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Coronary Artery Disease

Effect of Selective Thrombus Aspiration on Serum Lipoprotein-Associated Phospholipase A2 in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention with High Thrombus Burden

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Background: Lipoprotein-associated phospholipase A2 (Lp-PLA_2) is a potential therapeutic target in acute coronary syndromes. Although recent evidence does not support the routine use of manual thrombus aspiration (TA) in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI), the use of TA is associated with a significant improvement in myocardial reperfusion, especially in patients with high thrombus burden (HTB). We hypothesized that TA would reduce the serum Lp-PLA_2 levels in STEMI patients undergoing PPCI with HTB.

Methods and results: Our study cohort included 320 consecutive STEMI patients undergoing PPCI with HTB who were randomly assigned to receive either TA before PPCI (TA group, n = 160) or PPCI alone (standard PPCI group, n = 160). The baseline characteristics of study participants were well-matched. After 30 ± 2 days, serum Lp-PLA_2 levels decreased by 53.9% in the TA group (152.9 ± 58.1 ng/mL) and decreased by 31.2% in the standard PPCI group (84.2 ± 86.6 ng/mL, $p < 0.001$). The TA group had a significantly lower prevalence of balloon predilatation, number of stents used, total stent length and corrected thrombolysis in myocardial infarction frame count, and a higher percentage of myocardial blush grade ≥ 2 compared with the standard PPCI group (all $p < 0.001$). No significant difference between the groups was observed in 30 ± 2 days for major adverse cardiovascular and cerebrovascular events ($p = 0.702$).

Conclusions: After 30 ± 2 days of treatment, TA may significantly reduce serum levels of Lp-PLA_2 in STEMI patients undergoing PPCI with HTB.

Key Words: Lipoprotein-associated phospholipase A2 • Primary percutaneous coronary intervention • ST-elevation myocardial infarction • Thrombus aspiration

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INTRODUCTION

Inflammation plays a crucial role in the pathogenesis, progression, and rupture of atherosclerotic plaques. Lipoprotein-associated phospholipase A2 (Lp-PLA_2) is an enzyme produced and secreted by monocyte-macrophages, T-lymphocytes and other inflammatory cells,

and bound mainly to low-density lipoprotein (LDL) cholesterol, in particular small, dense LDL particles.[1] It is strongly expressed in the necrotic core and surrounding macrophages around vulnerable and ruptured atherosclerotic plaques.[2] Lp-PLA_2 is an inflammatory mediator and plays a significant role in the pathogenesis of atherosclerosis and the development of vulnerable atherosclerotic plaques.[3] The available experimental and clinical studies support the use of Lp-PLA_2 activity and mass for predicting cardiovascular events.[4] Furthermore, a meta analysis that included 32 prospective studies conducted on Lp PLA_2 including a total of 79,036 participants showed a relationship between Lp PLA_2 activity and mass and incidence of coronary artery disease, stroke, and cardiovascular mortality.[5] Based on this evidence, the major scientific societies have included in their guidelines the measurement of Lp-PLA_2 activity among the biomarkers that are useful in risk stratification of adult asymptomatic patients.[6] Lp-PLA_2 is therefore a potential therapeutic target in acute coronary syndromes.

The rationale for manual thrombus aspiration (TA) during primary percutaneous coronary intervention (PPCI) is the removal of intracoronary thrombus, thus avoiding distal embolization leading to impaired myocardial reperfusion. Early evidence supporting manual TA during ST-elevation myocardial infarction (STEMI) was promising, and this was once considered an important aspect of PPCI, especially in patients with high thrombus burden (HTB). However, recent clinical evidence from major randomized controlled trials (notably TASTE and TOTAL) does not support the routine use of manual TA in patients with STEMI undergoing PPCI.[7] Due to the ambivalent results, use of TA as a routine strategy in patients with STEMI cannot be supported. However, TA might be an attractive stragety in patients with low stroke risk and high lesion thrombus burden. Further studies are needed in order to clarify which patient or lesion subsets might benefit the most from TA.[8] Although the efficacy of TA in STEMI is unclear, the use of TA prior to angioplasty does improve myocardial reperfusion.[9] Therefore, we hypothesized that TA would reduce the Lp-PLA_2 levels in STEMI patients with HTB. In this randomized, controlled trial, we investigated the effect of TA on serum Lp-PLA_2 in these patients undergoing PPCI.

