Serum D-dimer Levels Are Proportionally Associated with Left Atrial Enlargement in Patients with an Acute Ischemic Stroke due to Non-valvular Atrial Fibrillation

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Abstract

Objective Left atrial enlargement (LAE) may predispose individuals to blood stasis in atrial fibrillation (AF), and thus play a crucial role in thrombogenesis. The D-dimer level is one of the surrogate markers for a hypercoagulable state and reflects thrombus formation in AF. Since the D-dimer level reflects hypercoagulability as well as thrombus and fibrin burdens, LAE could be associated with a D-dimer elevation. However, no studies have explored this association or which factors contribute to increases in the D-dimer levels in patients with AF. Therefore, we assessed whether the serum D-dimer levels are related to the left atrial volume index (LAVI) or other vascular risk factors and also evaluated the association between the D-dimer levels and the initial stroke severity.

Methods Ninety-eight consecutive patients with an acute ischemic stroke and non-valvular AF (NVAF) who were anticoagulation-naïve were enrolled, and all patients were stratified into moderate-to-severe and mild neurologic deficit groups using the National Institutes of Health Stroke Scale on admission. The association between the initial serum D-dimer levels and the LAVI was evaluated in all enrolled patients, and the serum D-dimer levels were compared between the two groups.

Results The patients were classified into two groups according to the severity of the neurologic deficit. In a partial correlation coefficient analysis adjusted for confounding factors, an increase in the initial serum D-dimer levels was significantly associated with LAVI (r=0.286; p=0.027). A linear regression analysis showed that a history of peripheral artery disease was the factor most strongly associated with the serum D-dimer level (t=3.90, p<0.001), followed by LAVI (t=2.37, p=0.021) and a history of congestive heart failure (t=2.16, p=0.035). The D-dimer levels were higher in the moderate-to-severe neurologic deficit group than in the mild deficit group, but this difference was not statistically significant (4.5±7.1 vs. 1.6±2.6 mg/L, p=0.068).

Conclusion The serum D-dimer levels were significantly associated with LAE in anticoagulation-naïve patients with an acute ischemic stroke and NVAF.

Key words: D-dimer, atrial fibrillation, acute ischemic stroke

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Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, and is associated with high risks of an ischemic stroke and systemic thromboembolism. The physiologic mechanism of thrombus formation in AF is explained by Virchow’s triad, which consists of atrial tissue damage, a hypercoagulable state and blood stasis (1, 2). The blood stasis in AF is attributed to left atrial enlargement (LAE) and the loss of normal atrial contraction (1, 2). LAE alone is not only an independent predictive factor of a first
ischemic stroke and other adverse cardiovascular events (3-7), but has also been reported to be proportionally correlated with the initial stroke severity in patients with AF, suggesting the possibility of the formation of a larger thrombus in the setting of LAE (8).

The D-dimer is a byproduct of the degradation of fibrin, and reflects thrombin and fibrin turnover (9). Regarding thrombogenesis in patients with AF, the D-dimer level is one of the surrogate markers for a hypercoagulable state, which is one component of Virchow’s triad (1, 10). Use of the D-dimer level as a reflection of the thrombogenic condition and the thrombus burden in patients with AF has been further supported by the findings that high serum D-dimer levels in AF were reduced by both anticoagulation and cardioversion to the sinus rhythm (11, 12).

The hypothesis tested in this study is that, if LAE is one of the crucial mechanisms of thrombogenesis with the subsequent formation of a larger thrombus and a severe stroke in patients with AF, LAE may be associated with D-dimer elevation, since the D-dimer level reflects hypercoagulability as well as the thrombus and fibrin burdens. In addition to this pathophysiologic association with LAE, if the serum D-dimer level is suggestive of the thrombus burden, it may be clinically reflected by the initial stroke severity.

Therefore, we assessed whether the serum D-dimer levels were related to the left atrial volume index (LAVI), as assessed by transthoracic echocardiography, and also to the initial stroke severity clinically in anticoagulation-naïve patients with an acute ischemic stroke due to non-valvular AF (NVAF).

Materials and Methods

Patients

The local ethics committee approved this study, and each patient provided written informed consent for participation. We studied 98 consecutive anticoagulation-naïve patients with an acute ischemic stroke due to NVAF who were admitted to the Department of Neurology at Seoul St. Mary’s Hospital between September 2010 and September 2013.

