Original Research

# D-Dimer Is Helpful for Differentiating Acute Aortic Dissection and Acute Pulmonary Embolism from Acute Myocardial Infarction

Kazuo Sakamoto, Yusuke Yamamoto, Hideharu Okamatsu, Masanori Okabe

*Saiseikai Fukuoka General Hospital, Fukuoka, Japan*

Key words: **Acute chest pain.**

**Introduction:** Acute aortic dissection (AAD), acute pulmonary embolism (PE) and acute myocardial infarction (AMI) are all emergent diseases with acute chest pain. However, it is sometimes difficult to diagnose these diseases by symptoms, ECG changes and/or cardiac biomarkers, especially immediately after onset. Because these diseases are all thrombogenic diseases, we considered that D-dimer could be helpful to differentiate these diseases. The purpose of this research was to define the D-dimer value for discrimination between AAD, PE and AMI.

**Methods:** Plasma D-dimer values of a consecutive series of 35 AAD, 22 PE and 206 AMI patients on admission were analyzed retrospectively.

**Results:** The D-dimer values of patients with AAD (32.9 ± 66.7 μg/ml, $p<0.001$) and PE (28.5 ± 23.6 μg/ml, $p<0.001$) were significantly higher than those of AMI patients (2.1 ± 3.7 μg/ml). A cutoff value of 5.0 μg/ml was effective in distinguishing AAD and PE from AMI, with a sensitivity of 68% and a specificity of 90%.

**Conclusions:** Our study showed the possibility that D-dimer could enable faster diagnosis and treatment of AAD, PE and AMI patients. We expect that the D-dimer test will be used more often for screening patients with possible AAD, PE or AMI in the emergency room. We would recommend contrast computed tomography first, not coronary angiography, in a patient with a D-dimer level higher than 5.0 μg/ml using our diagnostic kit.

*Manuscript received:*
June 6, 2010;
*Accepted:*
February 3, 2011.

*Address:*
Kazuo Sakamoto

*Department of Cardiovascular Medicine*
*Kyushu University*
*3-1-1 Maidashi*
*Higashi-ku*
*Fukuoka 812-8582*
*Japan*
*e-mail: kazuos@cardiol.med.kyushu-u.ac.jp*

Acute aortic dissection (AAD), acute pulmonary embolism (PE) and acute myocardial infarction (AMI) are all significant diseases with high mortality. Obviously, rapid diagnosis, followed by appropriate treatments, is required.[1] However, it is sometimes difficult to differentiate these diseases by symptoms, ECG changes and/or cardiac biomarkers, especially immediately after onset. To make a definite diagnosis of these diseases, we use more advanced imaging studies. Contrast computed tomography (CT) is widely used to get a definite diagnosis of AAD and PE, whereas AMI is finally diagnosed by coronary angiography (CAG), often followed by percutaneous coronary intervention.[2] Because these imaging studies are invasive, time consuming and expensive, it is important to decide whether we should choose contrast CT or CAG first to distinguish AAD and PE from AMI. Therefore, before beginning invasive imaging studies, performing a simple and quick diagnostic procedure would present significant advantages. Troponin is one of the useful biomarkers to detect AMI and D-dimer has been known to be helpful to exclude PE.[3,4] Although there are few biomarkers to detect AAD, there have been only a few reports, including one systemic review, that used D-dimer in acute aortic dissection.[5-9]

AAD, PE and AMI are all thrombo-

genic diseases. A coagulation cascade is activated in these diseases via the extrinsic pathway. Although D-dimer is a product of plasmin fibrinolysis of cross-linked fibrin, whether D-dimer could help to differentiate these three diseases has not yet been properly elucidated. We considered that the D-dimer value could be related to the amount of fibrin formation.[10] We therefore searched for a cutoff point for D-dimer levels to distinguish AAD and PE from AMI. This would allow us to make a better choice of final invasive imaging studies and hence make a quicker definite diagnosis.

## Methods

### Patients

From December 2005 to February 2008, we studied D-dimer values of a consecutive series of 35 AAD, 22 PE and 206 AMI patients and analyzed those results retrospectively. Patients with cardiopulmonary arrest were excluded. Definite diagnoses of AAD and PE were confirmed by contrast CT and those for AMI were confirmed by CAG and subsequent elevation of troponin T.

### Biochemical analysis

Blood for the examination of D-dimer levels was drawn in the emergency room as soon as possible. In about 90% of patients this was done within 24 hours from the onset of symptoms. The mean time from onset to blood draw was 13.7 hours. For the quantitative determination of D-dimer in sodium citrate plasma, a Latex-enhanced turbidimetric test (LIAS AUTO D-dimer neo, Sysmex corporation, Hyogo, Japan) was used (upper limit of normal 1.0 μg/ml). D-dimer values were obtained within 20 minutes of blood sampling.