METHODS

Study subjects

The study was performed at the Department of Cardiovasology of Yue Bei People's Hospital, Shaoguan, the fourth largest volume center of percutaneous coronary intervention (PCI) in Guangdong Province in 2015. Now there are more than 1000 PCIs performed annually, including > 300 emergency PPCIs annually. Between January 2014 and April 2016, 320 consecutive STEMI patients undergoing PPCI within 12 hours of symptom onset after emergency coronary angiography with HTB were enrolled in this study. All enrolled patients were transported immediately to the Cardiac Catheterization Laboratory after admission. STEMI was defined by the classic symptoms of coronary ischemia for at least 30 min, and serial changes on electrocardiogram: the detection of a $\geq$ 0.1 mV ST-segment elevation in the inferior leads, a $\geq$ 0.2 mV ST-segment elevation in the anterior chest leads occurring in two contiguous leads, or the presence of a new (or presumably new) left bundle branch block. A patient was considered to have a HTB if thrombolysis in myocardial infarction (TIMI) thrombus grades 4 or 5 was present. Exclusion criteria were previous myocardial infarction, previous coronary stent implantation, previous coronary artery bypass grafting (CABG), severe left main disease, rescue PCI after thrombolytic therapy, TIMI thrombus grades 0-3, inability to provide informed consent, cardiogenic shock, treatment with an intra-aortic balloon pump, need for emergency CABG, a < 2.5 mm in diameter of the infarct-related artery, and the infeasibility of performing TA, as judged by the treating cardiologist. In addition, patients with known malignancy, chronic liver or kidney disorder, history of trauma or an infection within 1 month of presentation, or a chronic inflammatory disorder (collagen tissue diseases and inflammatory intestinal diseases) were also excluded. The study was approved by the Human Ethics Committees of Yue Bei People's Hospital, and all patients provided their written informed consent before PPCI treatment.

PPCI procedure and medication

Eligible patients were randomly assigned, in a 1:1 ratio to receive either TA before PPCI (TA group) or PPCI alone (standard PPCI group). The PPCI and adjunctive pharmacological treatment were performed according

to the guidelines of the European Society of Cardiology.[11] PPCI was performed by one of three experienced interventionists who had performed more than 300 cases of PPCI. Baseline coronary angiography was performed via radial approach using the standard Judkins technique. The second option was the brachial approach if puncture of the radial artery had failed. For patients randomized to TA, guidewire placement was followed by TA with a manual TA catheter (Export® Catheter; Medtronic Inc, Minneapolis, MN, USA). TA was started proximal to the occluded site, gently advancing the TA catheter through the occlusion, and then pulling it in a proximal direction, maintaining negative pressure even when the occlusion was crossed. Withdrawal of the TA catheter from the artery and guiding catheter was performed with constant negative pressure. Extraction of 4-5 ml of blood from the guiding catheter was then performed to avoid residual thrombus. TA was terminated when successful TA was followed by aspiration without any debris, or when 7 aspiration attempts did not show any visible material. TA catheter should be completely flushed with heparinized saline before use and re-flushed before each re-use. Manual TA will be the only difference between the groups, and all other therapeutic procedures were similar in both treatment arms. Additional use of predilation or postdilation was based on the interventionist's decision. Only culprit lesions were treated using standard PCI techniques with drug-eluting stent (Firebird2™ Rapamycin-Eluting Coronary CoCr Stent System; Shanghai MicroPort Medical (Group) Co., Ltd, Shanghai, China) and a 6-Fr guiding catheter (Cordis®; Cordis Corporation, Miami Lakes, FL, USA). The decision to use a stent was left to the discretion of the interventionist, following review of patient characteristics and angiographic features. Procedural success for stent placement was defined as a residual stenosis < 20% in diameter with final grade 3 TIMI flow.