Patients who met all of the following inclusion criteria were enrolled: (1) ischemic stroke presenting within two days of stroke onset based on the clinical history and a neurologic examination with compatible new lesions on magnetic resonance (MR) diffusion-weighted images (DWI); (2) a past medical history of AF or evidence of AF on continuous electrocardiographic monitoring in the emergency department or stroke unit, as well as 24-hour Holter monitoring during admission, regardless of the AF pattern (paroxysmal, persistent or permanent); (3) no anticoagulant therapy within three months, and a normal activated partial thromboplastin time (aPTT) and prothrombin time international normalized ratio (PT INR); and (4) no cardiac valvular disease on echocardiography. Patients were excluded if they had any of the following: (1) focal atherosclerotic stenosis of the vessels proximal to the ischemic lesions as a possible cause of an artery-to-artery embolism; (2) any laboratory or clinical findings suggestive of infectious, inflammatory, vasculitic, demyelinating or connective tissue diseases; (3) a significant pre-existing disability (defined as modified Rankin scale ≥2) from any condition; (4) a history of stroke in the past three months; or (5) transient, reversible AF caused by hyperthyroidism or a perioperative state (within two weeks of surgery).

The clinical information obtained included age, sex, smoking status and a history of hypertension, diabetes mellitus, congestive heart failure (CHF), ischemic heart disease, peripheral artery disease (PAD) or a previous ischemic or hemorrhagic stroke. All patients underwent a detailed clinical evaluation including a neurologic examination, laboratory tests, chest radiography, 12-lead electrocardiography, continuous electrocardiographic monitoring, 24-hour Holter monitoring, transthoracic and/or transesophageal echocardiography, brain magnetic resonance imaging (MRI), and contrast-enhanced MR angiography (MRA) or computed tomography angiography (CTA).

Assessment of the stroke severity

The severity of a stroke was assessed at the time of admission using the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits) (13). The ischemic stroke symptom severity was dichotomized into mild versus moderate-to-severe neurologic deficits using an NIHSS score cut-off of 10, based on previous studies (14, 15).

Assessment of the left atrial volume index and serum D-dimer levels

A cardiologist (HP) used echocardiography to measure the LAVI. The left atrial volume (LAV) was assessed using the biplane area-length method, in accordance with the American Society of Echocardiography standard guidelines (16). The LAVI was calculated as the LAV divided by the body surface area for each patient.

A blood sample for measuring the serum D-dimer level was obtained immediately after admission to the emergency department, before any intravenous fluids or medications had been administered.

Statistical analyses

Statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, USA). Pearson’s χ² test, an independent sample t-test and Fisher’s exact test were used as appropriate. The correlations between serum D-dimer levels and LAVI were determined using the partial correlation coefficient and a multiple linear regression analysis adjusted for the CHA2DS2-VASc risk factors (CHF, hypertension, age, diabetes, a prior stroke/transient ischemic attack, vascular disease, female sex) (17). The D-dimer levels in the mild and moderate-to-severe neurologic deficit groups were compared using an analysis of covariance.
Table 1. Demographic and Clinical Characteristics of Moderate to Severe (defined as NIHSS ≥10) versus Mild Neurologic Deficit (NIHSS <10) Groups in Patients with Ischemic Stroke and Non-valvular AF.

|                          | Total (n=98) | Mild neurologic deficit group (n=61) | Moderate to severe neurologic deficit group (n=37) | p value |
|--------------------------|-------------|-------------------------------------|---------------------------------------------------|---------|
| Age (yrs), mean±SD       | 72.2±9.1    | 70.3±9.5                            | 75.2±7.6                                          | 0.009** |
| Male, No. (%)            | 64 (65.3)   | 40 (65.6)                           | 24 (64.9)                                         | 1.000   |
| Initial NIHSS score, mean±SD| 8.4±7.5     | 3.6±7.6                             | 16.4±6.0                                          | <0.001**|
| Location of stroke in left hemisphere, No. (%) | 48 (49.0) | 29 (47.5) | 19 (51.4) | 0.668   |
| Hypertension, No. (%)    | 63 (64.3)   | 34 (55.7)                           | 29 (78.4)                                         | 0.030*  |
| Diabetes mellitus, No. (%)| 25 (25.5)   | 16 (26.2)                           | 9 (24.3)                                          | 1.000   |
| Smoking, No. (%)         | 27 (27.8)   | 14 (22.9)                           | 13 (35.1)                                         | 0.253   |
| Previous stroke, No. (%) | 12 (12.2)   | 8 (12.6)                            | 4 (11.1)                                          | 0.769   |
| Ischemic heart disease, No. (%) | 19 (19.4) | 9 (14.8) | 10 (27.0) | 0.188   |
| Past history of congestive heart failure, No. (%) | 5 (5.1) | 0 | 3 (8.1) | 0.051   |
| Peripheral artery disease, No. (%) | 2 (2.0) | 1 (1.6) | 1 (2.7) | 1.000   |
| CHA2DS2-VASC score       | 3.0 ± 1.8   | 2.6 ± 1.7                           | 3.6 ± 1.9                                         | 0.010*  |
| Body mass index, mean±SD | 23.8±3.5    | 25.7±3.6                            | 23.8±3.3                                         | 0.880   |
| History of taking antiplatelet agents, No. (%) | 50 (51.0) | 32 (53.3) | 18 (48.6) | 0.681   |
| Statin use, No. (%)      | 20 (20.4)   | 8 (13.6)                            | 12 (32.4)                                         | 0.038*  |
| Diagnosed as AF previously, No. (%) | 45 (45.9%) | 23 (37.7) | 22 (59.5) | 0.040*  |
| PT INR, mean±SD          | 1.1±0.3     | 1.1±0.3                             | 1.1±0.3                                          | 0.200   |
| Serum creatinine (mg/dL) | 1.1±0.9     | 1.1±0.9                             | 1.0±0.4                                          | 0.375   |
| MDRD-eGFR (mL/min/1.73m2)| 79.1±28.4   | 86.6±23.5                           | 83.1±24.9                                        | 0.325   |
| Plasma total homocysteine (ȝmol/L) | 11.8±5.3 | 11.1±4.1 | 13.1±6.8 | 0.120   |
| Left ventricular ejection fraction (%), mean±SD | 58.0±10.6 | 58.6±11.2 | 57.0±9.4 | 0.384   |
| Left atrium volume index (mL/m2), mean±SD | 57.1±25.4 | 52.9±19.2 | 63.7±31.9 | 0.029*  |