### Statistical analysis

All statistical analyses were performed using Graphpad Prism 4.0 for Windows (GraphPad Software Inc., USA). Continuous variables were presented as mean ± SD, whereas categorical variables and frequencies were shown as percentages. Comparisons between the groups were made using the chi-square test for categorical variables, while analyses of variance for continuous variables were done using Welch's t-test and Kruskal-Wallis test with Dunnett's *post hoc* analysis as appropriate.

## Results

Baseline characteristics of AAD, PE and AMI patients, and D-dimer levels were collected and compared (Table 1). The proportions of males with AAD and AMI were larger than those with PE (63% and 73% vs. 32%, respectively). There were more diabetes mellitus patients with AMI than AAD and PE (44% vs. 15% and 14%), and more patients suffering from shock with AAD and PE than with AMI (17% and 23% vs. 2%). The D-dimer levels of the AAD (32.9 ± 66.7 μg/ml, $p<0.001$) and PE patients (28.5

**Table 1.** Patient characteristics.

| | AAD (n=35) | PE (n=22) | AMI (n=206) | p |
|---|---|---|---|---|
| Age (yrs) | 71.4 ± 11.0 | 67.5 ± 17.7 | 69.1 ± 14.3 | NS |
| Male/female | 22/13 | 7/15 | 151/55 | p<0.05 |
| BMI (kg/m$^2$) | 22.7 ± 4.2 | 22.3 ± 4.2 | 24.5 ± 4.0 | NS |
| Serum creatinine (mg/dl) | 1.14 ± 0.47 | 1.08 ± 1.07 | 1.1 ± 1.3 | p<0.05 |
| Hypertension | 31 (94%) | 7 (32%) | 135 (66%) | p<0.05 |
| Diabetes mellitus | 5 (15%) | 3 (14%) | 89 (44%) | p<0.05 |
| WBC (/μl) | 9597 ± 3357 | 9355 ± 3110 | 9397 ± 3319 | NS |
| CRP (mg/dl) | 1.86 ± 4.26 | 4.10 ± 4.68 | 1.6 ± 3.8 | NS |
| CK (IU/dl) | 96.5 ± 49.4 | 83.4 ± 37.2 | 430 ± 730 | p<0.05 |
| LDL (mg/dl) | 113 ± 36 | 116 ± 36 | 111 ± 38 | NS |
| Shock | 6 (17%) | 5 (23%) | 5 (2%) | p<0.05 |
| Smoking | 12 (34%) | 5 (23%) | 88 (43%) | NS |
| Atrial fibrillation | 1 (3%) | 3 (14%) | 26 (13%) | NS |
| D-dimer (μg/ml) | 32.9 ± 66.7 | 28.5 ± 23.6 | 2.1 ± 3.7 | p<0.05 |

AAD – acute aortic dissection; CRP – C-reactive protein; CK – creatine kinase; LDL - low-density lipoprotein; PE – acute pulmonary embolism; AMI – acute myocardial infarction.

± 23.6 μg/ml, p<0.001) were significantly higher than those of the AMI patients (2.1 ± 3.7 μg/ml) (Figure 1). In addition, we compared the D-dimer values between the AAD/PE group and the AMI group (Figure 2). The D-dimer levels of AAD/PE patients (31.2 ± 54.0 μg/ml, p<0.001) was also significantly higher than those of AMI patients (2.1 ± 3.7 μg/ml).

The receiver operating characteristic analysis yielded an optimal cutoff value to distinguish AAD/PE from AMI of 5.0 μg/ml for D-dimer, with a sensitivity of 68.4% and a specificity of 90.3% (Figure 3).

We measured serial D-dimer levels in several patients with AAD and examined three representative cases (Figure 4a). D-dimer gradually decreased in the communicating type while tending to be relatively low in the non-communicating type. In one case, D-dimer once decreased and then increased at day 5 after recanalization of the non-communicating aortic dissection. We also examined serial D-dimer measurements in three representative cases with PE (Figure 4b). D-dimer levels gradually declined after heparin infusion and only once increased further and then decreased suddenly in a patient who had intravenous tissue-type plasminogen activator (tPA) treatment followed by heparin infusion. In an elderly patient without treatment, D-dimer remained at high levels after admission. As for AMI, we examined the D-dimer of two patients serially (Figure 4c). Both were low, as normal, and had no peak after admission and treatment with percutaneous coronary angioplasty.