All patients received a loading dose of 300 mg aspirin and 300-600 mg clopidogrel immediately following admission, a bolus of unfractionated heparin (100 U/kg) during the PPCI, and subcutaneous low molecular weight heparin sodium injection (FUTOS®; Kuming Jida Pharmaceutical Co., Ltd, Yunnan Province, China) 1 mg/kg Bid for 4-7 days after PPCI. Glycoprotein IIb/IIIa inhibitor (tirofiban) was used at the discretion of the interventionist. A 75 mg clopidogrel daily dose was administered for 12 months after the PPCI, and 100 mg aspirin daily was prescribed indefinitely. In view of the effects of statins on Lp-PLA$_2$ levels,[10] a dose of 40 mg atorvastatin daily for 7 days was also prescribed, followed by 20 mg daily for 12 months post PCI for all patients. Other standard therapy post PPCI included beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, according to current society guidelines.

Angiographic analysis

Angiographic analysis was performed by two experienced investigators (Xin Xu and Liang-Qiu Tang), who were blinded to treatment allocation and clinical data.

Angiographic thrombus burden, TIMI thrombus grade, was classified as follows: Grade 0: no cineangiographic characteristics of thrombus are present; Grade 1: possible thrombus is present, with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus; Grade 2: there is definite thrombus, with greatest dimensions $\leq$ 1/2 the vessel diameter; Grade 3: there is definite thrombus but with greatest linear dimension > 1/2 but < 2 vessel diameter; Grade 4: there is definite thrombus, with the largest dimension $\geq$ 2 vessel diameter; and in TIMI thrombus grade 5: there is total occlusion.[12] The patients were stratified into low thrombus burden (LTB) (Grades 1, 2 and 3) and HTB groups (4 and 5) according to final thrombus score.

Prior to PPCI, immediately after stent implantation and final TIMI flow grade, myocardial blush grade (MBG), and corrected TIMI frame count (cTFC) were noted as previously defined.[13-15] In the event that final TIMI flow grade < 3, and MBG < 2, this was characterized as angiographic no-reflow.[16]

Blood samples and measurements

Peripheral venous blood samples were drawn immediately upon hospital admission before PPCI for the assessment of serum levels of Lp-PLA$_2$, high-sensitivity cardiac troponin T (hs-cTnT), creatinine kinase-myocardial band (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and glycosylated hemoglobin (HbA1c). Serum levels of Lp-PLA$_2$ were measured

again at 30 ± 2 days after PPCI. Serum levels of Lp-PLA_2 were evaluated by enhanced turbidimetric immunoassay (commercially brought from Nanjing Norman Biological Technology Co., Ltd, Nanjing, China). The blood samples were daily sent to the Clinical Laboratory of Yue Bei People's Hospital without undue delay for analyses.

Moreover, to evaluate kidney function, the estimated glomerular filtration rate (eGFR) was obtained by applying the Modification of Diet in Renal Disease Study formula.[17] To assess cardiac function, transthoracic echocardiography was routinely performed on each patient within 48 hours after PPCI (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). The left ventricular ejection fraction (LVEF) was also measured using the Simpson method according to the recommendations of the American Society of Echocardiography.[18]

Clinical follow-up

Patients were followed-up for 30 ± 2 days, excepting those who died during the study period. The primary end point was serum levels of Lp-PLA_2 at 30 ± 2 days; the secondary end points were MBG, TIMI flow grade and cTFC after PCI, and major adverse cardiovascular and cerebrovascular events (MACCE) at 30 ± 2 days. The MACCE were considered when the patients experienced death, stroke, recurrent myocardial infarction, urgent revascularization and definite or probable stent thrombosis.

Statistical analyses

Data analysis was performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The descriptive analysis used mean ± standard deviation for numerical variables, and percentages for categorical variables. Each continuous variable was checked for the normality of distribution by employing the Shapiro-Wilk test. For comparison between two groups, the Student's *t*-test was used for numerical variables and the Pearson's chi-square test for categorical ones. All tests were two-sided, and differences were considered statistically significant when $p < 0.05$.

