

Diagnostic Implications of Elevated Levels of Smooth-Muscle Myosin Heavy-Chain Protein in Acute Aortic Dissection

The Smooth Muscle Myosin Heavy Chain Study

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Background: A rapid 30-minute assay of circulating smooth-muscle myosin heavy-chain protein has been developed as a biochemical diagnostic tool for aortic dissection.

Objective: To determine the sensitivity and specificity of this assay.

Design: Cross-sectional study.

Setting: 8 major cardiovascular centers in Japan.

Patients: 95 patients with acute aortic dissection, 48 patients with acute myocardial infarction, and 131 healthy volunteers.

Measurements: Levels of circulating smooth-muscle myosin heavy-chain protein.

Results: Patients with acute aortic dissection who presented

within 3 hours after onset had elevated levels of circulating smooth-muscle myosin heavy-chain protein. In these patients, the assay had a sensitivity of 90.9%, a specificity of 98% compared with healthy volunteers, and a specificity of 83% compared with patients who had acute myocardial infarction; the clinical decision limit was 2.5 $\mu\text{g/L}$. All patients with proximal lesions had elevated levels of smooth-muscle myosin heavy-chain protein, and only patients with distal lesions had decreased levels ($<2.5 \mu\text{g/L}$).

Conclusions: Levels of smooth-muscle myosin heavy-chain protein can be used to diagnose aortic dissection soon after symptom onset. The assay had the greatest diagnostic value in patients with proximal lesions.

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Aortic dissection is an uncommon acute disease associated with high mortality and morbidity (1, 2). Initial management has a critical effect on survival. While diagnosis and treatment of the disease have greatly improved in recent years as a result of newer diagnostic (3) and therapeutic (4, 5) techniques, it is still difficult to recognize at clinical presentation (6).

To aid in the initial diagnostic screening, an assay of circulating smooth-muscle myosin heavy-chain protein, a protein specific to smooth muscle that is released from damaged aortic medial smooth muscle at the onset of aortic dissection, was developed (7). Biochemical diagnosis of acute aortic dissection is attractive because it is rapid, non-invasive, and relatively easy to perform. A rapid 30-minute assay was developed for clinical use after initial studies that used an experimental assay showed promising results (8–10). Our study addressed the sensitivity and specificity of the rapid assay in acute aortic dissection.

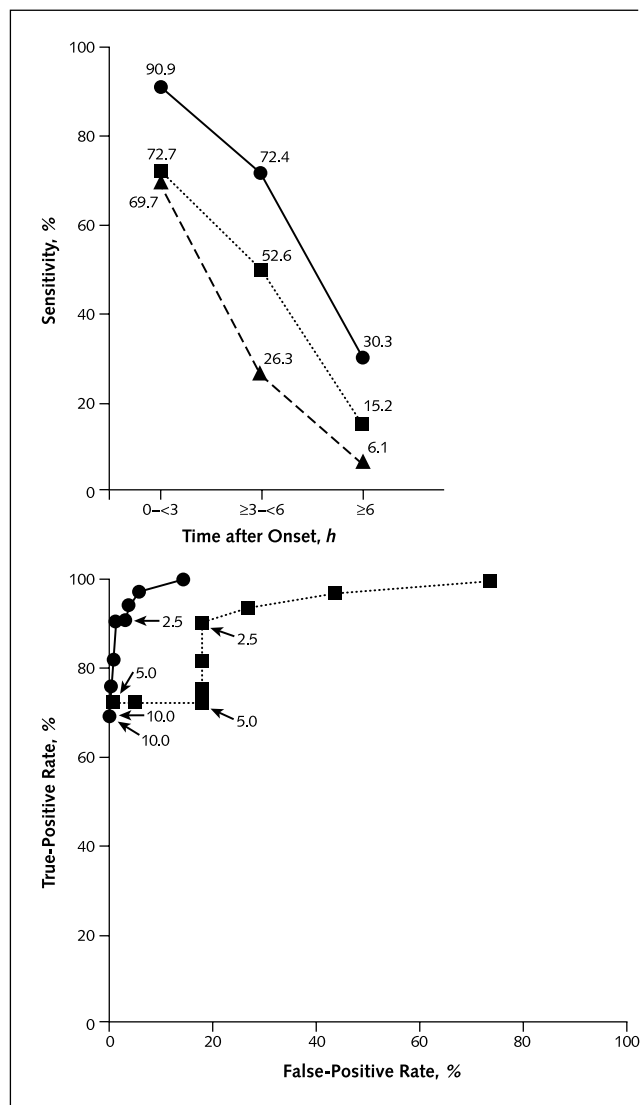
METHODS

The enzyme immunoassay of smooth-muscle myosin heavy-chain protein was developed with antibodies and re-

