excess activa-

tion of the coagulation system. AT-III suppresses the tissue factor-factor VIIa complex, factor IXa, factor Xa, and thrombin.

On the other hand, percutaneous coronary intervention itself activates hemostatic activity, reflecting platelet activation and thrombin formation in the coronary artery even in the setting of stable angina pectoris.^{15,16)} Thus, in the state of a transient decrease in AT-III activity, PCI with coronary stenting using heparin in patients with ACS has unfavorable effects. When we encounter heparin resistance and stent thrombosis during emergent PCI in the setting of ACS, we should consider that a transient decrease in AT-III activity may be one of the causes of the heparin resistance. In this situation, we should replace heparin with argatroban, which is a selective thrombin inhibitor.^{17,18)}

In this patient, we measured AT-III activity on the second day of admission. Large amounts of unfractionated heparin can decrease AT III activity.¹⁹⁾ We used a large amount of unfractionated heparin before measuring AT-III activity, because the ACT was not prolonged during emergent PCI and after transfer to the coronary care unit, despite the use of unfractionated heparin. Thus, we could not neglect the influence of the use of unfractionated heparin itself on the measurement of AT-III activity in this patient. However, even though no unfractionated heparin was used before emergent PCI, the ACT was not prolonged despite the use of 200 units/kg of unfractionated heparin during PCI in this patient. Thus, we believe that the decrease in AT-III activity might have already occurred during PCI. In this condition, the use of a large amount of unfractionated heparin due to heparin resistance might accelerate the decrease in AT-III activity, creating a vicious cycle.

If heparin resistance is encountered in the acute phase of ACS, the possibility of a decrease in AT-III activity should be considered.

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