RESULTS

No patient was lost to follow-up during the course of this study. During the period of 30 ± 2 days post PPCI, 1 patient assigned to the TA group withdrew from the study prematurely because of severe hepatic dysfunction (alanine aminotransferase more than 3 times the upper limit of normal) induced by atorvastatin. The secondary end points assessments were performed on the remaining 319 subjects (n = 159 in the TA group and n = 160 in the standard PPCI group). Six patients (3 per group) died of cardiac shock within 1 week after PPCI. One patient in the standard PPCI group died of left ventricular free wall rupture within 48 hours after PPCI. Overall, 312 (97.5%) patients completed the study. Primary end point assessment was also performed on the remaining 312 subjects (n = 156 per group).

Baseline characteristics, including angiographic characteristics before PPCI, were well matched between the two groups (Table 1). There were no significant differences in baseline serum Lp-PLA_2 levels between the TA group (268.4 ng/mL) and the standard PPCI group (280.8 ng/mL, $p = 0.263$). Also, there were no statistically significant differences observed between groups in the rate of tirofiban administration or stent deployed (Table 2). The TA group had a significantly lower prevalence of balloon predilatation, a lower number of stents used and a lesser total stent length compared with the standard PPCI group (all $p < 0.001$). The percentage of TIMI flow grade 3 immediately after stent implantation tended to show a statistically significant difference between the two groups ($p = 0.050$). However, the difference in the proportion of TIMI flow grade 3 between two groups disappeared upon completion of the procedure ($p = 0.478$). Compared to the standard PPCI group, the percent of MBG ≥ 2 was higher and cTFC was lower in the TA group (both $p < 0.001$).

After 30 ± 2 days, the primary end point (serum levels of Lp-PLA_2 at 30 ± 2 days) was: TA group, 115.5 (±52.6) ng/mL; standard PPCI group, 196.7 (±73.1) ng/ mL ($p < 0.001$). Lp-PLA_2 levels decreased by 53.9% in the TA group (152.9 ± 58.1 ng/mL) and decreased by 31.2% in the standard PPCI group (84.2 ± 86.6 ng/mL, $p < 0.001$) (Figure 1). However, no significant difference was observed in 30 ± 2 days in MACCE between the groups ($p = 0.702$) (Table 2).

DISCUSSION

Manual TA is a simple, intuitive idea to alleviate

Table 1. Baseline characteristics of patients

Variables*	TA group (*n* = 160)	Standard PPCI group (*n* = 160)	p value
Age (years)	60.9 ± 11.4	62.6 ± 11.0	0.181
Male, *n* (%)	140 (87.5)	141 (88.1)	0.864
Body mass index (kg/m^2)	25.3 ± 3.1	25.6 ± 3.0	0.283
Hypertension, *n* (%)	59 (36.9)	60 (37.5)	0.908
Diabetes mellitus, *n* (%)	23 (14.4)	26 (16.2)	0.641
Current smoking, *n* (%)	72 (45.0)	74 (46.2)	0.822
Dyslipidemia, *n* (%)	112 (70.0)	105 (65.6)	0.402
Prior stroke, *n* (%)	6 (3.8)	7 (4.4)	0.777
Heart rate (beats/min)	78.1 ± 12.9	80.1 ± 13.9	0.180
Systolic blood pressure (mmHg)	124.6 ± 25.6	129.4 ± 22.6	0.077
Pain-balloon time (min)	359.5 ± 171.6	353.1 ± 131.9	0.711
Door-balloon time (min)	64.5 ± 25.9	69.7 ± 32.1	0.111
Killip class, *n* (%)			0.884
I	112 (70.0)	108 (67.5)	
II	31 (19.4)	33 (20.6)	
III	17 (10.6)	19 (11.9)	
LVEF# (%)	55.8 ± 6.7	54.6 ± 7.3	0.133
NT-proBNP (pg/mL)	1390.0 ± 1182.9	1801.5 ± 3824.2	0.195
Peak hs-cTnT (pg/mL)	6315.7 ± 3469.8	5895.0 ± 3321.8	0.269
Peak CK-MB (U/L)	283.7 ± 179.3	261.2 ± 161.9	0.239
TC (mmol/L)	4.9 ± 0.9	5.0 ± 1.0	0.714
TG (mmol/L)	1.5 ± 0.7	1.4 ± 0.7	0.387
LDL-C (mmol/L)	3.4 ± 0.8	3.4 ± 0.8	0.435
HDL-C (mmol/L)	1.1 ± 0.2	1.2 ± 0.3	0.146
eGFR (ml/min/1.73 m^2)	87.6 ± 28.1	91.1 ± 25.5	0.244
HbA1c (%)	6.3 ± 0.5	6.5 ± 1.4	0.066
Lp-PLA_2 (ng/mL)	268.4 ± 86.9	280.8 ± 110.0	0.263
IRA, *n* (%)			0.929
LAD	118 (73.8)	117 (73.1)	
LCX	15 (9.4)	17 (10.6)	
RCA	27 (16.9)	26 (16.2)	
stenosis in IRA before PPCI, *n* (%)	97.9 ± 10.9	97.3 ± 12.2	0.678
TIMI thrombus grade before PPCI, *n* (%)			0.078
4	97 (60.6)	112 (70.0)	
5	63 (39.4)	48 (30.0)	
TIMI flow grade before PPCI, *n* (%)			0.255
≤ 1	122 (76.2)	113 (70.6)	
≥ 2	38 (23.8)	47 (29.4)	

