Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(4) 1–8
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/03000605221093303
journals.sagepub.com/home/imr
SAGE

Negative correlation between early recovery and lipoprotein-associated phospholipase A2 levels after intravenous thrombolysis

Yanzheng Li[1,2], Wei Wang[3], Hang Yang[2], Weiheng Guo[4], Jingyu Feng[2], Dejiu Yang[2], Li Guo[1] and Guojun Tan[1]

Abstract

Objective: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is considered a biomarker for systemic inflammation and the risk of myocardial infarction and stroke. However, little is known about the effect of acute vascular events on marker levels. The purpose of this study was to assess the potential association of early recovery with Lp-PLA2 levels in patients with acute ischemic stroke (AIS) after intravenous thrombolysis (IVT).

Methods: Forty-three consecutive AIS patients who had their first stroke and were hospitalized within 5 hours of the onset of stroke were enrolled. All patients were treated with IVT using alteplase or urokinase. Plasma Lp-PLA2 levels were measured within 24 hours after IVT. Variables that showed a significant association with Lp-PLA2 in univariate analysis were included in the multivariate ordered logistic regression model.

Results: Early recovery was associated with Lp-PLA2 levels after IVT, and Lp-PLA2 levels tended to decrease with increased probability of early recovery. This study is the first to report a negative correlation between early recovery and Lp-PLA2 levels after IVT.

Conclusion: Early recovery after IVT was negatively correlated with Lp-PLA2 A2 levels.

[1]Department of Neurology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province 050000, China
[2]Department of Neurology, North China University of Science and Technology Affiliated Hospital, North China University of Science and Technology, Tangshan, Hebei Province 063000, China
[3]Department of Radiotherapy and Chemotherapy, Tangshan People's Hospital, Tangshan, Hebei Province 063000, China
[4]Department of Statistics, Hebei Medical University, Shijiazhuang, Hebei Province 050000, China

Corresponding author:
Guojun Tan, Department of Neurology, The Second Hospital of Hebei Medical University, 215 Heping West Road, Shijiazhuang City, Hebei Province 050000, China.
Email: ydeytgj@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Keywords
Acute ischemic stroke, intravenous thrombolysis, lipoprotein-associated phospholipase A2, National Institute of Health Stroke Scale, early recanalization, inflammation, cardiovascular disease

Date received: 6 December 2021; accepted: 17 March 2022

Introduction

Acute ischemic stroke (AIS) is a leading cause of death and disability affecting societies around the world.[1] Early thrombolytic occlusion of arteries with a thrombolytic drug is associated with better clinical efficacy.[2] Intravenous thrombolysis (IVT) in AIS is time-dependent.[3] The functional prognosis after stroke depends on the recanalization time,[4] with earlier treatment having a greater benefit. Patients with AIS can benefit from IVT if they have evidence of salvageable tissue in advanced imaging studies. Treatment with alteplase, a thrombolytic drug, within 4.5 hours after the onset of stroke can significantly increase the overall probability of good prognosis, and early treatment has a greater proportional benefit.[5] Among patients with ischemic stroke and salvageable brain tissue, the use of alteplase 4.5 to 9.0 hours after the onset of stroke or when the patient woke up with stroke symptoms led to a higher proportion of patients with no or mild neurological deficits compared with the placebo group.[6,7] These results provide preliminary evidence for extending the time window of IVT in AIS patients. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a calcium-independent serine lipase that specializes in hydrolyzing sn-2 fatty acids from oxidized phospholipids.[8] Lp-PLA2 is considered a biomarker for systemic inflammation and the risk of myocardial infarction (MI) and stroke.[9–12] However, little is known about the effect of acute vascular events on marker levels. The purpose of this study was to assess the potential association of early recovery with Lp-PLA2 levels in AIS patients after IVT.

Methods

Subjects

AIS patients who had their first stroke and were hospitalized within 5.0 hours of the onset of stroke in the North China University of Science and Technology Affiliated Hospital from January 2020 to December 2020 were enrolled in the study. All patients were treated with IVT using alteplase or urokinase, depending on their choice. We excluded patients who matched the following criteria: (I) age <36 years or age >86 years; (II) National Institute of Health Stroke Scale (NIHSS)[13] score at admission <4; (III) have neurological abnormalities related to neurological disorders; (IV) have a history of MI; (V) have a history of cardiac failure; (VI) have a history of IVT therapy; (VII) underwent endovascular treatment after IVT. NIHSS scores were measured at admission for all patients. Early recovery was considered as an NIHSS score reduction ≥3 after IVT compared with the score at admission. Plasma Lp-PLA2 levels were measured within 24 hours after IVT. Patients were divided into three subgroups based on plasma Lp-PLA2 levels: low (<50 ng/mL), medium (50–150 ng/mL), and high (>150 ng/mL).

