Lipoprotein(a), Left Atrial Appendage Function and Thromboembolic Risk in Patients With Chronic Nonvalvular Atrial Fibrillation

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Lipoprotein(a) (Lp(a)) has a prothrombotic effect by modulating the fibrinolytic system. The purpose of the present study was to determine whether serum Lp(a) levels are associated with an increased risk of thromboembolism in chronic nonvalvular atrial fibrillation (NVAf). Clinical, laboratory and transesophageal echocardiographic data were collected in 172 consecutive, non-anticoagulated patients with chronic NVAf. Thirty-four patients (thromboembolic group) had a recent (<1 month) embolic event and/or a left atrial thrombus on transesophageal echocardiography. The thromboembolic group had a higher frequency of spontaneous echo contrast (94 vs 58%, $p<0.0001$), increased concentrations of Lp(a) (median: 31.5 vs 15.5 mg/dl, $p<0.0001$) and fibrinogen (median: 352 vs 314 mg/dl, $p=0.0015$), larger left atrial dimensions (median: 5.1 vs 4.8 cm, $p=0.0078$), and reduced left atrial appendage (LAA) flow velocities (median: 9.5 vs 21.2 cm/s, $p<0.0001$) than the nonthromboembolic group. Multivariate analysis identified 3 independent predictors of thromboembolism: Lp(a) level ≥ 30 mg/dl (odds ratio (OR) 9.5, 95% confidence interval (CI) 4.4–20.4, $p<0.0001$), LAA flow velocity of <20 cm/s (OR 8.7, 95% CI 3.3–23.0, $p=0.0003$) and a fibrinogen concentration of <377 mg/dl (OR 3.2, 95% CI 1.5–6.9, $p=0.0201$). The Lp(a) elevations and reduced LAA flow velocities are independently associated with thromboembolism in chronic NVAf. (*Jpn Circ J* 2000; 64: 93–98)

Key Words: Atrial fibrillation; Left atrial appendage; Lipoprotein(a); Thromboembolism; Transesophageal echocardiography

Several epidemiologic studies have established a strong link between lipoprotein(a) (Lp(a)) and atherosclerosis.^{1–3} In addition to the atherogenic nature of Lp(a), it has been suggested that Lp(a) elevations exert a thrombogenic effect by modulating the fibrinolytic system.^{4–6} Lipoprotein(a) consists of a low density lipoprotein bound by a disulfide bond to apoprotein(a), which has a striking structural similarity to the fibrinolytic proenzyme plasminogen.⁷ Several in vitro studies have demonstrated that Lp(a) binds to fibrin and competes with plasminogen and tissue-type plasminogen activator for both fibrin binding sites and endothelial cell binding sites.^{4,6,8} Survivors of myocardial infarction who fail to recanalize the infarct-related artery have greater plasma Lp(a) concentrations than those with a patent artery.⁹ A recent study described the attenuation of endogenous fibrinolysis by apoprotein(a) in an in vivo model of experimental venous thrombosis.¹⁰

Chronic nonvalvular atrial fibrillation (NVAf) is associated with an increased risk of ischemic stroke and peripheral embolism.^{11,12} In some patients with chronic NVAf, left atrial thrombi were observed on transesophageal

echocardiography (TEE).^{13,14} Transesophageal echocardiography provides other useful information such as the grade of spontaneous echo contrast (SEC) and the LAA function.^{15–18} The LAA behaves as an enlarged static pouch in NVAf, which may predispose to stasis of the blood and subsequent thrombosis.^{15,17,18} Recently, an association between elevated serum Lp(a) and left atrial thrombosis has been identified, correlating serum Lp(a) concentrations with thrombosis in vivo.¹⁹ The purpose of the present study was to determine whether serum Lp(a) elevations are associated with an increased risk of thromboembolism in chronic NVAf.