* Data was reported as mean (standard deviation) or *n* (%) as appropriate. # LVEF was measured within 48 hours after PPCI. CK-MB, creatinine kinase-myocardial band; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-cTnT, high-sensitivity cardiac troponin T; IRA, infarct related artery; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein-associated phospholipase A2; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; TA, thrombus aspiration; TC, total cholesterol; TG, triglyceride; TIMI, thrombolysis in myocardial infarction.

microvascular obstruction and improve flow in STEMI during PPCI. It doesn't take substantial persuasion to understand that removing part or all of the thrombus blocking the artery before implanting a stent is beneficial, both in terms of the obstruction, and at the level of the microcirculation. In the initial clinical trials, TA in ad-

Table 2. Angiographic characteristics and outcomes for end points

Variables*	TA group (*n* = 160)	Standard PPCI group (*n* = 160)	p value
Tirofiban administration, *n* (%)	131 (81.9)	132 (82.5)	0.884
Tirofiban dose, (mg)	12.0 ± 5.7	12.5 ± 5.8	0.440
Stent with balloon predilatation, *n* (%)	9 (5.6)	76 (47.5)	0.000
Stent deployed, *n* (%)	151 (94.4)	153 (95.6)	0.608
Number of stents used	1.1 ± 0.3	1.3 ± 0.5	0.000
Total stent length (mm)	26.3 ± 9.4	33.2 ± 16.8	0.000
TIMI flow grade after stent, *n* (%)			0.050
≤ 2	25 (15.6)	39 (24.4)	
3	135 (84.4)	121 (75.6)	
TIMI flow grade at completion, *n* (%)			0.478
≤ 2	8 (5.0)	11 (6.9)	
3	152 (95.0)	149 (93.1)	
MBG, *n* (%)			0.002
≤ 1	23 (14.4)	46 (28.8)	
≥ 2	137 (85.6)	114 (71.2)	
cTFC	26.8 ± 14.3	34.2 ± 22.5	0.001
Lp-PLA_2 [#] (ng/mL)	115.5 ± 52.6	196.7 ± 73.1	0.000
MACCE, *n* (%)	3 (1.9)	4 (2.5)	0.702

* Data was reported as mean (standard deviation) or *n* (%) as appropriate. [#] *n* = 156 per group.
cTFC, corrected TIMI frame count; Lp-PLA_2, lipoprotein-associated phospholipase A2; MACCE, major adverse cardiovascular and cerebrovascular events; MBG, myocardial blush grade; PPCI, primary percutaneous coronary intervention; TA, thrombus aspiration; TIMI, thrombolysis in myocardial infarction.