Demographics included age, sex, time from onset to admission, NIHSS score at admission, early recovery, thrombolytic drug, and history of coronary heart disease, hypertension, diabetes mellitus, and atrial fibrillation. This study was approved by the ethics committee of North China University of Science and Technology (20190038; 12 December 2019). Each patient provided written informed consent before participating.

Statistical analyses

SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Values are expressed as mean ± standard deviation (SD). Significant differences were defined as $P < 0.05$. Baseline and clinical characteristics were compared using the analysis of variance (ANOVA) or Kruskal–Wallis test. Variables that showed a significant association ($P < 0.1$) with Lp-PLA2 using univariate analysis were included in the multivariate ordered logistic regression model. The existence of the proportional advantage hypothesis was determined by a parallel line test. A deviance goodness of fit test was used to determine the fit of the model.

Results

In this study, early thrombolytic occlusion of arteries with thrombolytic drug was associated with better clinical efficacy. Early recovery was associated with Lp-PLA2 levels after IVT, and Lp-PLA2 levels tended to decrease with an increased probability of early recovery. This study is the first to report a negative correlation between early recovery and Lp-PLA2 levels after IVT.

Clinical characteristics of the patients examined in the study are shown in Table 1. Data are expressed as mean ± SD. Forty-three AIS patients were enrolled in the study. There were no significant differences among the groups in age (L = 60.5 ± 10.3, M = 66.4 ± 13.7, and H = 62.7 ± 11.8 years, $P = 0.431$) or sex ($P = 0.261$). The three groups were similar in the time from onset to admission ($P = 0.816$), NIHSS score at admission ($P = 0.148$), early

Table 1. Clinical characteristics of acute ischemic stroke (AIS) patients.

	Lp-PLA2 (ng/mL)			
	L (<50)	M (50–150)	H (>150)	*P*-Value
Number	13	16	14	–
Age (years), (mean ± SD)	60.5 ± 10.3	66.4 ± 13.7	62.7 ± 11.8	0.431
Sex (female), n (%)	5 (38.5)	2 (12.5)	3 (21.4)	0.261
Time from onset to admission (hours), (mean ± SD)	3.0 ± 1.2	3.0 ± 1.3	2.8 ± 1.4	0.816
NIHSS score at admission, (mean ± SD)	10.0 ± 6.4	8.8 ± 4.2	6.4 ± 2.1	0.148
Early recovery, n (%)	9 (69.2)	10 (62.5)	5 (35.7)	0.178
Thrombolytic drug (Alteplase), n (%)	11 (84.6)	12 (75.0)	12 (85.7)	0.713
Medical history, n (%)				
Coronary heart disease	3 (23.1)	5 (31.3)	0 (0)	0.084
Hypertension	5 (38.5)	7 (43.8)	5 (35.7)	0.902
Diabetes mellitus	2 (15.4)	2 (12.5)	3 (21.4)	0.804
Atrial fibrillation	0 (0)	2 (12.5)	1 (0.1)	0.430

Lp-PLA2, Lipoprotein-associated phospholipase A2; L, low; M, medium; H, high; SD, standard deviation; NIHSS, National Institute of Health Stroke Scale.

recovery ($P = 0.178$), and thrombolytic drug ($P = 0.713$). There were no significant differences among the groups in medical history, including coronary heart disease ($P = 0.084$), hypertension ($P = 0.902$), diabetes mellitus ($P = 0.804$), and atrial fibrillation ($P = 0.430$).

The effects of NIHSS score at admission and early recovery on plasma Lp-PLA2 levels were analyzed using multivariate ordered logistic regression consistent with the proportional advantage hypothesis (Table 2). The results of the parallel line test were $\chi^2 = 0.968$, $P = 0.616$, indicating the existence of the proportional advantage hypothesis. Deviance goodness of fit test results showed that the model fit well, $\chi^2 = 24.263$, $P = 0.760$. The model fitting information showed that this model was superior to the model with only constant terms, $\chi^2 = 10.550$, $P < 0.01$. The odds ratio (OR) value of plasma Lp-PLA2 in patients with early recovery was 4.559 times lower than that in patients without early recovery (95% confidence interval (CI): 1.283–16.198), $\chi^2 = 5.501$, $P = 0.019$. The plasma Lp-PLA2 level decreased by 16.9% (OR = 0.831, 95% CI: 0.721–0.958) for each increase of NIHSS score at admission, $\chi^2 = 6.532$, $P < 0.05$.