Methods

Patient Selection

The research protocol was approved by our institutional review board and informed consent was obtained from all patients before undergoing TEE. Transesophageal echocardiography studies were performed in 198 consecutive patients with chronic NVAf referred for evaluation of thromboembolic risk between December 1995 and May 1998. Patients with a history of atrial fibrillation of >6 months duration, and without evidence of rheumatic mitral stenosis, severe mitral regurgitation, or a history of mitral surgery were enrolled in the study. Patients with NVAf who had been treated with warfarin prior to TEE ($n=21$) were excluded. As most left atrial thrombi completely resolve after a median of 4 weeks of warfarin therapy,²⁰ the incidence of left atrial thrombi would be underestimated if

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patients with anticoagulation therapy were included. Patients (n=5) with a history of stroke or peripheral embolism >4 weeks prior to TEE were also excluded, as laboratory and echocardiographic data would not reflect those at the time of the embolic event. Therefore, 172 patients (109 men, 63 women) with a median age of 69 years (interquartile range 64–74 years) were included in the study.

Clinical Features and Thromboembolic Event

The medical records of all patients were reviewed to determine the following clinical features: age, sex, history of systemic hypertension, diabetes, or congestive heart failure, ischemic stroke or peripheral embolism. Ischemic stroke was defined as the sudden onset of a focal neurologic deficit that persisted and was associated with a nonhemorrhagic, nonlacunar infarct on brain imaging. A peripheral embolus was defined as the abrupt occlusion of an artery supplying the legs, arms, or viscera documented by either angiography or surgical inspection.

Echocardiography

All patients underwent transthoracic and transesophageal echocardiography, the details of which have been described previously.¹⁹ The M-mode left atrial dimension was measured in the parasternal long axis view according to the recommendations of the American Society of Echocardiography.²¹ Transesophageal echocardiography was performed within 1 week (mean±standard deviation (SD): 1.5±0.8 days) of transthoracic echocardiography using a biplane probe. In patients with ischemic stroke or

peripheral embolism, the TEE was performed within 4 weeks of the event (mean±SD: 15±4 days).

Thrombi were defined as a mass adhering to the wall of the left atrium or LAA with either independent motion or a different echogenic density. The SEC was defined as the presence of dynamic, swirling, smoke-like echoes, distinct from those caused by excessive gain.²² The LAA peak flow velocity was obtained by placing the pulsed Doppler sample volume at the orifice of the appendage. The emptying peak outflow velocity signals within each RR interval were averaged over a minimum of 8 cardiac cycles.

Transesophageal echocardiography studies were analyzed by 2 experienced echocardiographers who were unaware of the clinical and laboratory data. Any discrepancy was resolved by consensus. Interobserver concordance for the presence of left atrial thrombus and SEC, and interobserver variability of the LAA peak flow velocity have been described previously.¹⁹

Blood Sampling and Assay

Fasting blood samples were obtained on the day of the TEE study. In patients with an acute embolic event, Lp(a) levels were determined 4 weeks after the event, as Lp(a) may have characteristics similar to an acute-phase reactant.²³ Details of the blood assays have been described elsewhere.¹⁹

Statistical Analysis

Students t test was used to compare all continuous variables. The concentrations of Lp(a) and LAA flow velocity were evaluated using the Mann-Whitney test due to skewed distributions. All continuous variables are presented as median and interquartile ranges. Differences in categorical variables were compared using the chi-squared test or Fisher's exact test if applicable. Multivariate logistic regression analysis was performed to identify independent predictors of thromboembolism. Factors with a value <0.1 on univariate analysis were selected for multiple regression. Odds ratios were estimated using a multivariate logistic regression model as follows: serum Lp(a) concentration (≥30 mg/dl vs <30 mg/dl), LAA flow velocity (<20 cm/s vs ≥20 cm/s), left atrial dimension (>5.3 cm vs ≤5.2 cm) and fibrinogen concentration (>377 mg/dl vs ≤377 mg/dl). The pathologic effect of Lp(a) has been linked to a threshold value ≥30 mg/dl according to previous reports^{3,24} and a threshold value of LAA flow velocity <20 cm/s was used.^{25,26} A fibrinogen of 377 mg/dl and a left atrial dimen-

Table 1 Baseline Clinical Characteristics of the Subjects (n=172)

