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High-dose atorvastatin pretreatment could diminishes microvascular impairment in patients undergoing elective percutaneous coronary intervention

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Abstract

Objectives High-dose statins pretreatment is reasonable before percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial injury. However, the mechanism underlying this protective effect has not been elucidated. The aim of this study is to evaluate the effects of high-dose atorvastatin pretreatment on microvascular function and myocardial injury after elective PCI. **Methods** Eighty four patients underwent elective PCI were randomly assigned to high-dose atorvastatin (40 mg/d) and low-dose atorvastatin (20 mg/d) treatment for 7 days before PCI. The index of microcirculatory resistance (IMR) was measured by an intracoronary ressure/temperature sensor-tipped guidewire at maximal hyperemia after PCI. Fractional flow reserve (FFR) was measured before and after procedure. Troponin I levels were obtained at baseline and 20–24 h after procedure. **Results** IMR values were significantly lower in high-dose group when compared to low-dose group (16.5 ± 6.1 *vs*. 31.2 ± 16.0, $P < 0.001$). Pre-PCI troponin I levels between the two groups were similar (0.028 ± 0.05 *vs*. 0.022 ± 0.04, $P = 0.55$). However, post-PCI troponin I levels in high-dose group were significantly lower than low-dose group (0.11 ± 0.02 *vs*. 0.16 ± 0.09, $P < 0.001$). Multivariate analysis identified maximum inflation pressure > 20 atm as an independent predictor of IMR > 32 (Odds ratio (OR): 3.3, 95% confidence intervals (95%CI): 1.3–8.5, $P = 0.02$). High-dose atorvastatin was the only independent protective factor of IMR > 32 (OR: 0.29, 95%CI: 0.11–0.74, $P = 0.01$). **Conclusions** The present study confirmed that diminishing microvascular impairment is one of the mechanism underlying protecting effect of high-dose statins pretreatment from myocardial injury during PCI. These suggest that high-dose statin pretreatment is reasonable in patients undergoing elective PCI.

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Keywords: Statins; Index of microcirculatory resistance; Myocardial injury; Microvascular function; Percutaneous coronary intervention

1 Introduction

Troponin elevation, which reflects new irreversible myocardial injury,[1] is frequent after elective percutaneous coronary intervention (PCI).[2–4] Previous studies have shown that patients with cardiac marker increase after PCI had worse prognosis than those patients without cardiac marker increase.[5,6] The mechanism of cardiac markers elevation after PCI include microvascular embolization by plaque debris, side branch occlusion, and prolonged and/or high pressure balloon inflation.[1,2,7]

Statins (or 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors), which is widely used to lower cholesterol levels and treat coronary artery disease,[8,9] has been proved to be effective in reducing myocardial injury after PCI in patients with stable angina pectoris.[10,11] Administration of high-dose statin is recommended before PCI.[12] However, the mechanism underlying this protecting effect has not been elucidated yet. Except from lowering cholesterol levels, the "pleiotropic effects" of statins has become noticeable. These effects include enhancement of endothelial function through increasing nitric oxide content and bioactivity, anti-inflammatory effect, antioxidant effects, and stabilization of plaque. Therefore, we hypothesize that statins could diminish myocardial injury after elective PCI through its "pleiotropic effects" on microvascular function.

The index of microcirculatory resistance (IMR) has been successfully used to assess microvascular function in many clinical setting[13–15] for not only its quantitative nature and reproducibility, but also independence of epicardial vessel stenosis. In order to authenticate our hypothesis, we used IMR to evaluate microvascular function in patients underwent elective PCI.

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2 Methods

2.1 Study population and study protocol

A randomized non-blind, prospective single center study was performed. Patients were randomly assigned to either high-dose or low-dose of statin treatment independently of their lipid levels. Randomization number was generated by computer, with the use of sealed envelopes. All patients underwent stenting of all indicated lesions with drug-eluting stents (Resolute, Medtronic Inc., Santa Rosa, CA, USA).