Discussion

In this study, we showed that there was a negative correlation between early recovery and Lp-PLA2 levels after IVT. Starting intravenous alteplase treatment within 4.5 hours after the onset of stroke increases the chance of achieving functional improvement in patients with AIS.[5] Recent studies have extended the time window for IVT to 9.0 hours.[6,7] The earlier treatment starts, the greater the benefit.[14,15] The time window for IVT in this study was 5.0 hours after stroke onset. Earlier IVT after stroke is associated with faster IVT-induced early recanalization (ER).[16] A total of 43 patients were enrolled, and 24 patients (55.81%) achieved early recovery after IVT. We believe that patients with early recovery after IVT might have had an early complete or partial recanalization of the cerebrovascular vessels, despite the lack of a vessel imaging assessment (either invasive or noninvasive), as stated below in limitations.

ER proved to be a strong predictor of improved patient prognosis by intravenous alteplase treatment.[16–18] However, despite intravenous alteplase treatment, most patients (59.0%) did not achieve ER.[17] One out of every two mesovascular occlusion patients did not achieve good clinical results for 90 days under the best medical management.[17] The overall incidence of ER after IVT is considerable, emphasizing the importance of reliably predicting ER to limit ineffective transfers between hospitals.[19] Our results show that the early recovery rate after IVT was 55.8% in

Table 2. Predictors of Lipoprotein-associated phospholipase A2 (Lp-PLA2) levels and odds ratios (ORs) according to early recovery.

Variables	B	Std. Error	Wald	OR	95% CI	*P*-Value
Early recovery						
[Early recovery = 0]	1.517	0.647	5.501	4.559	1.283–16.198	0.019
[Early recovery = 1]	0[a]			1		
NIHSS score at admission	−0.185	0.072	6.532	0.831	0.721–0.958	0.011

ORs were calculated using a logistic regression model.

CI, confidence interval; NIHSS, National Institute of Health Stroke Scale.

[a]This was set to zero because this parameter is redundant.

patients with AIS, similar to the results of previous studies.

The incidence of no-ER is particularly high in cases of proximal occlusion and severe stroke.[19] In the multimodal magnetic resonance imaging protocol, delayed gadolinium-enhanced T1 (dGE-T1) is obtained by simply adjusting the scan sequence. This is a useful tool for estimating thrombus length and predicting middle cerebral artery recanalization after IVT.[20] Measuring thrombus volume can help determine recanalization strategies and may identify patients suitable for direct intravascular thrombus removal.[21] Recanalization after early thrombolysis depends not only on the location and length of the thrombus, but also on the severity of ischemia.[22] The severity of the stroke and results of vascular imaging on admission may help identify high-risk patients with worsening arterial patency within 24 hours.[18] There is less time dependence for penumbra rescue and infarct growth, but more for the measurement of collateral blood flow.[23] For patients with large infarctions, good collaterals can improve the prognosis and help select patients with IVT.[24] If IVT is not used for recanalization, good collateral blood flow may have limited prognostic value.[25]

Lp-PLA2 is a calcium-independent phospholipase A2 that circulates in plasma with lipoprotein particles. Increased circulating LP-PLA2 levels can help predict increased risks of MI, stroke, and cardiovascular death.[26] Elevated serum Lp-PLA2 levels have been reported in patients with ischemic stroke,[27,28] and is an independent risk factor for AIS.[29,30] The Lp-PLA2 G994T gene polymorphism may be an independent risk factor for ischemic stroke in a Chinese population.[31] Higher levels of Lp-PLA2 in the acute phase were associated with an increased short-term risk of recurrence of vascular events.[32] Furthermore, high serum LP-PLA2 levels are associated with the incidence, severity, and recurrence of AIS, which can be used to guide clinical practice.[29]

Lp-PLA2 is at the crossroads of lipid metabolism and the inflammatory response. This protein is produced by inflammatory cells, binds to low-density lipoprotein (LDL) and other lipoproteins, and participates in the metabolism of LDL into pro-inflammatory mediators.[33] The dysregulation of lipid metabolism may be an important factor in central nervous system injury and disorders. Lp-PLA2 is highly expressed in the necrotic core of atherosclerotic plaques, which is related to their instability.[34] Inflammation is being increasingly associated with a greater risk of stroke,[35,36] and the role of Lp-PLA2 as an inflammatory marker associated with stroke risk and prognosis is of particular interest.[36] Lp-PLA2 is a vascular-specific inflammatory enzyme associated with vascular inflammation,[37] producing two pro-inflammatory mediators: lysophosphatidylcholine and oxidized non-esterified fatty acids. These mediators play roles in the development of atherosclerotic lesions and formation of necrotic cores, leading to more vulnerable plaques.[26] These inflammatory responses can promote the formation and release of atherosclerotic plaques and thrombosis, and thus ischemic stroke.[38]