actions optimized for sensitive detection and minimal performance time (30 minutes). Cross-reactivity against aortic and uterine myosin was 100%; in contrast, cardiac and skeletal muscle showed cross-reactivity less than 0.05%. The measuring range of the assay was approximately 1.6 to 100 $\mu\text{g/L}$. Within-run and between-run reproducibilities as measures of analytical precision were $6.2\% \pm 1.3\%$ and $3.2\% \pm 1.4\%$, respectively (coefficient of variance). Recovery as a measure of analytical accuracy (defined as the observed vs. the expected value when purified human smooth-muscle myosin heavy-chain protein was added to patient serum) was $93.9\% \pm 10.0\%$. All assays were performed by the diagnostics division of Yamasa Corp. (Tokyo, Japan). The technical specifications and details of the assay are available from the authors.

We included patients with acute aortic dissection who presented to participating centers between August 1996 and March 1999. Eight major cardiovascular centers were selected for participation in the Smooth Muscle Myosin Heavy Chain Study because they had a large volume of early admissions for acute aortic dissection. Included patients had aortic dissection within 24 hours of onset of symptoms; the diagnosis was confirmed by imaging.

Figure 1. Sensitivity and specificity of the smooth-muscle myosin heavy-chain assay.



Top. Temporal sensitivity curves according to cutoff levels. The solid line represents a cutoff level of 2.5 µg/L, the dotted line represents a cutoff level of 5.0 µg/L, and the dashed line represents a cutoff level of 10.0 µg/L. **Bottom.** Analysis of receiver-operating characteristic curves of patients with aortic dissection compared with healthy volunteers (solid line) and patients with acute myocardial infarction (dotted line). Selected points are shown according to cutoff level (2.5, 5.0, or 10.0 µg/L). For acute myocardial infarction, the following modifications apply: x-axis, 1 - (specificity compared with acute myocardial infarction); y-axis, sensitivity compared with aortic dissection.

Traumatic aortic dissections were excluded. Each center approved the study protocols, and patient consent was obtained. Single-specimen blood sampling was done at initial presentation. Protocols for documenting clinical characteristics, including age, sex, time of onset, time of admission,

diagnosis, lesion site (according to DeBakey classification), and time of blood sampling, have been described elsewhere (9). We included 131 healthy volunteers presenting for an annual health examination as normal controls; we also included 48 patients with acute myocardial infarction to determine the specificity of the assay in distinguishing aortic dissection from other diseases that present with chest pain.

We analyzed receiver-operating characteristic (ROC) curves to show sensitivity and specificity. Results are presented as the mean ± SD. Statistical analysis was done by using commercially available software (StatView 4.0, Abacus Systems, Berkeley, California). Mann-Whitney U tests were used for two-group comparisons. A *P* value less than 0.05 was considered statistically significant. Analysis for differences across time or between healthy volunteers and patients with aortic dissection are conservative because they do not adjust for differences among centers.

RESULTS

We enrolled 95 consecutive patients with aortic dissection (58 men, 37 women; mean age, 64.7 ± 13.1 years) within the first 24 hours after onset of symptoms. This sample of predominantly male patients, ranging from middle-aged to elderly, is typical for aortic dissection. In all cases, diagnosis was confirmed by imaging. Thirty-three patients had DeBakey type I lesions, 12 had DeBakey type II lesions, and 50 had DeBakey type III lesions. Patients presented 5.9 ± 5.9 hours after symptom onset. Of importance, 35% of patients presented within 3 hours after onset and 65% presented within 6 hours after onset.

Sensitivity and Specificity

We compared serum levels of smooth-muscle myosin heavy-chain protein in patients with acute aortic dissection and 131 healthy volunteers (35 men, 13 women; mean age, 65.9 ± 11.9 years). Values were significantly higher in patients with acute aortic dissection (22.4 ± 40.4 µg/L vs. 0.9 ± 0.4 µg/L, respectively; *P* < 0.001). The highest levels (51.0 ± 52.3 µg/L) were seen in the 33 patients who presented within 3 hours after onset. Levels decreased significantly to 11.5 ± 28.5 µg/L in 29 patients in the next 3 hours (*P* < 0.001) and decreased further to 3.3 ± 5.2 µg/L in 33 patients thereafter. During the initial 3 hours after symptom onset, sensitivity was 90.9% (95% CI, 85% to 96.8%) at a cutoff level of 2.5 µg/L (the upper limit of the normal population) (Figure 1, top). Sensitivity de-