The study protocol was approved by the ethics committee in the first affiliated hospital of Guangxi University of Chinese Medicine. All patients provided written informed consent. An independent clinical events committee whose members were unaware of treatment assignments adjudicated all primary efficacy and key safety events. Data management and statistical analysis were performed by independent data analysis group in our university.

Inclusion criteria were as follow: the presence of typical stable effort angina, a positive stress test, and an indication for PCI of a lesion more than 80% diameter stenosis or fractional flow reserve (FFR) value is less than 0.75.

Patients were excluded if left ventricular ejection fraction < 30%, acute coronary syndrome in the previous month, a history of myocardial infarction in the target vessel-related territory, a history of coronary artery bypass grafts, any increase in creatine kinase-myocardial band (CK-MB) or troponin I above the upper normal limit at the time of randomization, renal dysfunction with creatinine > 3 mg/dL, chronic total occlusion, in-stent restenosis, left main coronary artery disease, contraindications to adenosine and statin, and contraindications to drug-eluting stents.

Between July 2012 and March 2013, 98 patients with stable angina pectoris underwent elective PCI were included. Of those, 3 patients were excluded because of chronic total occlusion, 2 patients because of in-stent restenosis lesion, 4 patients because of failure to advance pressure wire across the lesion due to tortuous or calcified vessels, and 5 patients because of left main coronary artery disease. Finally, 84 patients were enrolled in the study.

Fourty three patients were randomly assigned to high-dose atorvastatin (40 mg/d) for 7 days before PCI (high-dose group), fourty one patients were assigned to low-dose atorvastatin (20 mg/d) for 7 days before PCI (low-dose group). All patients received atorvastatin 20 mg/d for 6 months after PCI.

According to protocol, all patients without contraindications were treated with aspirin 100 mg/d and clopidogrel 75 mg/d at least 7 days before the procedure. Before PCI, all patients received 100 IU/kg intravenous bolus of unfractionated heparin. Additional heparin boluses were given to maintain activated clotting time (ACT) > 300 s.

2.2 Coronary physiological measurements and intervention

PCI was performed in standard techniques. All coronary physiological assessments and interventions were performed after intracoronary administration of 0.2 mg nitroglycerin. The FFR and IMR were measured with a coronary pressure/temperature sensor-tipped guidewire (Radi PressureWire Certus, St. Jude Medical, Minneapolis, Minnesota) at maximal hyperemia induced by intravenous adenosine triphosphate, which was administered at a rate of 140 μg/kg of body weight per minute through a central vein or large peripheral vein. FFR was measured in each patient before and after PCI, and IMR was measured after PCI. FFR is calculated as the mean distal coronary pressure (measured with the pressure wire) divided by the mean aortic pressure (measured simultaneously with the guiding catheter) during maximal hyperemia.[16] IMR was calculated as mean distal coronary pressure multiplied by the hyperemic mean transit time of 3 × 3 mL bolus of room-temperature saline injected into the coronary artery through guiding catheter at maximum hyperemia.[17] The hyperemic transit time was measured as the time elapsed between when one-half of the saline had been injected (defined as T0, and determined on the temperature curve from the shaft of the wire) and when one-half of the saline had passed the sensor.[15]

2.3 Assessment of cardiac markers

Myocardial injury was defined as an elevation of cardiac troponin I (cTnI) over 5 times 99th percentile upper reference limit. The levels of troponin I were measured in all patients before intervention, and at 20 to 24 h after procedure. Troponin I determinations were performed in the clinical chemistry laboratory by the chemiluminescence immunoassays methods (normal range: 0–0.1 ng/mL).

