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Serum Soluble Thrombomodulin Level on Admission Is a Useful Predictor of Treatment Response in Patients with Acute Pulmonary Thromboembolism

Taiju MATSUI, Makoto SHOJI, Masashi OTA,
Hiroto FUKUOKA, Norikazu WATANABE, Yoshino MINOURA,
Hiroyuki KAYANO, Shinji KOBA and Youichi KOBAYASHI

Abstract: Previous studies have reported elevated serum soluble thrombomodulin (sTM) concentrations in acute pulmonary thromboembolism (APTE), but no study has evaluated the relationship between the serum sTM concentration and prognosis. In the present study we investigated the correlation between the serum sTM concentration on admission and the duration of oxygen supplementation in patients admitted to the coronary care unit (CCU) for APTE to evaluate whether serum sTM is a useful predictor of treatment response. The study included 38 consecutive patients [14 men, 24 women; mean (± SD) age 59.9 ± 16.8 years] admitted to the CCU between March 2012 and July 2014 with a diagnosis of APTE confirmed by contrast-enhanced computed tomography within 7 days of onset. The severity of pulmonary embolism was classified as collapse and cardiac arrest type in three patients (8%), massive type in two (5%), submassive type in 19 (50%), and non-massive type in 14 (38%). Significant positive correlations were found for both age and creatinine clearance with duration of hospitalization, but not with duration of oxygen supplementation. There was a significant positive correlation between admission sTM concentrations and both days of hospitalization ($R = 0.57$, $P < 0.005$) and duration of oxygen supplementation ($R = 0.56$, $P < 0.01$). The findings of the present study suggest that serum sTM concentrations are promising predictors of treatment response and short-term prognosis in patients with APTE.

Key words: serum thrombomodulin, pulmonary embolism, oxygen supplementation

Introduction

Mortality during the acute phase of acute pulmonary thromboembolism (APTE) has been reported to be in the range 7%–14%\(^{1}\). In particular, patients presenting with shock caused by decreased cardiac output after substantial occlusion of the pulmonary vascular bed (patients with collapse and cardiac arrest-type or massive-type pulmonary embolism) have been reported to have a poor prognosis\(^{1–3}\). However, because poor prognosis is also observed in patients with submassive and non-massive types of pulmonary embolism in whom circulatory dynamics are

\(^{1}\)Department of Medicine, Division of Cardiology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142–8666, Japan.

\(^{*}\)To whom corresponding should be addressed.
stable, a predictor for prognosis other than hemodynamics is needed\(^4\).

Some studies have evaluated relationships of B-type natriuretic peptide and troponin T with the severity of APTE\(^5\),\(^6\), but no previous studies have focused on the relationship between treatment response and serum soluble thrombomodulin (sTM) concentrations in patients with pulmonary embolism.

In the present study we examined the correlation between serum concentrations of sTM, a blood biochemical marker, at the time of admission and the duration of either oxygen supplementation or hospitalization to determine whether sTM can be used as a predictor of treatment response.

**Methods**

The study was performed on 38 consecutive patients [14 men, 24 women; mean (± SD) age 59.9 ± 16.8 years; mean duration of hospitalization 19.9 ± 8.8 days] admitted to the coronary care unit (CCU) of Showa University Hospital between March 2012 and July 2014 with a diagnosis of APTE, confirmed by contrast-enhanced computed tomography, within 7 days of onset (Table 1). Patients with autoimmune diseases,\(^7\),\(^8\) renal failure [creatinine (Cr) > 2.0 mg / dl]\(^9\), current or previous arterial thrombosis\(^10\),\(^11\),\(^12\),\(^13\), or liver failure\(^14\),\(^15\), all of which can affect serum sTM concentrations, were excluded from the study. After hospitalization, anticoagulant therapy was administered to all patients and thrombolysis was performed in patients with unstable hemodynamics or those who were considered by their attending physicians to need such therapy.
Blood samples were collected from patients on admission before the initiation of anticoagulant therapy or thrombolysis. Serum sTM concentrations were determined in the 38 patients using a commercially available ELISA for the measurement of thrombomodulin (TM) in the blood (Kyowa Medex, Tokyo, Japan). In addition, concentrations of blood coagulation markers, namely D-dimer, thrombin–antithrombin complex (TAT), prothrombin fragment (PTF) 1 + 2, and plasminogen activator inhibitor-1 (PAI-1), were determined. The relationships of these markers with the duration of hospitalization and the duration of oxygen supplementation were compared between patients undergoing and not undergoing thrombolysis.