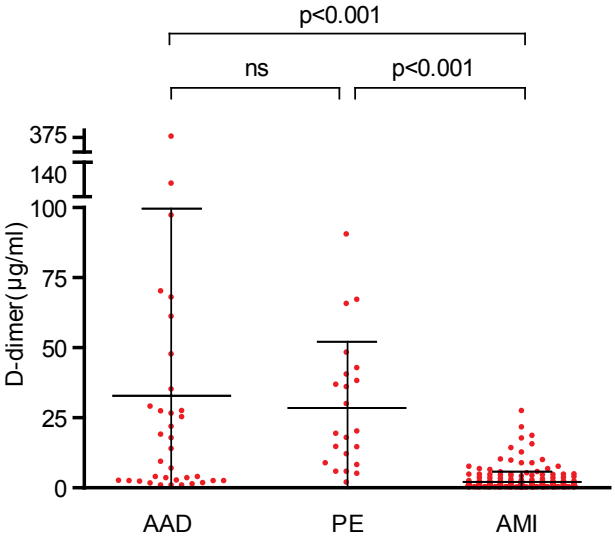


**Figure 1.** Comparison of D-dimer among AAD, PE and AMI groups. Values are mean ± SD. Statistical analysis was done using the Kruskal-Wallis test with Dunnett's *post hoc* analysis. AAD – acute aortic dissection; PE – acute pulmonary embolism; AMI – acute myocardial infarction.

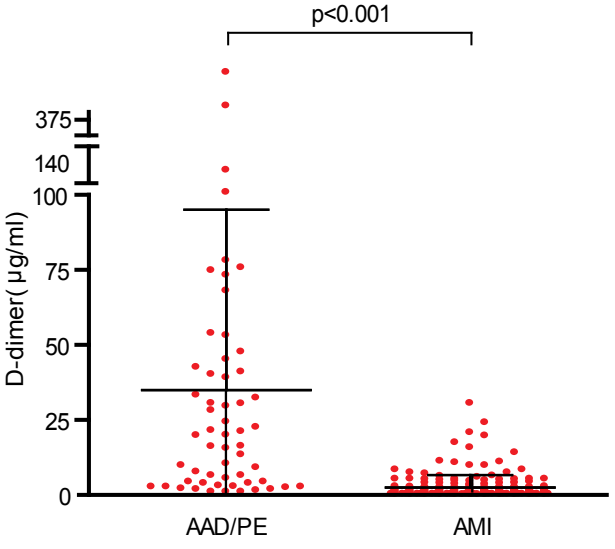


**Figure 2.** Comparison of D-dimer between the AAD/PE group and the AMI group. Values are mean ± SD. Statistical analysis was done using Welch's t-test. Abbreviations as in Figure 1.

## Discussion

Our study suggests that D-dimer could help to speed the diagnosis and treatment of AAD, PE and AMI patients, because the D-dimer value can be obtained within 20 minutes of admission to the emergency room. D-dimer in AAD/PE was significantly higher

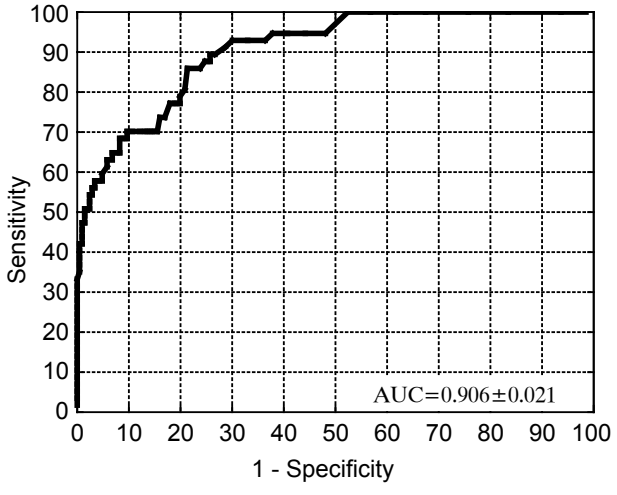


**Figure 3.** Calculation of optimal cutoff value between the AAD/PE group and the AMI group by receiver operator characteristic curve analysis. AUC – area under the receiver operator characteristic curve. Other abbreviations as in Figure 1.