2.4 Statistical analysis

All enrolled patients were included in the analysis of primary end points according to the intention-to-treat principle. Categorical variables are expressed as proportions and were compared with the use of the chi-square test. Continuous variables are expressed as mean ± SD and were compared with the use of an unpaired *t*-test with normal distributions or the Mann–Whitney *U* test if normality tests failed. A two-sided *P* value < 0.05 was considered as statistical significance. Multivariate logistic regression analysis was performed to determine independent predictors of impaired IMR (> 32)[18] after PCI. All demographic and clini-

cal variables, stent number (> 1), maximum inflation pressure (> 20 atm) and concomitant medication were tested in univariate regression analysis. Variables with $P < 0.2$ were entered into a multivariate stepwise backward logistic regression model to test for their independent effects on impaired IMR. Confounding variables (age, gender, smoke status, diabetes, hypertension, hyperlipidemia, previsous myocardial infarction, left ventricular ejection fraction (LVEF)) were forced to enter into the model for adjustment. The relative risks of the significant predictors for the increasing of IMR were expressed by using the odds ratio (OR) with 95% confidence intervals (CI).

3 Results

3.1 Baseline clinical characteristics

Baseline clinical and procedural variables in high-dose and low-dose groups are shown in Table 1. With regard to age, sex, angina classification, medical history, cardiovascular risk factors, left ventricular ejection fraction, and concomitant medication, there is no significant difference between high-dose and low-dose group.

Table 1. Baseline characteristics of the patients.

Characteristic	High-dose group (n = 43)	Low-dose group (n = 41)	P value
Demographic			
Age, yrs	66.8 ± 9.6	63.6 ± 10.4	0.15
Sex			0.53
Male	32 (74.4)	28 (68.3)	
Female	11 (25.6)	13 (31.7)	
Clinical			
Angina classification*			0.83
Ⅰ	8 (18.6)	8 (19.5)	
Ⅱ	15 (34.9)	12 (29.3)	
Ⅲ	11 (25.6)	14 (34.1)	
Ⅳ	9 (20.9)	7 (17.1)	
Previous MI	9 (21.0)	13 (31.7)	0.26
Previous PCI	13 (30.2)	8 (19.5)	0.28
Diabetes	11 (25.6)	14 (34.1)	0.39
Hypertension	28 (65.1)	25 (61.1)	0.69
Hypercholesterolem	31 (72.1)	29 (71.0)	0.97
Family history	13 (30.2)	6 (14.6)	0.09
Current smoker	11 (25.6)	14 (34.1)	0.39
LVEF	58.9% ± 11.0%	62.4% ± 10.0%	0.13
Medication			
Beta-blocker	26 (60.5)	20 (48.8)	0.28
Calcium antagonist	10 (23.3)	16 (39.0)	0.12
Nitrate	15 (34.9)	12 (29.3)	0.58
ACE inhibitor	19 (44.2)	22 (53.7)	0.39
ARB	8 (15.1)	12 (29.3)	0.25

Data are expressed as mean ± SD or as n (%), unless other indicated. *Canadian Cardiovascular Society Angina Class. ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention.

3.2 Results of PCI

Procedural characteristics were shown in Table 2. Drug-eluting stents were placed in all patients (100%). The procedure time was similar in two groups (75 ± 38 min in high-dose group and 79 ± 42 min in low-dose group, P = 0.65). Differences of target vessels, number of stents per patient, average diameter and total length of stents in two groups were no significant. In order to obtain optimal stent expansion, we performed high pressure post-dialation in majority of patients (35 patients in high-dose group and 39 patients in low-dose groups, P = 0.26) with noncompliant balloon. The maximum inflation pressures for post-dilation were usually 20 – 26 atm (21.2 ± 3.1 *vs*. 22.1 ± 1.5 atm, P = 0.09). All patients were free from in hospital major adverse cardiac events.

3.3 Physiological measurements and cTnI

FFR and IMR values were successfully measured in all target vessels. FFR values pre-PCI were similar between the

Table 2. Results of PCI.