Several limitations of this study are acknowledged. First, computed tomographic angiography (CTA) should be performed for further follow-up radiological assessment to clarify the ER of occluded vessels after IVT. Second, ultrasonography should be used for vessel evaluation. Furthermore, magnetic resonance angiography (MRA) studies in association with dGE-T1 sequences were not carried out because of research funding constraints. Finally, this was a single-center study with a limited sample size. Data from only 43 patients were available for analysis. The limited number of subjects may not

have provided sufficient comparisons of risk factors associated with stroke in patients with different levels of Lp-PLA2.

Our results suggest that early recovery after IVT was negatively correlated with Lp-PLA2 levels. This may be because of the early complete or partial recanalization of occluded vessels, recovery of nerve function, and reduction of the inflammatory response and Lp-PLA2 levels in stroke patients after IVT.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work was supported by the Hebei Provincial Science and Technology Research Projects (19277746D).

ORCID iD

Guojun Tan https://orcid.org/0000-0001-7749-4107

Supplemental material

Supplemental material for this study is available online.

References

1. Campbell BCV and Khatri P. Stroke. *Lancet* 2020; 396: 129–142.
2. Campbell BCV, Ma H, Parsons MW, et al. Association of Reperfusion After Thrombolysis With Clinical Outcome Across the 4.5- to 9-Hours and Wake-Up Stroke Time Window: A Meta-Analysis of the EXTEND and EPITHET Randomized Clinical Trials. *JAMA Neurol* 2020; e204123.
3. Akbik F, Xu H, Xian Y, et al. Trends in Reperfusion Therapy for In-Hospital Ischemic Stroke in the Endovascular Therapy Era. *JAMA Neurol* 2020; 77: 1–110.
4. Ospel JM, Singh N, Almekhlafi MA, et al. Early Recanalization With Alteplase in Stroke Because of Large Vessel Occlusion in the ESCAPE Trial. *Stroke* 2021; 52: 304–307.
5. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; 384: 1929–1935.
6. Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. *N Engl J Med* 2019; 380: 1795–1803.
7. Psychogios K, Magoufis G, Safouris A, et al. Eligibility for intravenous thrombolysis in acute ischemic stroke patients presenting in the 4.5-9 h window. *Neuroradiology* 2020; 62: 733–739.
8. MacPhee CH, Moores KE, Boyd HF, et al. Lipoprotein-associated phospholipase a2, platelet-activating factor acetylhydrolase, generates two bioactive products during the oxidation of low-density lipoprotein: Use of a novel inhibitor. *Biochem J* 1999; 338: 479–487.
9. Yang EH, McConnell JP, Lennon RJ, et al. Lipoprotein-associated phospholipase a2 is an independent marker for coronary endothelial dysfunction in humans. *Arterioscler Thromb Vasc Biol* 2006; 26: 106–111.
10. Winkler K, Winkelmann BR, Scharnagl H, et al. Platelet-activating factor acetylhydrolase activity indicates angiographic coronary artery disease independently of systemic inflammation and other risk factors: The Ludwigshafen Risk and Cardiovascular Health Study. *Circulation* 2005; 111: 980–987.
11. Koenig W, Twardella D, Brenner H, et al. Lipoprotein-associated phospholipase a2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. *Arterioscler Thromb Vasc Biol* 2006; 26: 1586–1593.
12. Mannheim D, Herrmann J, Versari D, et al. Enhanced Expression of Lp-PLA2 and Lysophosphatidylcholine in Symptomatic

