Evidence of pleiotropy by statins: Leukocyte Rho kinase (ROCK) activity and pretreated statin before percutaneous coronary interventions are clinical vascular outcome predictors

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Statin therapy prior to PCI is associated with overall improvement of cardiovascular outcome, mortality and peri-procedural myocardial injury after PCI in coronary artery disease (CAD) patients [1–3]. In one meta-analysis report [4], statin pre-treated was better than nothing in the odds ratio of future coronary event outcomes. Interestingly, the level of low-density lipoprotein (LDL) cholesterol did not correlate with their outcome after PCI. This result probably implied that statin therapy has vascular protection beyond LDL lowering effect, but not for the whole group. However, it remained unknown what factors or conditions can be more beneficial from statin pretreatment during the PCI procedure. Mechanisms had been proposed as the inhibition of Rho-associated coiled-coil containing protein kinase (ROCK) [5–7] and inflammation reaction including c reactive protein (CRP) [8]. These so-called "pleiotropic" or cholesterol-independent effects of statins have been associated with the mechanisms via improvement in flow-mediated vasodilation [9,10], anti-inflammation [8,11] and also enhancement function of circulating vascular endothelial progenitor cells [12]. To test whether these important vascular biomarkers can predict those "high-risk" subgroup to be more beneficial to statin pretreatment strategy during PCI procedure, we conduct a clinical observational study based on the interplay of "pretreatment statin or not" and "the level of CRP or leukocyte ROCK activity" at baseline or after PCI, partially according our previous reports and methodologies [13–16]. We studied 138 patients who were documented as CAD with another 50 patients with normal coronary

Table 1
Baseline characteristics of control and CAD patients, subdivided into statin pretreatment or naïve before PCI procedures.

	Control (n = 50)	CAD (n = 138)	Statin naïve (n = 58)	Statin pretreated (n = 80)
Age, years	62 ± 10	61 ± 13	61 ± 15	61 ± 15
Male, sex (%)	35 (70)	94 (68.1)	40 (68.9)	54 (67.5)
Smoking (%)	20 (40)	67 (48.6)*	27 (46.5)	40 (50.0)
Diabetes mellitus (%)	5 (10)	27 (19.5)**	10 (17.2)	14 (17.5)
Hypertension (%)	12 (24)	76 (55.0)**	30 (52)	43 (53.7)
Total cholesterol, mg/dl	196 ± 40	206 ± 34*	208 ± 25	205 ± 30
HDL-cholesterol, mg/dl	52 ± 14	46 ± 20*	47 ± 26	46 ± 14
LDL-cholesterol, mg/dl	123 ± 38	131 ± 40**	132 ± 33	131 ± 47
Triglycerides, mg/dl	133 ± 42	135 ± 43	136 ± 55	135 ± 53
BMI, kg/m^2	22.1 ± 4.2	23.0 ± 5.1	23.1 ± 4.3	23.0 ± 3.1
Number of risk factors	1.3 ± 1.5	2.3 ± 1.7**	2.3 ± 1.9	2.5 ± 2.3
CRP, mg/dl	0.46 (0.18–2.56)	3.25** (1.28–5.88)	3.23 (1.28–4.98)	3.26 (1.33–5.88)
ROCK activity (pMBS/tMBS ratio)	0.21 (0.12–0.62)	0.40** (0.27–1.02)	0.42 (0.27–0.89)	0.40 (0.28–1.02)
Previous MI (%)	–	21 (15.2)	8 (13.7)	13 (16.2)

Values are expressed as mean ± SD or number, or median with inter-quartile range. BMI = body mass index; CRP = C – reactive protein; MI = myocardial infarction; PCI = percutaneous coronary intervention; LDL = low-density lipoprotein; HDL = high-density lipoprotein; NA = not analyzed; ROCK = Rho kinase. *$P < 0.05$, **$P < 0.01$ compared between normal control and CAD groups; there was no difference between statin naïve and statin pretreated subgroups.