Variable	High-dose group (n = 43)	Low-dose group (n = 41)	P value
Procedure time, min	75 ± 38	79 ± 42	0.65
Target vessel			0.68
LAD	21	18	
LCX	9	12	
RCA	13	11	
No. of stents per patient			
Mean	2.3 ± 1.3	1.9 ± 1.6	0.21
Median (interquartile range)	3 (2–3)	2 (1–3)	
Average diameter per patient, mm	3.03 ± 0.46	3.18 ± 0.52	0.16
Total length per patient, mm	33.8 ± 16.2	28.5 ± 12.7	0.10
Post-dilation, n	35	39	0.26
Maximum inflation pressure, atm	21.2 ± 3.1	22.1 ± 1.5	0.09
FFR			
pre-PCI	0.61 ± 0.13	0.55 ± 0.16	0.06
post-PCI	0.93 ± 0.07	0.95 ± 0.04	0.11
IMR post-PCI	16.5 ± 6.1	31.2 ± 16.0	< 0.001
cTnI, ng/mL			
pre-PCI	0.028 ± 0.05	0.022 ± 0.04	0.55
post-PCI	0.11 ± 0.02	0.16 ± 0.09	< 0.001

Data are expressed as mean ± SD or as n (%), unless other indicated. cTnI: cardiac troponin I; FFR: fractional flow reserve; IMR: microcirculatory resistance; LAD: left anterior decending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; PCI: percutaneous coronary intervention.

two groups (0.61 ± 0.13 *vs*. 0.55 ± 0.16, $P = 0.06$). Differences of FFR values post-PCI between two groups were not also statistical significant (0.93 ± 0.07 *vs*. 0.95 ± 0.04, $P = 0.11$). However, IMR values were significantly lower in high-dose group when compared to low-dose group (16.5 ± 6.1 *vs*. 31.2 ± 16.0, $P < 0.001$).

Pre-PCI troponin I levels between the two groups were not significantly different (0.028 ± 0.05 *vs*. 0.022 ± 0.04, $P = 0.55$). Elevation of troponin I levels occurred in 46.5% of patients in high-dose group and 51.2% in low-dose group after procedure ($P = 0.27$). However, post-PCI troponin I levels in high-dose group were significantly lower than low-dose group (0.11 ± 0.02 *vs*. 0.16 ± 0.09, $P < 0.001$).

Side branch occlusion occurred in 4 patients (9.3%) in high-dose group and 5 patients (12.2%) in low-dose group ($P = 0.74$). Post-PCI Troponin I levels were significantly elevated in patients with side branch occlusion when compared to those without side branch occlusion (0.19 ± 0.1 *vs*. 0.05 ± 0.06, $P < 0.001$). However, Post-PCI IMR values were similar between patients with and without side branch occlusion (29.2 ± 18.8 *vs*. 23.0 ± 13.4, $P = 0.21$).

Post-PCI troponin I levels were significantly greater in patients with post-PCI IMR values > 32 than those with post-PCI IMR values < 32 (0.14 ± 0.08 *vs*. 0.12 ± 0.02, $P = 0.02$).

3.4 Predictors of microcirculation damage after PCI

Multivariate logistic regression analysis was performed to determine the independent predictors of high post-PCI IMR values. Variables with $P < 0.2$ in univariate analysis were as follow: age, gender, smoke status, diabetes, hypertension, hyperlipidemia, previsous myocardial infarction, LVEF, maximum inflation pressure (> 20 atm). Multivariate analysis identified maximum inflation pressure > 20 as an independent predictor of IMR > 32 (OR = 3.3, 95%CI: 1.3–8.5, $P = 0.02$). High-dose atorvastatin was the only independent protective factor of IMR > 32 (OR = 0.29, 95% CI: 0.11–0.74, $P = 0.01$).

