The benefits of coronary reperfusion therapy for patients with acute myocardial infarction (AMI) are well established, but this therapy must be instituted as soon as possible to achieve a good outcome. However, patients with acute aortic dissection of the ascending aorta (AADa) often have both symptoms and electrocardiogram (ECG) changes that are similar to those of AMI patients. Differentiating AMI from AADa is made more difficult because the conditions may coexist if the dissecting membrane extends into the coronary ostium. Erroneous reperfusion therapy, including thrombolysis, for patients with AADa can produce adverse outcomes. Although advanced imaging modalities such as helical computed tomography, magnetic resonance imaging and transesophageal echocardiography play an important role in the diagnosis of AADa, they cannot be used to exclude such patients from those with AMI because of the time and cost constraints. Moreover, the diagnosis of AADa by transthoracic echocardiography is limited by the need for optimal technical performance which is both operator dependent and affected by patient factors such as obesity, chronic lung disease and mechanical ventilation. Therefore, simple laboratory tests that can be routinely performed to identify patients with AADa prior to reperfusion therapy are needed.

The aim of this study was to find a simple test to distinguish such patients. Data were collected from 29 consecutive patients with AADa and 49 consecutive patients with AMI who were admitted within 4 h of the onset of symptoms. The D-dimer concentration and the ratio of the maximum upper mediastinal diameter to the maximum thoracic diameter on plain chest radiograph (M-ratio) were studied retrospectively. Setting the cutoff values of the D-dimer concentration and the M-ratio to 0.8 or 0.9 μg/ml and 0.309, respectively, gave a sensitivity of 93.1% and 93.1% for AADa, respectively, and a sensitivity of 91.8% and 85.7% for AMI, respectively.

Conclusions The D-dimer value and the M-ratio, with appropriate cutoff values, have potential as tests that can be routinely used to exclude AADa patients from patients diagnosed with AMI prior to reperfusion therapy. (Circ J 2005; 69: 677–682)
Methods

Patients

We enrolled 29 consecutive AADa patients (AADa group) and 49 consecutive AMI patients (AMI group) from January 2001 until December 2003. All patients were admitted to Osaka Mishima Emergency and Critical Care Center within 4 h of the onset of symptoms. Ten patients received heparin before arrival at the hospital and were excluded from this study. A chest radiograph, ECG and blood tests were performed for each patient immediately after admission. Diagnosis of AMI was defined as confirmation of the infarct-related artery by coronary angiography and subsequent elevation of the CK isozyme MB (MB) to more than twice the upper normal limit. Diagnosis of AADa was confirmed by chest and abdominal enhanced computed tomography.

Clinical Record Review

After approval by the Human Research Committee of the hospital, we reviewed the clinical records of each patient. We reviewed the time from the onset of symptoms to admission (TIME) and examined the results for myoglobin, CK, MB, LDH, WBC, Ht and D-dimer (Latex agglutination, Roche Diagnostic, Tokyo, Japan; measurement range: 0.22–4.5 μg/ml, normal limit ≤0.4 μg/ml, measurement time: ≈15 min) and calculated the M-ratio. An anteroposterior chest radiograph with the focal point set at 110 cm above the body surface was taken while the patients were supine in the emergency room.

Statistical Analysis

The frequency and percentage for the categorical data were determined. For continuous variables, the 25% and 75% percentiles, median, mean and standard deviation were calculated. Comparison of continuous variables between 2 groups was performed using a Mann-Whitney U test. Comparison of demographic variables for categorical data was performed using a chi-square or the Fischer exact test, as appropriate. Correlation between 2 data sets was estimated by a Spearman correlation. A value of p<0.05 was considered to be significant. Moreover, receiver-operating characteristic (ROC) curves were constructed after calculation of the sensitivity for AADa and AMI to determine the best cutoff value. The area under the curve (AUC) was also calculated and shown with 95% confidence interval (CI).

All statistical calculations were performed with commercially available statistical software (SPSS II for Windows, Version 11.0; Chicago, IL, USA).