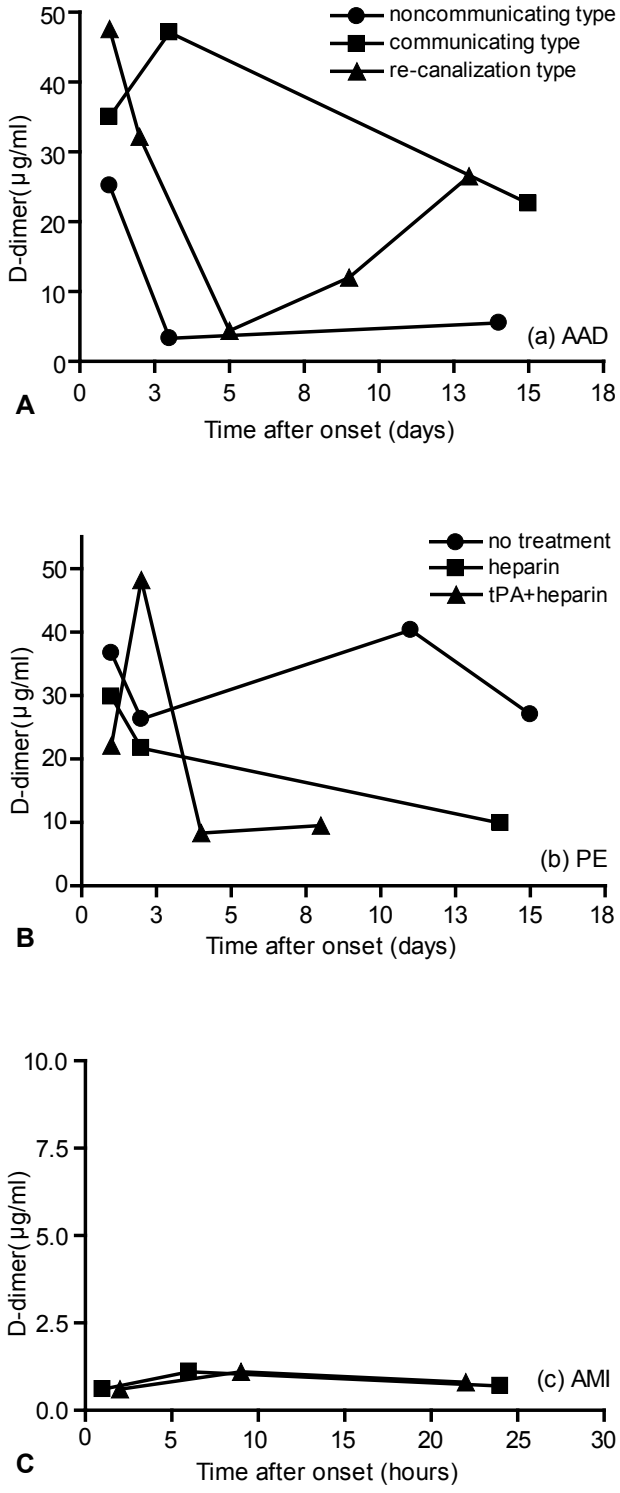


**Figure 4.** Serial D-dimer of representative (a) AAD, (b) PE and (c) AMI patients. Abbreviations as in Figure 1.

than in AMI. The cutoff D-dimer value of 5.0 μg/ml could be a useful tool to distinguish between AAD/PE and AMI, with an adequate sensitivity of 68.4% and a high specificity of 90.3%. From a clinical point of view, D-dimer values above 5.0 μg/ml suggest that patients with acute chest pain could have AAD or PE and should be sent for contrast CT first, rather than CAG, to get a definite diagnosis. A higher sensitivity (88%) but with a lower specificity (75.0%) can be achieved by using an additional cutoff value of 2.0 μg/ml, which is also clinically useful. As mentioned above, D-dimer is the degradation product of cross-linked fibrin; it is therefore suggested that the D-dimer level could be proportional to the amount of generated fibrin[10] and could be higher in larger vessel thrombosis.

We were able to demonstrate the effectiveness of our findings in an emergency case. A patient suffering from obstructed right coronary artery ostium due to acute aortic dissection, categorized as AAD, was admitted to our hospital. In this case, the D-dimer value was 70.0 μg/ml, which was far higher than the 5.0 μg/ml cutoff level. This value allowed us to send the patient to contrast CT first, rather than emergent CAG, in spite of an apparent ST elevation on the ECG. This step resulted in a significant saving in time and resources compared to current standard procedures. In addition, any attempt to administer intravenous tPA for AMI would have been risky.