Age (years)	69 (64, 74)
Male (n)	109 (63%)
Lp(a) (mg/dl)	17.0 (9.0, 27.5)
Fibrinogen (mg/dl)	322 (269, 377)
Plasminogen activity (%)	97 (84, 107)
Total cholesterol (mg/dl)	190 (162, 213)
Left atrial dimension (cm)	4.8 (4.4, 5.3)
LAA flow velocity (cm/s)	18.6 (13.2, 26.7)
Spontaneous echo contrast (n)	112 (65%)
Hypertension (n)	98 (57%)
NIDDM (n)	23 (13%)
Congestive heart failure (n)	22 (13%)

LAA, left atrial appendage; Lp(a), lipoprotein(a); NIDDM, non-insulin dependent diabetes mellitus. Data presented are the median and interquartile range.

Table 2 Comparison of Clinical, Echocardiographical and Laboratory Variables Between Patients With and Without Thromboembolism

	Thromboembolism		p
	Present (n=34)	Absent (n=138)	
Age (years)	67 (63, 73)	69 (64, 74)	0.98
Male (n)	25 (74%)	84 (61%)	0.17
Lp(a) (mg/dl)	31.5 (18.0, 39.0)	15.5 (8.0, 23.0)	<0.0001
Fibrinogen (mg/dl)	352 (295, 453)	314 (263, 369)	0.0015
Plasminogen activity (%)	97 (86, 110)	96 (83, 105)	0.18
Total cholesterol (mg/dl)	189 (154, 224)	190 (163, 211)	0.96
Left atrial dimension (cm)	5.1 (4.7, 5.5)	4.8 (4.4, 5.2)	0.0078
LAA flow velocity (cm/s)	9.3 (8.3, 14.0)	21.2 (15.3, 28.8)	<0.0001
Spontaneous echo contrast (n)	32 (94%)	80 (58%)	<0.0001
Hypertension (n)	22 (65%)	76 (55%)	0.31
NIDDM (n)	6 (18%)	17 (12%)	0.63
Congestive heart failure (n)	5 (15%)	17 (12%)	0.77

LAA, left atrial appendage; Lp(a), lipoprotein(a); NIDDM, non-insulin dependent diabetes mellitus. Data presented are the median and interquartile range.

Fig 1. Frequency distribution of serum lipoprotein(a) (Lp(a)) levels and box plot graph of serum Lp(a) concentration in patients with and without thromboembolism. Values shown are median (center rule in box) with 25th percentile (lower rule of box), 75th percentile (upper rule of box), 10th percentile (lower short bar) and 90th percentile (upper short bar).

Fig 2. Frequency distribution of left atrial appendage (LAA) flow velocity and box plot graph of LAA flow velocity. Values shown are median (center rule in box) with 25th percentile (lower rule of box), 75th percentile (upper rule of box), 10th percentile (lower short bar) and 90th percentile (upper short bar).

sion of 5.3 cm were determined as the 75th percentile. p values <0.05 were considered significant.

Results

Baseline Characteristics

The baseline characteristics of the 172 patients studied are displayed in Table 1. Overall, 98 (57%) had a history of systemic hypertension, 23 (13%) had a history of diabetes mellitus, and 22 (13%) had a prior history of congestive heart failure.

The predominant etiologies predisposing to atrial fibrillation were systemic hypertension ($n=91$), hyperthyroidism ($n=12$), hypertrophic cardiomyopathy ($n=8$), dilated cardio-

myopathy ($n=6$), chronic obstructive lung disease ($n=2$), coronary artery disease ($n=2$), and sinus node dysfunction ($n=1$). No cause was identified in 50 of the patients. The median serum Lp(a) concentration was 17.0 mg/dl (interquartile range 9.0–27.5), and the median fibrinogen concentration was 322 mg/dl (interquartile range 269–377). The median left atrial diameter was 4.8 cm (interquartile range 4.4–5.3), with a LAA peak flow velocity median of 18.6 cm/s (interquartile range 13.2–26.7). The SEC was detected by TEE in 112 (65%) of the 172 patients.

Characteristics of Patients With Thromboembolism

During the study period, 26 patients were documented as having a stroke or peripheral embolism, with 3 patients

Fig 3. Bar graphs showing frequency (top) and odds ratio (bottom) of thromboembolism for each quintile of patients based on lipoprotein(a) concentration.

