From the results depicted in Fig. 1, the observed plasma DA increment in the study of Jacob et al. [650 ng/L (4.2 nmol/L) *(4)*] would have corresponded to ~2% contamination of the TYR infusate—well within quality-control limits. Infusion of relatively uncontaminated TYR in the present study produced much smaller increments in plasma DA that were not associated with forearm vasodilation. In healthy humans, intravenous DA infusion ($0.5–2.0 \ \mu g \cdot kg^{-1} \cdot min^{-1}$) also does not affect forearm vascular resistance *(9)*.

One might expect that forearm vascular resistance would increase during TYR infusion, because of local NE release. In humans, however, the pressor response to intravenous TYR reflects cardiac stimulation, not systemic vasoconstriction *(10)*, as confirmed in the present study. Apparently, TYR releases NE from sympathetic nerves in the myocardium, where they are much more abundant than in skeletal muscle. If TYR released NE from sympathetic nerves in the forearm, then the venous–arterial difference for plasma NE in the arm should have increased; instead, the small arm venous–arterial difference for plasma NE did not change. Meanwhile, increments in cardiac stroke volume were strongly positively correlated with increments in arterial plasma NE.

During infusion of uncontaminated TYR, arterial plasma concentrations of DA, NE, and DHPG all increased in a correlated manner, with the largest increments in plasma DHPG and the smallest in plasma DA. One can understand these results in terms of TYR displacing NE from vesicular stores into the axoplasm, where the NE would undergo oxidative deamination to an aldehyde intermediate, followed by reduction of the aldehyde to DHPG *(1, 11, 12)*. A small amount of vesicular NE would enter the extracellular fluid and occupy postsynaptic cardiovascular adrenoceptors or reach the plasma, explaining the strong positive correlation between increments in cardiac stroke volume and in arterial plasma NE concentrations. An even smaller amount of DA would enter the plasma, reflecting vesicular DA not yet converted to NE.

From the results of incubating TYR solutions at 37 °C, we inferred that DA formed from oxidation of TYR is itself rapidly oxidized, particularly in tap water solutions. Iron ions in tap water would be expected to catalyze oxidation of DA to dopaminechrome *(13)*.

Before the discovery of tyrosine hydroxylase as the rate-limiting step in biosynthesis of catecholamines, researchers considered the possibility that endogenous catecholamines might arise from autooxidation of tyrosine. In the body, the rate of 3,4-dihydroxyphenylalanine (DOPA) formation by autooxidation of tyrosine was found to be negligible compared with the rate of formation by enzymatic catalysis. The present findings serve as a reminder that DA can be synthesized ex vivo by nonenzymatic oxidation of TYR. For both scientific and ethical reasons, investigators who carry out clinical studies involving TYR administration should assay DA concentrations to exclude contamination of the infusate. From a practical point of view, to minimize this contamination,

we recommend that TYR be dissolved in deionized water and stored frozen at −70 °C.

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Effects of 4 Weeks of Atorvastatin Administration on the Antiinflammatory Cytokine Interleukin-10 in Patients with Unstable Angina, *Jian-Jun Li[1*] and Chun-Hong Fang[2]* ([1] Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, People's Republic of China; [2] Renmin Hospital, Wuhan University School of Medicine, Wuhan, People's Republic of China; * address correspondence to this author at: Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, People's Republic of China; fax 86-10-68331730, e-mail lijnjn@yahoo.com.cn)

Atherosclerosis is currently considered a chronic inflammatory disease of the vessel wall. Systemic markers of inflammation have been shown to be of significant prognostic relevance for assessing the risk of atherosclerotic disease progression *(1–4)*. Previous data showed that

proinflammatory markers, such as C-reactive protein (CRP), play an important role in acute coronary events (5–7) and that decreased plasma concentrations of antiinflammatory cytokines, for example, interleukin-10 (IL-10) were also associated with acute coronary syndrome (ACS) (8–10).

Statins, 3-hydroxy-3-methyglutaryl-coenzyme A reductase inhibitors, represent a well-established class of drugs that effectively lower serum cholesterol concentrations and are widely used for the treatment of cardiovascular disease (11–13). In addition to their cholesterol-lowering activity, statins have been demonstrated to possess pleiotropic effects, including antiinflammatory effects (14–17). Results obtained in numerous investigations have suggested that administration of statins could modify concentrations of CRP and other proinflammatory cytokines with a concurrent decrease in cardiovascular events. However, the potential influence of statins on the antiinflammatory cytokine IL-10 in patients with ACS has not been investigated.

In the present study, 42 patients with unstable angina (UA) were randomly assigned immediately after admission to standard therapy plus either 20 mg/day atorvastatin or placebo. The standard therapy included aspirin, beta-blockers, heparin/low–molecular-weight heparin, angiotensin-converting enzyme inhibitors, and oral nitrates. The protocols of the study were approved by the Ethics Review Board of the Hospital, and all patients gave written, informed consent. The patients with UA presented with ischemic chest pain at rest in the absence of extracardiac cause with ST-segment depression ≥ 0.1 mV in 2 or more contiguous leads on 12-lead electrocardiograms at administration. Echocardiography was performed in all patients to exclude patients with an impaired left ventricular ejection fraction ($<50\%$) as well as myocardial hypertrophy. Patients with evidence of myocardial infarction, including ST elevation, formation of Q waves, and increased entry concentration of cardiac troponin T or I, were excluded from the study. Patients with evidence of congestive heart failure, poorly controlled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >105 mmHg), statin therapy in the prehospitalization period, valvular heart disease, a history of dysphagia, swallowing as well as intestinal motility disorders, and untreated thyroid disease were also excluded from the study.