Results

Baseline Characteristics

The clinical differences between the AADa and AMI patients are shown in Table 1. The AADa group had significantly comprised fewer male patients, less history of smoking and diabetes mellitus, a greater occurrence of hypertension, and a lower total cholesterol concentration, compared with the AMI patients. Differences in age, and in the incidence of shock, ventricular fibrillation, atrial fibrillation or renal dysfunction were not significant between the 2 groups.

Six of the AADa patients presented with ST changes on the ECG (2 of the 6 showed both ST elevation and ST depression), and 6 of the AMI patients did not present with ST elevation. The AADa group included 13 patients with a thrombosed false lumen and 16 with a patent false lumen, and 23 patients with Debakey type I (contained Debakey type retrograde IIIb) and 6 patients with Debakey type II.

Clinical Data

There were no significant differences in TIME, myoglobin or WBC between the 2 groups (Table 2). In the AADa group, the concentrations of LDH and D-dimer and the M-ratio were significantly higher, and those of CK, MB and Ht were significantly lower than the AMI group (Table 2, Fig 1).

The sensitivities for AADa and AMI of each cutoff value were calculated and used to construct the ROC curves (Fig 2). The AUC values were 0.978 (95%CI: 0.953–1.000) for the D-dimer, 0.912 (0.842–0.982) for the M-ratio, 0.840 (0.736–0.944) for LDH, 0.342 (0.217–0.466) for MB, 0.362 (0.234–0.491) for CK and 0.336 (0.204–0.468) for Ht. If the cutoff values for the D-dimer concentration and the M-ratio were set to 0.8 or 0.9 μg/ml and 0.309, respectively, the sensitivity for AADa is 93.1% and 93.1%, respectively, and the sensitivity for AMI is 91.8% and 85.7%, respectively (Fig 2). Hence, this indicates that AADa patients should have a D-dimer concentration >0.8 or 0.9 μg/ml and an M-ratio >0.309.

| Table 1 Baseline Characteristics of the Patients With AADa or AMI |
|----------------------|----------------------|----------------------|
|                       | AADa group           | AMI group            | p value |
|                       | (n=29)               | (n=49)               |         |
| Age (years)           | 65±11                | 61±9.2               | 0.103   |
| Male gender           | 16 (55.2)            | 41 (83.7)            | 0.006   |
| Smoking               | 11 (37.9)            | 31 (63.3)            | 0.030   |
| Diabetes mellitus     | 1 (3.4)              | 10 (20.4)            | 0.046   |
| Hypertension          | 25 (86.2)            | 21 (42.9)            | <0.001  |
| Total cholesterol (mg/dl) | 189±243.7           | 217±35.1             | 0.002   |
| Shock                 | 5 (17.2)             | 3 (6.1)              | 0.495   |
| Ventricular fibrillation | 0 (0)                | 0 (0)                | 0.290   |
| Atrial fibrillation   | 0 (0)                | 1 (2.0)              | 1.000   |
| Renal dysfunction     | 2 (6.9)              | 1 (2.0)              | 0.552   |

Data are presented as the mean±standard deviation or no. (%) of patients. Shock is defined as systolic blood pressure <90 mmHg and perspiration or disturbance of consciousness. Renal dysfunction is defined as serum creatinine concentration >2.0 mg/dl. AADa, acute aortic dissection of the ascending aorta; AMI, acute myocardial infarction.

| Table 2 TIME and Tests for Patients With AADa or AMI |
|----------------------|----------------------|----------------------|
|                       | AADa group           | AMI group            | p value |
|                       | (n=29)               | (n=49)               |         |
| TIME (min)            | 93±34                | 104±56.0             | 0.311   |
| Myoglobin (ng/ml)     | 118±128              | 141±136              | 0.807   |
| CK (U/L)              | 101±69.8             | 132±73.6             | 0.043   |
| MB (U/L)              | 0.9±4.7              | 2.1±2.8              | 0.012   |
| LDH (U/L)             | 224±51.6             | 167±55.0             | <0.001  |
| WBC (×10⁹)            | 12,786±4,954.7       | 11,673±6,725.2       | 0.363   |
| Ht (%)                | 40±4.5±71            | 43±3.4±30            | 0.016   |
| D-dimer (μg/ml)       | 45±68.1              | 40±5±0.4             | <0.001  |
| M-ratio               | 0.37±0.059           | 0.28±0.039           | <0.001  |