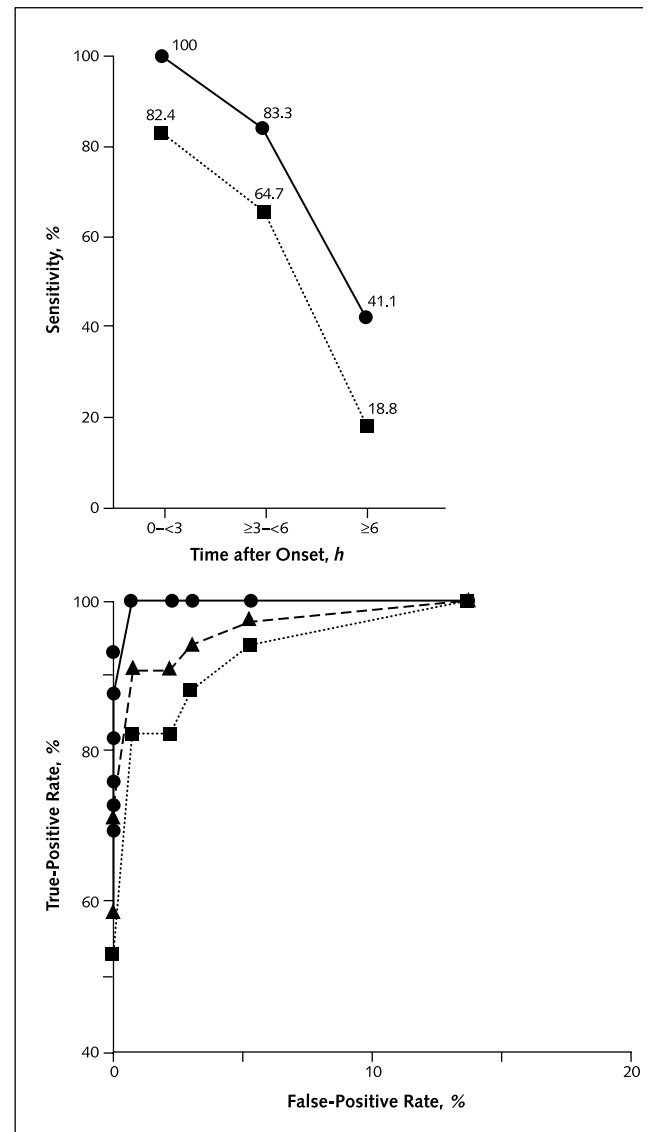
creased to 72.4% (CI, 65.3% to 79.5%) in the following 3 hours and decreased to 30.3% (CI, 23.9% to 36.7%) thereafter. The assay had a specificity of 98% and a diagnostic accuracy of 96% at the cutoff level of 2.5 $\mu\text{g/L}$ in patients with aortic dissection compared with healthy volunteers (Figure 1, bottom).

To determine the specificity of the assay in distinguishing aortic dissection from diseases that present with similar symptoms, such as chest pain, we examined levels of smooth-muscle myosin heavy-chain protein in 48 patients with acute myocardial infarction who presented within 3 hours after onset (35 men, 13 women; mean age, 65.9 ± 11.9 years). In these patients, the serum level of smooth-muscle myosin heavy-chain protein was 2.1 ± 1.6 $\mu\text{g/L}$ ($P < 0.001$ compared with acute aortic dissection). The assay had a specificity of 83% at the cutoff level of 2.5 $\mu\text{g/L}$ in patients with acute myocardial infarction (Figure 1, bottom). On the basis of these data, 2.5 $\mu\text{g/L}$ was set as the clinical decision limit because analysis of the ROC curve showed favorable sensitivity and specificity compared with normal volunteers and patients with acute myocardial infarction. Levels of smooth-muscle myosin heavy-chain protein that exceeded 10 $\mu\text{g/L}$ showed 100% specificity for aortic dissection.

Analysis according to Type of Aortic Dissection

In the first 3 hours after onset, all patients who had proximal lesions that were classified as DeBakey type I or II also had levels of smooth-muscle myosin heavy-chain protein that exceeded the clinical decision limit of 2.5 $\mu\text{g/L}$. Conversely, patients who presented with definitive aortic dissection within the first 3 hours after onset and had levels of smooth-muscle myosin heavy-chain protein less than 2.5 $\mu\text{g/L}$ had distal lesions that were classified as DeBakey type III. Levels of smooth-muscle myosin heavy-chain protein were probably lower in patients with distal lesions because the abdominal aorta has less smooth muscle than the thoracic aorta. Analysis of samples taken within 3 hours of symptom onset confirmed that levels of smooth-muscle myosin heavy-chain protein were significantly higher in proximal lesions than in distal lesions (71.4 ± 59.5 $\mu\text{g/L}$ vs. 31.8 ± 36.7 $\mu\text{g/L}$, respectively; $P = 0.03$). The assay had superior sensitivity for proximal lesions 3 to 6 hours after onset and thereafter, which was confirmed by analysis of the ROC curve (Figure 2). Thirty-three patients, 16 of whom had proximal lesions, were tested within 3 hours after symptom onset.