Fig 4. Bar graphs showing frequency (top) and odds ratio (bottom) of thromboembolism for each quintile of patients based on left atrial appendage (LAA) flow velocity.

suffering a fatal stroke. Transesophageal echocardiography examination was not performed in 5 stroke survivors due to a persistent disturbance in consciousness. Thus, 18 patients underwent TEE, and a thrombus was found in the LAA in 15 (83%). Sixteen (10%) of the 154 patients without an embolic event were found to have a left atrial thrombus, with all but one confined to the LAA. Therefore, the thromboembolic group consisted of 34 (20%) patients.

Comparisons of the clinical, laboratory and echocardiographic data are displayed in Table 2. The median Lp(a) concentration in the thromboembolic group was significantly higher than that in the nonthromboembolic group (31.5 vs 15.5 mg/dl, $p<0.0001$, Fig 1). Median LAA peak

flow velocity was reduced significantly in the thromboembolic group compared to that in the nonthromboembolic group (9.3 vs 21.2 cm/s, $p<0.0001$, Fig 2). The SEC was more prevalent in the thromboembolic group than in the nonthromboembolic group (94% vs 58%, $p<0.0001$). The median fibrinogen concentration was greater in the thromboembolic group (352 vs 314 mg/dl, $p=0.0015$). The median left atrial dimension was larger in the thromboembolic group than in the nonthromboembolic group (5.1 vs 4.8 cm, $p=0.0078$).

Role of Lp(a) and the LAA Peak Flow Velocity

Multivariate logistic regression analysis identified 3

independent predictors for thromboembolism. Serum Lp(a) elevation ≥ 30 mg/dl was the most potent independent predictor (odds ratio 9.5, 95% CI 4.4–20.4, $p < 0.0001$). The odds ratios for an LAA flow velocity < 20 cm/s and a fibrinogen concentration > 377 mg/dl were 8.7 (95% CI 3.3–23.0, $p = 0.0003$) and 3.2 (95% CI 1.5–6.9, $p = 0.0201$), respectively.

The frequency and odds ratio of thromboembolism in the fifth quintile of serum Lp(a) concentration were 58% and 12.7 (95% CI 5.8–27.7, $p < 0.0001$), respectively (Fig 3), while those of thromboembolism in the first quintile of LAA flow velocity were 61% and 12.9 (95% CI 5.8–28.5, $p < 0.0001$), respectively (Fig 4).

Discussion

The present study is the first to examine the pathophysiologic implications of Lp(a) elevations for thromboembolism in patients with chronic NVAF. In addition to such well-known risk factors as decreased LAA flow velocity and an increased fibrinogen concentration, serum Lp(a) elevation is an independent predictor for thromboembolism.

Atrial fibrillation is one of the most common arrhythmias seen in clinical practice, and is the major cardiovascular disorder predisposing patients to systemic embolization. The risk of systemic embolism among patients with NVAF is estimated to be 5 times greater than that of patients in sinus rhythm.¹¹ The incidence of atrial fibrillation increases with age and is found in $> 5\%$ of patients over 75 years of age.¹² Anticoagulation therapy has been demonstrated to reduce the risk of stroke and systemic embolism in patients with NVAF.^{12,27} Although the risk of hemorrhagic complications associated with anticoagulation therapy is relatively low, the risk ratio for major bleeding in patients over 75 year old is 3.1.²⁸ Accordingly, it is necessary to identify a subgroup with a high risk of thromboembolism in which the risk/benefit ratio of anticoagulation may be most favorable.