Data are presented as the mean±standard deviation. TIME, the time from the onset of symptoms to admission; AADa, acute aortic dissection of the ascending aorta; AMI, acute myocardial infarction; CK, creatine kinase; MB, CK isozyme MB; LDH, lactate dehydrogenase; WBC, leukocyte count; Ht, haematocrit; M-ratio, the ratio of the maximum upper mediastinum diameter to the maximum thoracic diameter on plain chest radiograph.
Cutoff Value for the D-Dimer Concentration

No significant correlation between the D-dimer concentration and TIME was obtained in either group (AADa group; $r=−0.077$, $p=0.690$, AMI group; $r=−0.225$, $p=0.120$; Fig 3), suggesting that elevation of D-dimer does not depend on TIME. The sensitivity for AADa was 93.8% during the first 90 min after the onset of symptoms, 90.9% in the following 90 min, and 100% beyond 180 min. There were 2 patients with a D-dimer concentration <0.8 g/ml in the AADa group, and 4 patients with a D-dimer concentration >0.9 g/ml in the AMI group. The 2 patients with a D-dimer concentration <0.8 g/ml in the AADa group had a thrombosed false lumen, so the sensitivity with or without a thrombosed false lumen was 84.6% or 100%, respectively. In addition, the D-dimer value was significantly lower in patients with a thrombosed false lumen than with a patent...
false lumen (10.1±15.4 µg/ml vs 73.9±80.7 µg/ml, p=0.001) and in patients with DeBakey type II than with DeBakey type I, indicating that the D-dimer value depends on the length of the dissection (2.0±1.0 µg/ml vs 56.6±72.5 µg/ml, p=0.004). However, patients with DeBakey type II tended more often to have a thrombosed false lumen than patients with DeBakey type I (66.6% vs 39.1%, p=0.364).

**Cutoff Value for the M-Ratio**

There were 2 patients with an M-ratio <0.309 in the AADa group and 7 patients with an M-ratio >0.309 in the AMI group. The M-ratio was also shown to be independent of TIME (data not shown).

**Sensitivity for AADa**

The correlation between the D-dimer concentration and the M-ratio was examined, and this is plotted in Fig.4. No significant correlation was obtained in AADa group (AADa group; r=0.041 p=0.831, AMI group; r=0.474 p=0.001). Both AADa patients with a D-dimer concentration <0.8 µg/ml showed an M-ratio >0.309 (0.390 and 0.315, respectively), and 2 other patients with an M-ratio <0.309 had a D-dimer concentration >0.9 µg/ml (9.3 µg/ml and 2.7 µg/ml, respectively).

Hence, simultaneous use of the original cutoff values for the D-dimer concentration or M-ratio gives a sensitivity of 100% for AADa.

**Discussion**

In the present study, the D-dimer concentration and the M-ratio were shown to have high sensitivity for AADa and AMI. These are parameters that can be determined promptly and inexpensively, and hence they may have potential as
tests that can be routinely performed for exclusion of AADs before initiation of reperfusion therapy for patients diagnosed with AMI.

D-Dimer Concentration

We propose that setting the cutoff value for the D-dimer beyond the normal limit, instead of the upper limit of normal, is important for discriminating between AMI and AADs. A previous report, which showed the efficacy of the D-dimer assay as a screening test for aortic dissection, set the cutoff value at the upper limit of normal and in the present study there were 10 AMI patients (20.4%) with a D-dimer value beyond that value and 2 AAD patients (6.9%) with a D-dimer value less than it (ie, 100% sensitivity for AADs could not be achieved). Moreover, the incidence of cases of AMI that need urgent reperfusion therapy is more frequent than AADs, so the test requires high sensitivity not only for AADs but also for AMI.

Suzuki et al reported that the sensitivity of a rapid 30-min assay for myosin heavy chain decreased with time; 100% for AAD patients within 3 h of the onset of symptoms, 83.3% for 3–6 h of onset, and 41.1% beyond 6 h, and the sensitivity for AMI patients was 83.0%. As the half-life of D-dimer is approximately 8 h, D-dimer has an advantage over myosin heavy chain in differentiating AADs from AMI.