Figure 2. Levels of smooth-muscle myosin heavy-chain protein according to type of aortic dissection.



Top. Temporal sensitivity curves for proximal lesions (solid line) and distal lesions (dotted line) at the cutoff level of 2.5 $\mu\text{g/L}$. Bottom. Analysis of receiver-operating characteristic curves according to lesion site for patients with aortic dissection compared with healthy volunteers. The solid line indicates proximal lesions, the dotted line indicates distal lesions, and the dashed line indicates all lesions.

DISCUSSION

We found that the rapid assay of smooth-muscle myosin heavy-chain protein had a high sensitivity (90.9%) and acceptable specificity (98% compared with healthy controls, 83% compared with patients who had acute myocardial infarction) in patients with aortic dissection who presented within the first 3 hours after symptom onset.

The assay performed best in patients with proximal lesions and was less sensitive in patients who presented at a later point in the disease and had decreased levels of smooth-muscle myosin heavy-chain protein.

The sensitivity and specificity of this assay in the first 3 hours after onset are similar if not superior to those of transthoracic echocardiography (sensitivity, 59% to 85%; specificity, 63% to 96%) (11), conventional computed tomography (sensitivity, 83% to 94%; specificity, 87% to 100%) (3, 12), or aortography (sensitivity, 88%; specificity, 94%) (12). However, the assay's sensitivity and specificity were lower than those of transesophageal echocardiography (sensitivity, 98% to 99%; specificity, 77% to 97%) (3, 12), helical computed tomography (both almost 100%) (13), or magnetic resonance imaging (both 98%) (14, 15). Because this assay is the first available biochemical diagnostic tool for aortic dissection, it is important to note that comparison with these established diagnostic methods (all of which are imaging procedures) provides only an estimate of its performance. Another important point is that biochemical testing can be done at a fraction of the cost of computed tomography or magnetic resonance imaging (approximately 10%) and is similar in cost to measuring cardiac enzymes (for example, myoglobin or troponin) (16, 17). The cost of a relatively inexpensive blood test is likely to outweigh the small risk for overlooking or failing to exclude the diagnosis of aortic dissection. In addition, manual or automated measurements can be performed easily in a manner similar to that of other conventional enzyme immunoassays.

Important issues surround the practicality of this assay in clinical settings. This biochemical test would be most useful at the initial decision-making stage (triaging) in the emergency department or clinic. When examining patients presenting with acute chest pain, physicians can use the assay to help determine whether aortic dissection is a possibility. The assay may be most effective in its negative predictive role, given the low prevalence of aortic dissection in patients with chest pain (1% to 2%). It is important to note that the assay is best at detecting proximal lesions, which are more often associated with an unfavorable outcome and are therefore more likely to have devastating consequences if overlooked (18, 19). A recent registry of acute aortic dissection showed that chest pain is a marked feature of proximal lesions (20). Distal lesions are significantly more likely to present with back or abdominal pain. Therefore, the assay is likely to be most useful for

physicians determining diagnoses in patients who present with chest pain.

The diagnostic strategy for aortic dissection often involves chest radiography; echocardiography (preferably transesophageal); and an imaging procedure, such as computed tomography (preferably helical), magnetic resonance imaging, or angiography. Because it is important to diagnose this unstable disease quickly, we recommend that serum testing be performed with the initial blood panel as early as possible. The results of the assay, combined with those of a rapid imaging procedure (for example, chest radiography or echocardiography), should help physicians initially decide whether to schedule patients for surgical consultation or transfer them to a tertiary care center. The need for and urgency of additional diagnostic procedures (for example, computed tomography, magnetic resonance imaging, or angiography) may also be judged by this assay. Measurements of smooth-muscle myosin heavy-chain protein may also play an important role in risk stratification and optimal use of diagnostic procedures. Only 35% of the patients in our study presented within 3 hours of onset, thus precluding the necessary adjustments for intercenter variability and possible related confounding. A larger prospective study of an early-presenting patient sample should be done to clarify the diagnostic efficiency and accuracy of this assay combined with rapid imaging in the initial diagnostic algorithm.

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