Usefulness of Measuring the Serum Elastin Fragment Level in the Diagnosis of an Acute Aortic Dissection

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Previous reports have shown that serum elastin fragments (SEFs) may be a useful biomarker for the diagnosis of an acute aortic dissection (AAD). However, because the reference interval of SEFs has not been established, it has not been determined whether SEFs are really useful for the diagnosis of AAD. The purpose of this study was to determine the usefulness of measuring SEFs for the diagnosis of AAD. A total of 42 consecutive patients aged 68 ± 18 years who were diagnosed with an AAD were studied. Patient background and SEF levels were examined on admission. SEF levels were also measured in patients undergoing a medical examination (n = 531, age 54 ± 17 years) to compare with those with an AAD. In the control group, SEF levels increased with age (R = 0.725, p <0.001). Then, we defined the upper limit of the reference interval of SEF levels as the 97.5th percentile of control SEF grouped by decade of life from the sixth to ninth decade. The overall risk of AAD exceeding the upper limit of the reference interval at each decade was 10% (4 of 42). For patients in their 60s and 70s, median SEF levels in the AAD group (89 [77 to 104], 93 [60 to 123] ng/ml, respectively) were not significantly higher than those in the control group (79 [68 to 92], 90 [79 to 106] ng/ml, respectively; p = 0.081 and 0.990, respectively). Our data suggest that measuring SEF levels may not be useful in the diagnosis of an AAD as the upper limit of the reference interval of the SEF level was unexpectedly higher. **(Am J Cardiol 2016;■:■−■)**

An acute aortic dissection (AAD) is a life-threatening medical emergency. One of the reasons for the high mortality of AADs is that a specific diagnostic biomarker is not available. Serum elastin fragment (SEF) level was proposed as a possible diagnostic biomarker for an AAD.[1] However, confirmative studies as to the usefulness of SEFs in this capacity have not been performed, and the normal range of blood SEF levels have not been fully established. This study evaluates the usefulness of measuring SEF levels in the diagnosis of an AAD.

Methods

The study population consisted of 42 consecutive patients who were diagnosed with an AAD; 24 with communicating false lumen and 18 with non-communicating false lumen, and admitted to our academic medical center within 48 hours of symptom onset. Patient demographics, such as age, gender, Stanford classification type, and the time from symptom onset to admission, were examined. SEF levels on admission were also measured.

To determine the upper limit of the reference interval (reference range, normal range) of SEF blood levels in control subjects and to compare patients with AAD to control subjects, blood samples were obtained from 531 subjects without AAD who visited our institution for undergoing a medical examination. As previous reports showed that SEF levels increased with age,[2] we individually measured the upper limit of the SEF reference interval at each decade of life from the 50s to the 80s. SEF levels in patients with AAD were then compared to those in the control group at each decade of life. We also determined the upper limit of the reference interval of patients aged <60 or ≥ 60 years and calculated the risk of the patients with AAD whose SEF level exceeded the upper limit of these reference intervals. A comparison of SEF levels in patients with AAD and controls was also performed. The samples were collected and frozen at −80°C, and SEF levels were measured using an enzyme-linked immunosorbent assay system using a previously described method.[3] To understand the characteristics of our control group, we examined several potential clinical indicators in healthy subjects, such as age, gender, blood pressure, smoking status, and the following blood levels: total cholesterol, triglycerides, uric acid level, fasting blood glucose, and hemoglobin A1C.

The definitions of the terms used in the present study are as follows. A communicating false lumen in an AAD is the opacification of at least a portion of the false lumen with contrast media except in cases of an ulcer-like projection. A

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See page 4 for disclosure information.

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non-communicating false lumen in an AAD is the complete occlusion of the false lumen by a thrombus. Ulcer-like projections were included in this group. Hypertension is defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the active use of antihypertensive drugs. Dyslipidemia is defined as a serum total cholesterol ≥220 mg/dl, serum triglycerides ≥150 mg, or the active use of drugs for antihypercholesterolemia. Diabetes mellitus is diagnosed in patients with a fasting blood glucose ≥126 mg/dl or with a history of active drug use for diabetes. One patient with AAD was a 47-year-old man. As this was the only patient in his 40s, we classified him as being in 50s.

Statistical analysis was performed using SPSS software version 21.0 (IBM, Armonk, New York). As SEF levels appeared to be inconsistently distributed, normality was assessed using the Kolmogorov−Smirnov test. SEF distributions in some groups were not normally distributed, so they were expressed as median (twenty-fifth percentile to seventy-fifth percentile), and the Mann−Whitney *U* test was used to perform 2-group comparisons. According to the protocol recommended by the International Federation of Clinical Chemistry and National Committee for Clinical Laboratory Standards,[4,5] a reference interval was calculated as the central 95% (between the 2.5th and the 97.5th percentile) of the reference population using a nonparametric method, and the 97.5th percentile based on value ranking was considered the upper limit of that reference interval. Parametric continuous variables were expressed as a mean ± SD. The Students *t* test was used to analyze significant differences in continuous variables between the 2 groups. Differences in categorical variables between the 2 groups were evaluated using Fisher's exact test. Linear regression analyses were performed to correlate age and SEF levels, and the Pearson correlation coefficients were calculated. A value of $p < 0.05$ was considered statistically significant.