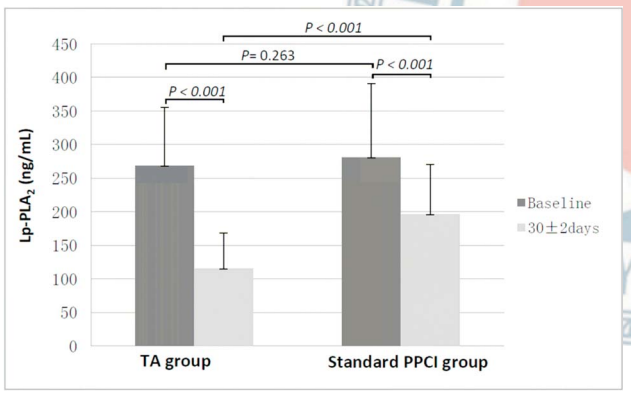

Figure 1. *Effect of selective thrombus aspiration (TA) before PPCI (TA group) compared to PPCI alone (standard PPCI group) on Lp-PLA_2 levels. Data represent mean ± standard deviation. After 30 ± 2 days, serum Lp-PLA_2 levels decreased by 53.9% in TA group (152.9 ± 58.1) and decreased by 31.2% in standard PPCI group (84.2 ± 86.6, p < 0.001).*

dition to conventional PCI demonstrated benefits regarding coronary flow and myocardial perfusion, and was therefore recommended in practice guidelines. However, two recent large randomized studies aimed to evaluate clinical outcomes; each study including almost 10,000 patients, which included a randomized study associated with a registry study namely Thrombus Aspiration in ST elevation Myocardial Infarction in Scandinavia (TASTE),[19] and a large-scale international trial Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL).[20] The results in terms of myocardial reperfusion were less salient than in the TAPAS study, although they did trend in the same direction, and thrombectomy was shown to reduce distal emboli. However, the results in terms of clinical outcomes were less encouraging, namely that there was no benefit affecting mortality at 1-year in either study.[21,22] Furthermore, an increased risk of stroke after TA raises safety concerns. Therefore, it may not be appropriate to recommend it routinely in all STEMI PCI procedures. Rather, TA could be considered as a reasonable option in the setting of PPCI in selected patient and lesion subsets (such as patients with low stroke risk and high lesion thrombus burden). The 2014 ESC/EACTS guidelines on myocardial revascularization suggest that while routine use of manual TA is not essential in patients undergoing PPCI for STEMI, selected use may facilitate the improvement of TIMI 3 flow or prevent stent thrombosis.[23] TA in selected patients during PPCI has a class IIb indication (level of evidence A). These guidelines take into account the evi-

dence including the TASTE trial but predate publication of the TOTAL trial, so far the largest trial addressing this question. During daily clinical work, although such research has not been conducted, we did find that TA in STEMI patients with HTB could reduce the no/slow flow phenomenon, reduce tirofiban utilization and improve myocardial perfusion; however, similar results were not found in STEMI patients with low LTB.

In the present study, we found that in STEMI patients undergoing PPCI within 12 hours of symptom onset after emergency coronary angiography with HTB, manual TA before PPCI, as compared with PPCI alone, did not reduce the risk of MACCE within 30 $\pm$ 2 days. However, the percentage of MBG $\geq$ 2 was significantly higher and cTFC was significantly lower in the TA group than those in the standard PPCI group. Furthermore, the TA group had a significantly lower prevalence of balloon predilatation, number of stents used and total stent length. Although there was no difference between groups in the proportion of TIMI flow grade 3 upon completion, the percent of TIMI flow grade 3 immediately after stent implantation tended to manifest a statistical difference between the TA group (84.4%) and the standard PPCI group (75.6%, p = 0.050). Perhaps the reason there was no apparent clinical benefit from our study was the short-term of clinical follow-up, or the small sample size. Considering that there were differences in foregoing aspects of angiographic data after PPCI between two groups, further analysis might be necessary to assess their impacts on serum Lp-PLA_2 levels at 30 + 2 days. The novel finding of our present research is that more improvements of serum Lp-PLA_2 levels were found in the TA group than those in the standard PPCI group after 30 $\pm$ 2 days of treatment (p < 0.01), although the improvements of serum Lp-PLA_2 levels in both groups were significant compared to baseline serum Lp-PLA_2 levels.