Another previous report supports our finding that the D-dimer concentration is influenced by the presence of a thrombosed false lumen, but there was not an excessive deterioration of sensitivity for AADs in cases with a thrombosed false lumen. Shimohara et al reported that the sensitivity of the soluble elastin fragment for aortic dissection with and without a thrombosed false lumen was 0% and 88.9%, respectively. These results indicate that the D-dimer assay also has an advantage over measurement of the soluble elastin fragment.

With regard to the mechanisms underlying the elevation of D-dimer in AADs, some reports have shown the presence of a tissue factor in the smooth muscle layer of the aorta, with this factor being abundant following progression of atherosclerotic changes. In AADs, this tissue factor would pour into the bloodstream where it would activate the coagulation cascade, stimulating fibrinolytic activity and the formation of D-dimer. Moreover, in patients with a thrombosed false lumen, fresh thrombi in the lumen may also cause an elevation of the D-dimer concentration through activation of the fibrinolytic system.

The D-dimer concentration tends to be elevated in many diseases, such as pulmonary embolism, disseminated intravascular coagulation, cancer, ventricular tachycardia and fibrillation, congestive heart failure, and atrial fibrillation. Therefore, further investigation is necessary to clarify whether the D-dimer assay can differentiate AADs from these diseases, but we believe that by setting an appropriate cutoff value for the assay AADs can be differentiated from AMI in the emergency department before initiation of reperfusion therapy, even if the D-dimer value is not diagnostic for AADs because of its lack of specificity.

M-Ratio

The findings on plain chest radiographs that are suggestive of AADs include tracheal displacement, an indistinct arch, abnormal aortic contour, separation of calcification, and a wide mediastinum. Although a definition of an abnormally widened mediastinum on a plain chest radiograph has been used as the M/C ratio for exclusion of blunt aortic injury, an equivalent definition has not been developed for exclusion of AADs, as far as we are aware. Klompas reported a large variation (from 11% to 94%) in the incidence of a widened mediastinum in AADs in the present study we introduced the M-ratio. Interestingly, there was no correlation between the D-dimer concentration and the M-ratio in AADs, and simultaneous use of our cutoff values for the D-dimer concentration (0.8 or 0.9 µg/ml) or M-ratio (0.309) gave a sensitivity of 100%. If we take into account the occasional AAD patient in whom either the D-dimer or M-ratio is beyond the cutoff values, and for AMI on the occasion that both the D-dimer and M-ratio are below the cutoff values, the sensitivity for AADs and AMI is 100% and 81.6%, respectively.

Other Blood Components

In this study, there were significant differences in CK, MB, LDH and Ht between the AMI and AAD groups, but it was impossible to discriminate between them using the cutoff values for these blood components.

Study Limitations

Our study group comprised patients who had been already diagnosed with AMI or AADs, which is different to the clinical setting. We have to compare AMI patients with AAD patients who have similar symptoms and ST displacement on the ECG at least to achieve the primary purpose of our study. However, we could not design such a study because the number of AAD patients who satisfied our criteria was very small. In addition, our study has a relatively small number of patients, is retrospective and patients with acute aortic dissection of the descending aorta only (AADb) were excluded. However, it is more important for physicians to differentiate AADs from AADb before performing coronary reperfusion therapy. We regard our study as the first step to setting the cutoff value for discrimination between AMI patients and AAD patients or to detect patients with aortic dissection from patients with chest pain. Our result must be reconfirmed in a prospective and large trial of patients with chest pain and ST displacement on ECG similar to AMI. Our study, which evaluated patients within 4 h of the onset of symptoms, also has a temporal limitation for the importance of CK and MB, which mainly begin to be elevated from 6 h after the onset of symptoms in AMI patients.

Conclusions

Through the setting of appropriate cutoff values (D-dimer: 0.8 or 0.9 µg/ml; M-ratio: 0.309), these 2 simple tests can be routinely used for exclusion of AAD patients prior to reperfusion therapy for patients diagnosed with AMI. We recommend considering AAD if either the D-dimer or M-ratio value is beyond our suggested cutoff values and AMI if both the D-dimer and M-ratio values are below the cutoff values.

References