*Posterior circulation infarction includes infarction in the vertebral, basilar, posterior cerebral artery territories. AF: Atrial fibrillation, PT INR: Prothrombin time international normalized ratio, MDRD-eGFR: Estimated Glomerular Filtration Rate using Modification of Diet in Renal Disease, T: total participants, M: male, F: female

Analyses were performed by the independent sample t-test, Fisher’s exact test or χ² test.

*p<0.05, **p<0.01.

(ANCOVA) adjusted for the CHA2DS2-VASC risk factors.

**Results**

**Baseline characteristics**

A total of 98 consecutive anticoagulation-naïve patients with an acute infarction and NVAF were included. The study population included 64 (65.3%) men, and the mean age at the time of the baseline examination was 72.2±9.1 years (range, 46-92). Hypertension (n=63, 64.3%) was the most common vascular risk factor, followed by smoking (n=37, 37.8%), diabetes mellitus (n=25, 25.5%), dyslipidemia (n=20, 20.4%), an ischemic heart disease (n=19, 19.4%), a previous stroke (n=12, 12.2%), CHF (n=3, 3.1%) and PAD (n=2, 2%). The median body mass index (BMI) was 23.8±3.5 kg/m² (range, 16-36). Among 45 patients who had been diagnosed with NVAF previously, 25 were taking anti-platelet agents, and among 19 with an ischemic heart disease and 12 with a stroke, 25 were taking anti-platelet agents. The mean value for the LAVI was 57.1±25.4 mL/m².

Table 1 shows the clinical and demographic characteristics of the moderate-to-severe neurologic deficit group, the mild neurologic deficit group and the entire study population.

**Association between the serum D-dimer levels and left atrial volume index**

After adjusting for the CHA2DS2-VASC risk factors, the serum D-dimer levels were positively correlated with LAVI (r=0.286; p=0.027) in a partial correlation coefficient analysis (Fig. 1).

**Association between the serum D-dimer levels and other parameters**

The patient age, initial NIHSS scores, CHA2DS2-VASC total scores, serum creatinine, estimated glomerular filtration rate, homocysteine and left ventricular ejection fraction were

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were classified into the mild neurologic deficit group. Among the 98 ischemic stroke patients, 37 were classified into the moderate-to-severe neurologic deficit group and 61 into the severe neurologic deficit group and 61 stroke severity (11).

Association between the serum D-dimer levels and stroke severity

Among the 98 ischemic stroke patients, 37 were classified into the moderate-to-severe neurologic deficit group and 61 were classified into the mild neurologic deficit group. After adjusting for the CHA$_2$DS$_2$-VASc risk factors using an ANCOVA test, the D-dimer levels were higher in the moderate-to-severe neurologic deficit group than in the mild group; this difference was not statistically significant, but showed a strong trend (4.5±7.1 vs. 1.6±2.6 mg/L, p=0.068) (Fig. 2).

Discussion

In this study of anticoagulation-naïve patients with an acute ischemic stroke due to NVAF, increases in the serum D-dimer levels were significantly associated with increases in LAE. A history of PAD and a history of CHF were also independently associated with a D-dimer elevation. Regarding the stroke severity, the D-dimer levels were higher in the moderate-to-severe neurologic deficit patients than in the mild patients, although this was not statistically significant.