Oxygen supplementation was initiated if a patient’s oxygen saturation ($S_O_2$) fell below 95% on room air. Oxygen supplementation was discontinued when a patient’s $S_O_2$ could be maintained at $\geq 95\%$. Of the 26 patients requiring oxygen supplementation, three were excluded from analyses of the relationship between the duration of oxygen supplementation and biochemical markers because they initiated home oxygen therapy following discharge. In addition, one patient who died of recurrent pulmonary embolism was excluded from analyses of relationships of the duration of oxygen supplementation and hospitalization with biochemical markers.

**Statistical analysis**

The significance of differences between the two patient groups was evaluated using Student’s $t$-test, whereas Tukey’s honestly significant difference (HSD) test was used for comparisons among four groups. Differences were considered significant at two-tailed $P < 0.05$. Simple regression analysis was performed to evaluate the relationship between serum sTM concentrations and the severity of pulmonary embolism, duration of hospitalization, and the duration of oxygen supplementation. Statistical analyses were performed using JMP Pro 12 (SAS Institute, Cary, NC, USA).

**Ethics**

This study was approved by the Ethics Committee of Showa University School of Medicine (Approval no. 1703).

**Results**

The baseline clinical characteristics of the patients are given in Table 1. In terms of the severity of pulmonary embolism, three patients (8%) were classified as collapse and cardiac arrest type, two (5%) were classified as massive type, 19 (50%) were classified as submassive type, and 14 (37%) were classified as non-massive type. Of these patients, three with collapse, two with massive, 16 with submassive, and 10 with non-massive type pulmonary embolism underwent thrombolysis. Of the patients undergoing thrombolysis, three (two with submassive and one with non-massive type pulmonary embolism) developed bleeding as an adverse event.

Table 2 shows the correlation between blood coagulation markers and the duration of oxygen supplementation. There was a significant positive correlation between D-dimer and the duration of oxygen supplementation. However, the correlation between serum sTM concentrations and
the duration of oxygen supplementation was more significant ($R = 0.56$, $P < 0.01$) than that between D-dimer and duration of oxygen supplementation. There were significant correlations between the duration of hospitalization and both age ($R = 0.36$, $P < 0.01$) and Cr clearance ($R = 0.32$, $P < 0.05$). However, oxygen supplementation was not significantly correlated with either age or Cr clearance.

There were significant positive correlations between admission serum sTM concentrations and both the duration of hospitalization ($R = 0.57$, $P < 0.005$) and the duration of oxygen supplementation ($R = 0.56$, $P < 0.01$; Fig. 1). There were no significant differences in the duration of hospitalization or oxygen supplementation between the groups undergoing and not undergoing thrombolysis (Fig. 2).

In evaluating the relationship between the severity of pulmonary embolism and the duration

### Table 2. Correlations between duration of oxygen supplementation and plasma concentrations of blood coagulation markers on admission

<table>
<thead>
<tr>
<th></th>
<th>$r$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTM</td>
<td>0.56</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>0.54</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>PAI-1</td>
<td>0.39</td>
<td>n.s.</td>
</tr>
<tr>
<td>TAT</td>
<td>0.28</td>
<td>n.s.</td>
</tr>
<tr>
<td>PTF1 + 2</td>
<td>0.38</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

sTM, soluble thrombomodulin; PAI-1, plasminogen activator inhibitor; TAT, thrombin-antithrombin complex; PTF1 + 2, prothrombin fragment 1 + 2.
of oxygen supplementation, the duration of oxygen supplementation in the cardiac arrest and collapse group was significantly greater than in the submassive and non-massive groups (Fig. 3). In addition, serum sTM concentrations were significantly higher in the cardiac arrest and collapse group than in the non-massive group (Fig. 3).