The underlying mechanism of TA in decreasing the serum levels of Lp-PLA_2 is not clear. The coronary thrombus material is associated with triggering thrombotic, inflammatory, vasoconstrictor, and other pathways. Therefore, evacuating a portion of the thrombus and plaque material by TA catheter may attenuate the local inflammation of infracted related artery and systemic inflammation. Lp-PLA_2 is mainly produced and secreted by monocyte-macrophages and foam cells in the atherosclerotic plaques.[24-26] It is strongly expressed in the necrotic core and surrounding macrophages around vulnerable and ruptured atherosclerotic plaques.[2] Therefore, the levels of serum Lp-PLA_2 may decrease after TA. Lp-PLA_2 is a highly specific marker of vascular inflammation. It has been demonstrated that the higher the plasma Lp-PLA_2 activity, the greater the severity of vascular inflammation and endothelial dysfunction.[27,28] Potentially, that is another mechanism of TA in improving myocardial reperfusion. Unfortunately, we have not yet measured serum levels of Lp-PLA_2 immediately and 7 days after PPCI. Therefore, the changes of serum Lp-PLA_2 within a short time after PPCI are unknown.

Recently, Wu et al.[24] consecutively enrolled 351 STEMI patients who underwent PPCI. They found that plasma Lp-PLA_2 level had a high correlation with thrombus burden score before PPCI, and it was found to be a significant independent predictor of HTB in STEMI patients. Plasma Lp-PLA_2 levels in HTB were significantly elevated as compared to those in LTB patients before PPCI, and were markedly increased immediately after PPCI compared to those before PPCI. Furthermore, they found that the plasma Lp-PLA_2 level in the coronary sinus was higher than those in the peripheral vein before and after PPCI therapy in 12 patients with STEMI, indicating that plasma Lp-PLA_2 may be released into coronary circulation from ruptured plaques in the criminal vessel. The reason for an increase in plasma Lp-PLA_2 level immediately after PPCI may be related to the degree of damage of the fissure or ruptured plaque by stent implantation procedures, and the exact reason needs to be further studied.[29] Therefore, we speculated that, after 30 $\pm$ 2 days of PPCI, the serum Lp-PLA_2 levels gradually decreased with the development of tissue repair.

Studies have shown that elevated plasma Lp-PLA_2 levels are associated an increased risk of cardiovascular disease in a healthy population as well as in patients with vascular disease.[25] Several other epidemiological studies have found the same association between elevated plasma Lp-PLA_2 and the development of coronary heart disease or cardiovascular disease.[26,30] However, there were several other studies where no correlation was found between the Lp-PLA_2 levels and risk of major adverse cardiovascular events.[31,32] Based on this evidence, the major scientific societies have included in their guidelines the measurement of Lp-PLA_2 activity

among the biomarkers that are useful in risk stratification of adult asymptomatic patients.[6] Lp-PLA_2 is therefore a potential therapeutic target in acute coronary syndromes. However, darapladib, a potent and reversible oral inhibitor of Lp-PLA_2, did not significantly reduce the risk of the primary composite end point of cardiovascular death, myocardial infarction, or stroke in patients with stable coronary heart disease[33] or the risk of major coronary events in patients of acute coronary syndromes.[34]

Limitations

Our study did have certain limitations. First, this study was a single center study with a small number of patients. Second, since 5 patients died within 1 week and 1 patient withdrew from the study because of severe hepatic dysfunction induced by atorvastatin, their blood samples at 30 $\pm$ 2 days after PPCI could not be obtained for accession of the serum Lp-PLA_2 levels. Furthermore, we have not measured serum levels of Lp-PLA_2 immediately and 7 days after PPCI, and did not clarify the changes within a short time after PPCI. Our study should not permit inferences to be made regarding causality, yet other interpretations of our data are possible and further studies are warranted.

CONCLUSIONS

In conclusion, we have demonstrated in STEMI patients with HTB undergoing PPCI that serum Lp-PLA_2 levels are significantly lowered by TA before PPCI after 30 $\pm$ 2 days compared to PPCI alone. However, TA did not promote additional clinical benefit within 30 $\pm$ 2 days, although it reduced the percent of balloon predilatation, number of stents used, total stent length and cTFC, improved the percent of MBG $\geq$ 2, and slightly increased the percent of TIMI flow grade 3 immediately after stent implantation.

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CONFLICT OF INTEREST

Authors declare they have no conflicts of interest.

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