Our findings could provide possible novel explanations as to why serum D-dimer levels are increased in patients with AF (18) and are related to adverse cerebrovascular events (19) because, to the best of our knowledge, this study is the first to explore which factors in patients with NVAF contribute to and are associated with increases in D-dimer levels. The anticoagulation-naïvet of the entire study population was also an advantage over other studies in evaluating the D-dimer levels, since anticoagulation reduces these levels (11).

The positive correlation between D-dimer levels and LAE in this study further supports the assertion that LAE may be related to the formation of a larger thrombus due to increases in the stagnant blood volume and the surface area within the asystolic left atrium, and this thrombogenic condition may be reflected by the D-dimer level. Therefore, the D-dimer level may serve as a surrogate marker for LAE, blood stasis, and thrombogenic conditions. The serum D-dimer level could be helpful for refining the clinical risk stratification for predicting a stroke and thromboembolism in patients with AF. The D-dimer level has been reported to have a strong trend (4.5±7.1 vs. 1.6±2.6 mg/L, p=0.068) (Fig. 2).

Table 2. Associations of D-dimer with Risk Factors Including Left Atrial Volume Index and CHA$_2$DS$_2$-VASc Risk Factors by Multiple Linear Regression Analysis in Patients with Acute Ischemic Stroke due to Non-valvular AF.

| Variables                          | β ± SE | t value | p value |
|------------------------------------|--------|---------|---------|
| Congestive heart failure           | 5.44 ± 2.52 | 2.16 | 0.035*  |
| Hypertension                       | 2.10 ± 1.07 | 1.95 | 0.055   |
| Age                                | -0.02 ± 0.06 | -0.42 | 0.676   |
| Diabetes mellitus                  | -1.14 ± 1.03 | -1.10 | 0.276   |
| Previous stroke                    | 1.50 ± 1.52 | 1.03 | 0.276   |
| Ischemic heart disease             | 1.22 ± 1.17 | 1.03 | 0.276   |
| Peripheral artery disease          | 12.93 ± 3.32 | 3.90 | 0.000** |
| Female sex                         | -0.29 ± 0.12 | -2.37 | 0.021** |
| Left atrium volume index           | 0.05 ± 0.02 | 2.37 | 0.021** |

SE : standard errors
*adjusted R$^2$ = 0.467, F=8.021 (p=0.001).
be significantly associated with increased frequencies of stroke, stroke progression and even death (19-23).

Our findings of significant associations between D-dimer levels and LAE as well as CHF in AF imply that elevated D-dimer levels may be a secondary phenomenon of blood stasis resulting from the structural changes of the heart, rather than an independent thrombogenic marker (24). Substantial synergism between AF and CHF has been reported (25). For instance, patients with AF tend to have decompensation and changes that lead to CHF and, conversely, patients with CHF also tend to develop AF caused by an elevated filling pressure and an endothelial dysfunction in the left atrium. In addition, LAE has been regarded as a barometer of chronic diastolic dysfunction and burden. Therefore, these three conditions frequently coexist and interact on a daily clinical basis, and the serum D-dimer levels seem to be associated with all of these conditions in which blood stasis or stagnation occurs.

Our study has demonstrated a non-significant but strong trend in the D-dimer level as an indicator of the stroke severity. However, another previous study showed that, while the D-dimer levels were higher in patients with a severe stroke, after adjusting for confounding factors, this was not statistically significant (26). Further studies are thus necessary to address the relationship between the D-dimer level and the stroke severity.

The finding of increased serum D-dimer levels in patients with PAD in this study agrees with several cross-sectional studies that demonstrated an association between elevated D-dimer levels and lower ankle-brachial indices (27-29). However, there continues to be a controversy surrounding the relationship between the D-dimer level and PAD (30), and the number of patients with PAD in this study was too small to establish an association.

There are several limitations to this study. First, the number of enrolled patients was small because the number of anticoagulation-naïve acute ischemic stroke patients with NVAF was smaller than expected. Further large-scale studies are needed to confirm our findings. Second, there could have been a selection bias because we included only patients capable of undergoing echocardiography, and thus patients in a poor clinical condition may have been excluded.

In conclusion, increased serum D-dimer levels were significantly associated with LAE and had a strong trend for an association with more severe initial neurologic deficits in anticoagulation-naïve patients with an acute ischemic stroke due to NVAF. The evaluation of the serum D-dimer levels could be helpful as a potential surrogate and predictive marker for LAE and adverse cardiovascular events.

The authors state that they have no Conflict of Interest (COI).

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