Clinical predictors of stroke in patients with NVAF include a history of previous stroke, hypertension, congestive heart failure and advanced age.^{29–32} Left ventricular dysfunction and left atrial size on transthoracic echocardiography are predictors of thromboembolism.³³ Furthermore, the presence of SEC or LAA dysfunction as evaluated by TEE both have significant prognostic implications.^{8,26}

In addition to these clinical and echocardiographic risk factors, the present study demonstrates that serum Lp(a) elevation is a risk factor for thromboembolism in patients with chronic NVAF. We previously demonstrated that chronic atrial fibrillation patients with left atrial thrombi have greater Lp(a) concentrations than those who do not.¹⁹ Although definitive evidence of left atrial thrombi leading to increased thromboembolism risk had been lacking, Leung et al³⁴ recently reported that the presence of left atrial thrombi is an independent predictor of subsequent events. Patients with left atrial thrombi appear to have a high risk of subsequent stroke and peripheral embolism.

Lipoprotein(a) is a complex lipoprotein macromolecule that contains apoprotein(a). Sequencing of cloned human apoprotein(a) complementary deoxyribonucleic acid (DNA) has shown that the structure of apoprotein(a) is strikingly similar to human plasminogen.⁷ Lipoprotein(a) has an inhibitory effect on the fibrin-stimulated tissue-type plasminogen activator that mediates activation of plasminogen to plasmin in vitro.⁴ Several in vitro studies have shown that Lp(a) competes for fibrin binding and is capable

of interacting with cell plasminogen receptors with an affinity comparable to plasminogen.^{6,8} Recently, Biemond et al¹⁰ demonstrated the attenuation of endogenous fibrinolysis by apoprotein(a) using an in vivo model of experimental venous thrombosis. These findings clearly favor a thrombogenic effect of Lp(a) mediated by an impairment of the fibrinolytic process. Lipoprotein(a) remains remarkably constant in healthy individuals from an early age.⁵ Therefore, Lp(a) may be an inherited individual risk factor for thromboembolism in patients with chronic NVAF.

In the present study, a decreased LAA flow velocity was also significantly associated with thromboembolism. In healthy subjects with sinus rhythm, the LAA is a highly contractile muscle sac that normally produces a LAA peak flow velocity of 81 ± 19 cm/s;²⁵ however, it is a common site of thrombus formation in patients with atrial fibrillation.^{20,25} Mugge et al reported a flow velocity of 25 cm/s as an arbitrary cutoff point separating low and high risk groups.¹⁷ In a study by Zabalgaitia et al, LAA flow velocities of 20 cm/s were associated with increased thromboembolic events.²⁶ The LAA behaves as a static pouch, and both the extent of blood stasis within the LAA and reduction in contractile function may be important determinants of thromboembolic risk.

In addition to Lp(a) and LAA dysfunction, an elevated fibrinogen concentration was an independent predictor of thromboembolism in the present study. Previous studies have shown an increased fibrinogen concentration to be an independent predictor of spontaneous echo contrast,^{35,36} which may contribute to the thrombogenic state in patients with NVAF.

Limitations and Clinical Implications

A TEE was not performed in all patients who developed stroke during the study period. There were 26 patients with chronic NVAF who had stroke or peripheral embolism during the study period. Three patients died of stroke. We could not obtain informed consent from 5 stroke survivors who had an altered mental state, and consequently did not perform a TEE examination in these patients for ethical reasons.

Although Lp(a) concentrations remain remarkably constant in an individual, Lp(a) may increase transiently in patients with unstable angina and acute myocardial infarction.^{23,37} It has been suggested that Lp(a) has characteristics similar to acute-phase reactant. In the study by Oshima et al,²³ Lp(a) concentrations in patients with unstable angina increased from 7 to 14 days after admission, but decreased by the 21st day. In patients with acute myocardial infarction, gradual increases in serum Lp(a) concentrations are observed during the first few days after onset, with return to basal levels within 4 weeks.³⁷ For this reason, only Lp(a) levels were determined 4 weeks after an ischemic stroke or peripheral embolism.

Both serum Lp(a) and LAA dysfunction are closely associated with thromboembolism in patients with chronic NVAF. To our knowledge, this is the first report demonstrating a significant correlation between Lp(a) elevations and thromboembolism in chronic NVAF. Large prospective studies are clearly required to definitely establish the relation between Lp(a) and thromboembolism. Furthermore, it will be useful for understanding the pathophysiology of thromboembolism in chronic NVAF to examine the relation between the Lp(a) level and markers of the coagulation-fibrinolytic system.

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