Our study protocol was approved by the ethics committee at our institution. Written informed consent was obtained from all patients and control subjects before data collection and blood sampling.

Results

The demographics of the 42 patients with AAD were as follows: average age was 68 ± 10 years, 67% (28 of 42) were men and 48% (20 of 42) were Stanford type A. Time from AAD symptom onset to blood sampling was 8.1 ± 10.6 hours across all patients with AAD, 7.8 ± 9.6 hours in those with communicating false lumen, and 8.9 ± 13.9 hours in AAD with a non-communicating false lumen. The SEF levels of patients with AAD were 100 (78 to 115) ng/ml across all patients with AAD. The SEF level in AAD with communicating false lumen of 97 (78 to 115) ng/ml was similar to that of those with non-communicating false lumen, 102 (75 to 118) ng/ml ($p = 0.979$). SEF levels in both types of AAD were shown together with controls in Figure 1.

The demographics of the 531 patients in the control group are provided in Table 1. The average age of these patients was 54 ± 17 years. We diagnosed subjects with hypertension (26%), dyslipidemia (33%), and diabetes mellitus (8%) according to the results of their physical examination and laboratory data. SEF levels were 65 (49 to 85) ng/ml in this cohort. A strong positive association existed between age (x) and SEF (y) ($y = 1.25x + 2.71$, $R = 0.725$, $p < 0.001$), illustrating a direct relation (Figure 1).

The upper limit of the reference interval at each decade of life was calculated (Figure 2) to be 116.4 (50s), 172.5 (60s), 155.1 (70s), and 222 ng/ml (80s). The risk of patients with AAD whose SEF level exceeded the upper limit of the reference interval at each decade of life was 0% (0 of 10, 50s), 6% (1 of 17, 60s), 25% (2 of 8, 70s), and 14% (1 of 7, 80s; Figure 2). The sum of the positive risk was 10% (4 of 42). For patients in their 60s and 70s, during which AAD most frequently occurred, SEF levels in the AAD group (89 [77 to 104] and 93 [60 to 123] ng/ml, respectively) were not significantly higher than those in the control group (79 [68 to 92] and 90 [79 to 106] ng/ml, $p = 0.081$ and 0.990, respectively; Figure 2, *upper*). The upper limit of reference interval 60-year-old cutoff used was 98.9 (<60) and 153.9 (≥60) ng/ml. The risk of the patients with AAD whose SEF level exceeded the upper limit of the reference interval was 70% (7 of 10, <60 years) and 22% (7 of 32, ≥60 years) (Figure 2, *lower*). The sum of the positive risk was 33% (14 of 42). In addition, comparison of SEF levels in patients with AAD and control subjects at age <60 or ≥60 years was also performed. SEF levels in patients with AAD (101 [95 to 110] and 98 [78 to 129] ng/ml) were higher than those in controls (52 [41 to 62] and 85 [71 to 103] ng/ml; $p = 0.000$ and 0.027, respectively).

Discussion

On the basis of the upper limit of the reference interval of SEF blood levels that we defined in the present study, the risk of the patients with AAD whose SEF levels exceeded the upper limit of their age group's reference interval was limited. SEF levels in patients with AAD were not significantly greater than those in control subjects in their 60s and 70s.

AAD is an important cardiovascular emergency because of its high mortality. One of the reasons for the high mortality of AAD is that a specific diagnostic biomarker, such as troponin T or troponin I for acute myocardial infarctions, is not available in AAD. Some biomarkers, such as myosin heavy chain,[6] creatinine phosphokinase BB,[7] calponin,[8] and transforming growth factor β,[9] were previously proposed. However, they have not been useful clinically. One reason for this is that they have a low specificity, and another reason is that a rapid measuring system for these biomarkers has not been established. The D-dimer level has been used clinically in patients with AAD. Although D-dimer's specificity for diagnosing AADs is low, its high sensitivity is useful for excluding AAD.[10,11] However, even if a D-dimer is normal in a patient with suspected AAD, a computed tomography scan should still be performed to avoid overlooking AAD as its sensitivity for AAD diagnosis is about 95%, not 100%.[12] SEFs were proposed as a specific biomarker for the diagnosis of AADs in 2003[1] and have been recognized as a potential biomarker for an AAD since that time.