Some reports have discussed the usefulness of D-dimer in the diagnosis of AAD and PE.[2,4,6-9,11] However, with the exception of a few studies,[5,9,12] D-dimer has not been reported to differentiate these thrombogenic diseases. Hazui et al investigated the discrimination between only AAD and AMI using D-dimer, and found similar results to ours.[12] Eggebrecht et al showed the elevation of D-dimer in both AAD and PE compared to AMI and non-cardiac chest pain in a smaller group than ours.[5] Although their results were mostly consistent with ours, they reported lower D-dimer than those in our studies, such as 2.2 μg/ml in AAD, 1.5 μg/ml in PE and 0.17 μg/ml in AMI patients. These differences could be due to the different measuring equipment used. Even though they measured with a latex-enhanced turbidimetric test, they used a different machine with an upper limit of normal (0.25 μg/ml) which was lower than ours (upper limit of normal 1.0 μg/ml). Suzuki et al used a cutoff value of 0.5 μg/ml, lower than the 5.0 μg/ml cutoff of our study.[9] This difference was also due to the measuring machine and/or the criterion that they used to enroll patients with suspected AAD, i.e. not all acute chest pain syndrome patients.

### Study limitations

There could be several factors influencing the D-dimer value in addition to the amount of generated thrombus. The proportion of shock state patients in the AAD and PE groups was more than in the AMI groups (17% and 32% vs. 2%). The shock state could elevate D-dimer because of the activation of systemic inflammation. Although diabetes mellitus and atrial fibrillation could increase D-dimer levels,[13,14] the D-dimer of our AMI patients was lower, despite a large number of diabetic patients. Our results might have been affected by other unknown existing factors, such as silent deep vein thrombosis,[15] malignancies,[16] and so on. Although this study was not analyzed serially by time from onset, we would expect D-dimer values to change throughout the time course.[9] Our study was a retrospective study and focused on only three thrombogenic diseases: AAD, PE and AMI. A prospective study is needed, which will enroll a larger number of patients with acute chest pain.

### Conclusions

Our study suggests that D-dimer could enable faster diagnosis and treatment of AAD, PE and AMI patients. We expect that D-dimer tests will be used more often for screening patients with possible AAD, PE or AMI in the emergency room. We would recommend contrast CT first, not CAG, in a patient with a D-dimer value higher than 5.0 μg/ml using our diagnostic kit.

### Acknowledgements

The authors would like to thank the doctors and nurses in the emergency room and the laboratory staff in our hospital.

## References

1. Erbel R, Alfonso F, Boileau C, et al. Diagnosis and management of aortic dissection. Eur Heart J. 2001; 22: 1642-1681.
2. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006; 354: 2317-2327.
3. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost. 2008; 6: 1059-1071.
4. Schutgens REG, Ackermark P, Haas FJLM, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. Circulation. 2003; 107: 593-597.
5. Eggebrecht H, Naber CK, Bruch C, et al. Value of plasma fibrin D-dimers for detection of acute aortic dissection. J Am Coll Cardiol. 2004; 44: 804-809.
6. Weber T, Högler S, Auer J, et al. D-dimer in acute aortic dissection. Chest. 2003; 123: 1375-1378.
7. Marill KA. Serum D-dimer is a sensitive test for the detection of acute aortic dissection: a pooled meta-analysis. J Emerg Med. 2008; 34: 367-376.
8. Sutherland A, Escano J, Coon TP. D-dimer as the sole screening test for acute aortic dissection: a review of the literature. Ann Emerg Med. 2008; 52: 339-343.
9. Suzuki T, Distante A, Zizza A, et al. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. Circulation. 2009; 119: 2702-2707.
10. Hochuli M, Duewell S, Frauchiger B. Quantitative d-dimer levels and the extent of venous thromboembolism in CT angiography and lower limb ultrasonography. Vasa. 2007; 36: 267-274.
11. Sodeck G, Domanovits H, Schillinger M, et al. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. Eur Heart J. 2007; 28: 3067-3075.
12. Hazui H, Fukumoto H, Negoro N, et al. Simple and useful tests for discriminating between acute aortic dissection of the ascending aorta and acute myocardial infarction in the emergency setting. Circ J. 2005; 69: 677-682.
13. Dunn EJ, Ariëns RAS. Fibrinogen and fibrin clot structure in diabetes. Herz. 2004; 29: 470-479.
14. Nakagawa K, Hirai T, Shinokawa N, et al. Relation of fibrillatory wave amplitude with hemostatic abnormality and left atrial appendage dysfunction in patients with chronic nonrheumatic atrial fibrillation. Jpn Circ J. 2001; 65: 375-380.
15. Kearon C, Ginsberg JS, Douketis J, et al. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. Ann Intern Med. 2005; 142: 490-496.
16. Costantini V, Zacharski LR. Fibrin and cancer. Thromb Haemost. 1993; 69: 406-414.