Carotid Atherosclerotic Plaques. *Stroke* 2008; 39: 1448–1455.
13. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2019; 50: e344–e418.
14. Lees KR, Emberson J, Blackwell L, et al. Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes: A Pooled Analysis of 9 Trials. *Stroke* 2016; 47: 2373–2379.
15. Muruet W, Rudd A, Wolfe CDA, et al. Long-Term Survival After Intravenous Thrombolysis for Ischemic Stroke: A Propensity Score-Matched Cohort With up to 10-Year Follow-Up. *Stroke* 2018; 49: 607–613.
16. Tsivgoulis G, Saqqur M, Sharma VK, et al. Timing of Recanalization and Functional Recovery in Acute Ischemic Stroke. *J Stroke* 2020; 22: 130–140.
17. Ospel JM, Menon BK, Demchuk AM, et al. Clinical Course of Acute Ischemic Stroke Due to Medium Vessel Occlusion With and Without Intravenous Alteplase Treatment. *Stroke* 2020; 51: 3232–3240.
18. Marto JP, Lambrou D, Eskandari A, et al. Associated Factors and Long-Term Prognosis of 24-Hour Worsening of Arterial Patency After Ischemic Stroke. *Stroke* 2019; 50: 2752–2760.
19. Seners P, Turc G, Maïer B, et al. Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis: A Systematic Review and Meta-Analysis. *Stroke* 2016; 47: 2409–2412.
20. Yan S, Chen Q, Xu M, et al. Thrombus Length Estimation on Delayed Gadolinium-Enhanced T1. *Stroke* 2016; 47: 756–761.
21. Yoo J, Baek JH, Park H, et al. Thrombus Volume as a Predictor of Nonrecanalization After Intravenous Thrombolysis in Acute Stroke. *Stroke* 2018; 49: 2108–2115.
22. Seners P, Turc G, Lion S, et al. Relationships between brain perfusion and early recanalization after intravenous thrombolysis for acute stroke with large vessel occlusion. *J Cereb Blood Flow Metab* 2020; 40: 667–677.
23. Vagal A, Aviv R, Sucharew H, et al. Collateral Clock Is More Important Than Time Clock for Tissue Fate. *Stroke* 2018; 49: 2102–2107.
24. Tan BY, Wan-Yee K, Paliwal P, et al. Good Intracranial Collaterals Trump Poor ASPECTS (Alberta Stroke Program Early CT Score) for Intravenous Thrombolysis in Anterior Circulation Acute Ischemic Stroke. *Stroke* 2016; 47: 2292–2298.
25. Schuler F, Rotkopf LT, Apel D, et al. Differential Benefit of Collaterals for Stroke Patients Treated with Thrombolysis or Supportive Care: A Propensity Score Matched Analysis. *Clin Neuroradiol* 2020; 30: 525–533.
26. Tselepis AF, Rizzo M and Goudevenos LA. Therapeutic modulation of lipoprotein-associated phospholipase A2 (Lp-PLA2). *Curr Pharm Des* 2011; 17: 3656–3661.
27. Qiao J, Zhou K, Huang C, et al. Comparison of serum Lp-PLA2 levels in ischemic stroke patients with H-type hypertension or non-H-type hypertension. *J Clin Lab Anal* 2020; 34: e23068.
28. Delgado P, Chacón P, Penalba A, et al. Temporal profile and prognostic value of Lp-PLA2 mass and activity in the acute stroke setting. *Atherosclerosis* 2012; 220: 532–536.
29. Li X, Xu L and Xu Z. The diagnostic and prognostic performance of Lp-PLA2 in acute ischemic stroke. *Med Clin (Barc)* 2021; 156: 437–443.
30. Persson M, Berglund G, Nelson JJ, et al. Lp-PLA2 activity and mass are associated with increased incidence of ischemic stroke: a population-based cohort study from Malmö, Sweden. *Atherosclerosis* 2008; 200: 191–198.
31. Ni J, Gu H, Hu W, et al. Association of Lp-PLA2 G994T gene polymorphism with risk of ischemic stroke in Chinese population. *J Biochem Mol Toxicol* 2017; 31: e21999.
32. Lin J, Zheng H, Cucchiara BL, et al. Association of Lp-PLA2-A and early

recurrence of vascular events after TIA and minor stroke. *Neurology* 2015; 85: 1585–1591.
33. Epps KC and Wilensky RL. Lp-PLA_2- a novel risk factor for high-risk coronary and carotid artery disease. *J Intern Med* 2011; 269: 94–106.
34. Ishida K and Cucchiara B. Therapeutic Options to Reduce Lp-PLA2 Levels and the Potential Impact on Vascular Risk Reduction. *Curr Treat Options Cardiovasc Med* 2013; 15: 313–321.
35. Low A, Mak E, Rowe JB, et al. Inflammation and cerebral small vessel disease: A systematic review. *Ageing Res Rev* 2019; 53: 100916.
36. Esenwa CC and Elkind MS. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. *Nat Rev Neurol* 2016; 12: 594–604.
37. Braun LT and Davidson MH. Lp-PLA2: A new target for statin therapy. *Curr Atheroscler Rep* 2010; 12: 29–33.
38. Adibhatla RM and Hatcher JF. Altered lipid metabolism in brain injury and disorders. *Subcell Biochem* 2008; 49: 241–268.