4 Discussion

In this study, we have shown that high-dose atorvastatin pretreatment before PCI was associated with diminished myocardial injury, microvascular impairment, which is assessed by invasive measurement of IMR post-procedure. As expected, pretreatment with high-dose (40 mg/d) atorvastatin for 7 days before PCI significantly diminished cardiac troponin I elevation after PCI. Multivariate analysis identified maximum inflation pressure > 20 atm as an independent predictor of microvascular impairment. High-dose atorvastatin was an independent protective factor of microvascular damage.

Cardiac markers elevation, especially troponin I, usually occurs post procedure and represents myocardial injury even successful PCI.[2–4] It has been documented that patients with troponin I elevation post PCI had worse prognosis than did those patients with normal troponin I levels.[5,6] The mechanism of cardiac markers elevation post PCI is widely considered as microvascular embolization of atheroma debris accompanying the plaque disruption caused by balloon inflation.[19] In this study, multivariate analysis results indicated that high pressure inflation is associated with microvascular impairment. Side branch occlusion is another major cause for cardiac markers elevation after PCI.[20] Although troponin I levels were remarkably increased in patients with side branch occlusion, this effect of high-dose statin cannot be attributed to protecting side branch from occlusion, since the number of patients with side branch occlusion in both groups were similar and IMR values in patients with side branch occlusion were not different from those without side branch occlusion. Except from angiography, we could not identify the real culprit of cardiac markers elevation after PCI. The IMR has been successfully used to assess the microvascular function in patients with stable angina pectoris,[19] acute myocardial infarction,[18] and even cardiac transplatation.[21]

In order to eliminate the influence of wedge pressure of collateral circulation, IMR values were measured after stenting and no functional residual stenosis present (FFR > 0.90) in this study. Patients treated with high-dose atorvastatin had significantly lower IMR values than did those patients treated with lose dose atovastatin.

Several studies have focused on the benefit of statin therapy after PCI in patients with stable angina pectoris.[22,23] A previous study[10] demonstrated that atorvastatin (40 mg/d) pre-treatment for 7 days reduced serum cardiac marker elevation after PCI. Few studies focused on the potential effect of statins on myocardial microvascular. In this study, atorvastatin (40 mg/d) was started 7 days before PCI regardless of their cholesterol levels and IMR values were measured post PCI.

Although not completely clear, the mechanisms underlying the beneficial effects of atorvastatin might be related to "pleiotropic effects" but not to low density lipoprotein cholesterol (LDL-C) reduction. A resent study founded that post-PCI IMR values were not associated with LDL-C reduction by pravastatin pretreatment for one month.[24] Both animal study and clinical studies revealed that statin treatment could stabilize plaque through repressing inflammatory cells and matrix metalloproteinase expression,[25] reducing lipid pool and increasing fibrous content in plaque.[26]

Another potential mechanism may be through Endothelial Nitric Oxide Synthase /Nitric Oxide (eNOS/NO) signaling. Statins could increase eNOS expression, bioactivity and NO concentration through inhibiting RhoA isoprenylation and Rho kinase activity.[27,28] Otherwise, anti-inflammation could also participate in protecting effects of statin. Chan *et al*.[29] reported that the higher C-reactive protein level is, the more beneficial the statins. The anti-inflammatory effect of statins might diminish microvascular damage caused by plaque debris embolism during the procedure.

In line with previous study, the results of present study indicated that high-dose statin pretreatment is associated with myocardial protection after PCI. The mechanism underlying this effect is diminishing myocardial microvascular damage during procedure through the "pleiotropic effects", which include anti-inflammation, stabilization of plaque, protection of microvascular endothelium and increasing NO bioavailability through inhibiting Rho/ROCK signaling.

In conclusion, the present study confirmed that diminishing microvascular impairment is one of the mechanisms underlying protecting effect of high-dose statins pretreatment from myocardial injury during PCI. These date suggest that routin daily use of high-dose statins pretreatment is reasonable in patients undergoing elective PCI for stable angina pectoris.

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