**Discussion**

TM is a membrane protein present on vascular endothelial cells that binds to thrombin, thereby augmenting protein C activation and inhibiting thrombin coagulation activity. If endothelial cells are damaged, the TM expressed on endothelial cells is cleaved from the cell membrane and the cleavage product is detectable in a soluble form (sTM) in the circulating peripheral blood. Thus, sTM can be a marker of damage to endothelial cells \( ^{16-20} \).

It is known that sTM is metabolized by the liver and is excreted through the kidneys, and that sTM levels are elevated in a variety of diseases, including disseminated intravascular coagulation, acute respiratory distress syndrome, and collagen diseases \( ^{21} \). In addition, elevated blood sTM levels have been reported in patients with acute pulmonary embolism, with the mechanism responsible considered to involve an increased release of TM as a result of damage to pulmonary artery endothelial cells \( ^{21} \).

The present study demonstrated a significant correlation between the duration of oxygen supplementation and serum sTM concentrations. The mechanism is speculated to involve an increase in the release of TM from endothelial cells as a result of more pulmonary vascular beds being damaged by blood clots. This may result in elevated serum sTM concentrations.

The difference in treatment modalities between groups undergoing and not undergoing throm-
Thrombolysis was considered to have no effect on the results evaluated herein because there was no difference in the duration of oxygen supplementation between these two groups. The American College of Chest Physicians (ACCP) guidelines do not recommend the use of thrombolysis in patients whose systolic blood pressure is less than 90 mmHg (Grade 2C)\(^2\). In contrast, the Japanese guidelines recognize that thrombolysis is indicated for a wider range of diseases and that thrombolysis can be considered for patients with shock, those with unstable hemodynamics, and those with right heart strain (Grade 2A)\(^1\). Thus, the frequency of thrombolysis in patients with pulmonary embolism in Japan is higher than that in Europe and the US\(^3\). According to Marti \textit{et al}, thrombolysis decreased all-cause mortality in patients with acute pulmonary embolism, but it did not significantly decrease all-cause mortality in intermediate-risk (hemodynamically stable with objective evidence of RV dysfunction) patients with acute pulmonary embolism\(^4\). According to Chatterjee \textit{et al}, thrombolysis for intermediate-risk patients with pulmonary embolism was associated with a decreased risk of all-cause mortality, but with increased risks of major bleeding and intracerebral hemorrhage\(^5\). Thus, there is still no definitive conclusion about whether thrombolysis is indicated for acute pulmonary embolism, and further studies are needed to evaluate its indications.

The duration of oxygen supplementation tended to become longer with a higher degree of severity of pulmonary embolism. Furthermore, the present study suggests a significant relationship between serum sTM concentrations and the severity of pulmonary embolism. In the
population studied herein, the number of severe cases was small, and so increasing the sample size could increase the reliability of the statistical analysis. In an aggregate survey by the Tokyo CCU Network Scientific Committee, the rates of collapse, massive, submassive, and non-massive type pulmonary embolisms were 3%, 6%, 18%, and 46%, respectively. These rates do not differ significantly from those obtained in the present study.

**Study limitations**

The present study has several limitations. First the study was retrospective in nature; therefore, a future prospective study is needed to confirm the results reported herein. Second, only admission sTM concentrations were evaluated. Evaluation of sTM concentrations at discharge or during the late period could make the results more relevant. Third, the sample size in the present study was small. Increasing the population size would enable inclusion of a larger number of severe cases, allowing for a more reliable statistical evaluation.

**Conclusion**

Some studies have reported elevated sTM concentrations in acute pulmonary embolism, but no study has evaluated the relationship between sTM concentrations and oxygen supplementation. The results of the present study suggest that sTM concentrations may be a useful marker for predicting treatment response.

**Conflict of interest disclosure**

None of the authors have any conflicts of interest to declare.

**References**


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