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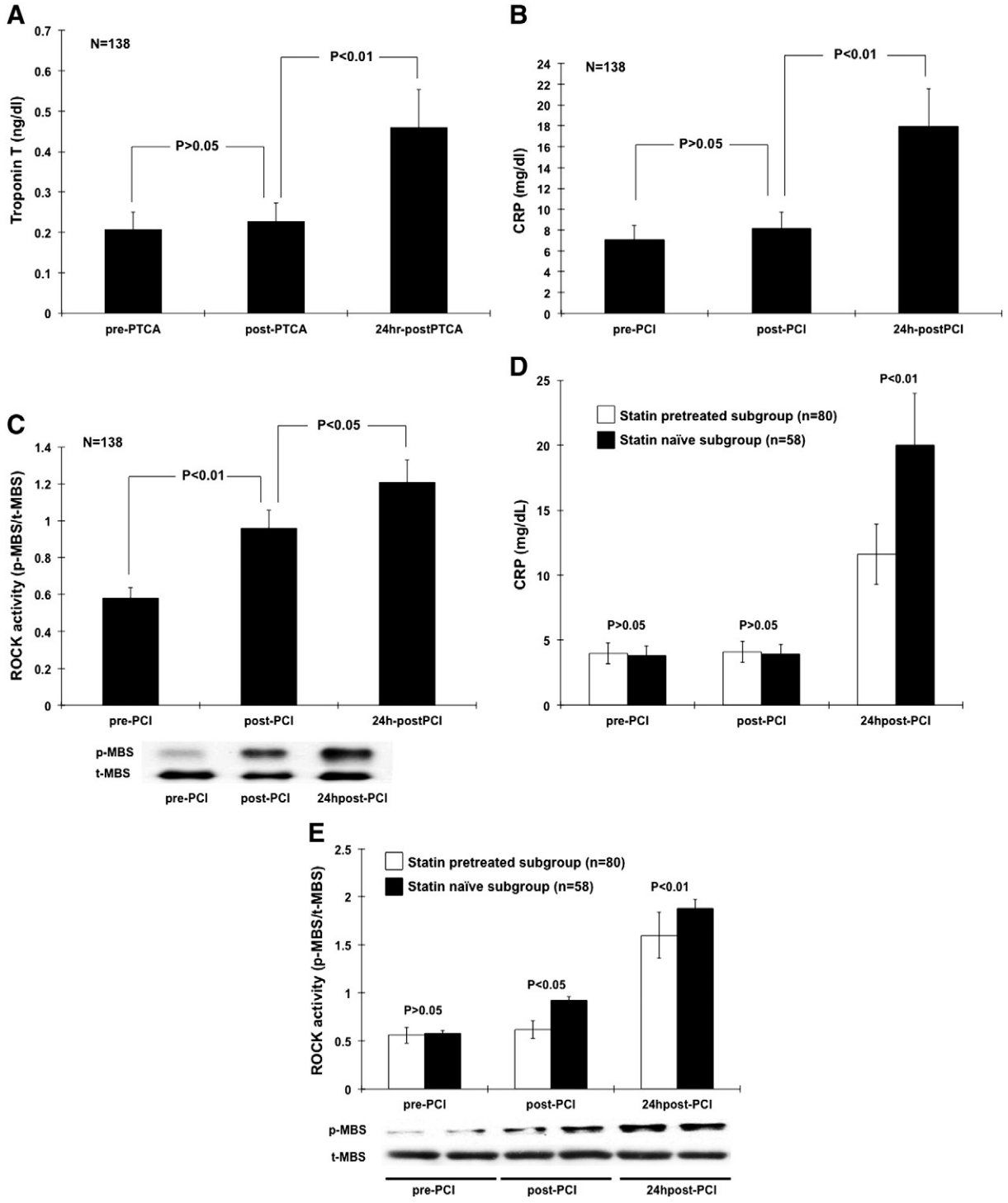

Fig. 1. Serial changes of biochemical markers before and after PCI. (A) and (B): Troponin-T and C-reactive protein (CRP) elevated significantly only at 24 h after PCI. (C): Rho kinase (ROCK) activity on isolated peripheral leukocytes increased immediately after PCI and persistent till 24 h after PCI. (D): Pretreated statin subgroup showed less elevation of C-reactive protein (CRP) at 24 h after PCI than the statin naïve subgroup. (E): Pretreated statin showed less elevation of Rho kinase (ROCK) activity elevation on isolated peripheral leukocytes both immediately after PCI and also at 24 h after PCI than the statin naïve subgroup. PCI = percutaneous coronary intervention; p-MBS = phosphor-myosin binding subunit; t-MBS = total myosin binding subunit.

arteries who were compared as the control group. Patients' characteristics were presented in Table 1. The prevalences of smoking behavior history, diabetes mellitus, hypertension, the levels of cholesterol as well as the baseline CRP and ROCK activity were all higher in the CAD group. There was no difference in the traditional cardiovascular risk factors, LDL-C levels and other inflammatory biomarkers when we divided the CAD group subjects into statin naïve or statin pretreated subgroups (Table S1). These data indicated that our study subgroups were well matched. The comparative procedural and angiographic characteristics of the subgroup defined by the pretreatment of statin or not were similar and presented in Table S1. The baseline ROCK activity did not correlate with baseline CRP levels ($P = 0.33$). Multiple logistic regression analysis with forward stepwise selection showed that in addition to hypertension (Odds ratio (OR) 3.2), smoking behavior (OR 2.3) and diabetes mellitus (OR 2.1), baseline higher levels of ROCK activity (>0.38) remained an