Selective coronary angiography for all enrolled patients was performed in multiple views by the standard Judkin techniques within 1 week, and the results were analyzed by at least 2 interventional physicians, as described in our previous study (18, 19). The severity of coronary stenosis was evaluated by the incremental score method.

Blood samples for measurement of lipids, CRP, and IL-10 were drawn on days 0 and 28 from all patients after a 12-h overnight fast (8–12 h after administration of either 20 mg/day atorvastatin or placebo). Serum concentrations of total cholesterol (TC) and triglycerides (TGs) were measured by enzymatic methods on an Olympus AE 1000 analyzer. HDL-cholesterol concentrations were measured by an anionic detergent method (Sigma Biochemical). LDL-cholesterol concentration was computed with the Friedewald formula as reported previously (15). We also measured serum hepatic enzymes, including glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and total lactic dehydrogenase, in all patients in each treatment group at days 0 and 28 (CL 1000 biochemical analyzer). Serum IL-10 concentrations were measured by ELISA (R&D systems) as reported previously (8, 9). The lower limit of detection was 0.5 ng/L. No significant cross-reactivity or interference was observed with recombinant human or recombinant mouse IL-10, and the intraassay CVs between duplicates were $<10\%$. The reference interval for IL-10 in our laboratory is 0.8–1.9 ng/L. The concentrations of high-sensitivity CRP were measured by immunoturbidimetry (Beckman Assay 360). The upper limit of the reference interval for CRP in a healthy population, as measured by this assay, was 0.8 mg/L, with 90% of values for a healthy population being <0.3 mg/L; the lower detection limit is 0.2 mg/L. The interassay CVs were 4.4% and 4.8%, respectively, and intraassay CVs were 3.5% and 5.1%, respectively (18, 19).

Data are reported as the mean (SD). Continuous variables were tested for gaussian distribution with the Kolmogorov–Smirnov test and compared by one-way ANOVA. Categorical variables were compared by the χ^2 test. In the case of nongaussian distribution, the Mann–Whitney U-test was used. Coefficients of correlation (r) were calculated by the Pearson correlation analysis. A P value <0.05 was considered statistically significant.

A total of 42 patients were randomly enrolled in the study. Six patients were excluded from the study because of increased cardiac troponin T or I and coronary inter-

Table 1. Changes in median and mean plasma CRP and IL-10 concentrations in patients with UA treated by atorvastatin therapy or placebo.

	CRP, mg/L				IL-10, ng/L			
	Median		Mean (SD)		Median		Mean	
	At[a] (n = 19)	Pl (n = 17)	At (n = 19)	Pl (n = 17)	At (n = 19)	Pl (n = 17)	At (n = 19)	Pl (n = 17)
Day 0	5.4	5.7	9.8 (0.9)	11.0 (1.0)	7.6	8.1	16.0 (1.1)	15.8 (1.0)
Day 28	4.2	5.8	7.6 (0.6)	11.8 (1.2)	10.7	8.5	22.3 (1.3)	17.2 (1.1)
Change	−1.2 (23%)[b]	+0.1 (2%)	−2.2 (23%)[b]	+0.8 (7%)	+3.1 (29%)[b]	+0.4 (5%)	+6.3 (39%)[b]	+1.4 (8%)

[a] At, atorvastatin; Pl, placebo.
[b] $P < 0.01$ compared with day 0 and placebo group.

vention resulting from acute exacerbation of symptoms. Data were available for 19 patients who received the 20 mg/day atorvastatin treatment in the present study, in addition to 17 patients who were given placebo. None were interventionally treated throughout the study. There were no significant differences in baseline clinical characteristics between the 20 mg/day atorvastatin group (n = 19) and the placebo group (n = 17) in age, sex, body mass index, lean body mass, systemic hypertension, diabetes mellitus, smoking, lipid profile, left ventricle function, history of coronary intervention including percutaneous transluminal coronary angioplasty or/and stents, severity of coronary artery stenosis, and medication therapy.

By day 28 of atorvastatin therapy (20 mg/day), TC was significantly decreased compared with baseline values [182 (6.7) mg/L on day 28 vs 235 (12.1) at baseline; a 22% decrease], as was LDL-cholesterol [103 (4.1) mg/L vs 155 (7.5) mg/L; a 32% decrease]. The decrease in the TG concentration [111 (5.4) mg/L vs 127 (6.5); a 17% decrease] was much smaller than the decreases in TC and LDL-cholesterol. There was no significant difference in the mean HDL-cholesterol concentration by day 28 of atorvastatin therapy compared with baseline. The median CRP concentrations deceased from 5.4 mg/L at baseline to 4.2 mg/L (Table 1), whereas the mean CRP decreased from 9.8 mg/L at baseline to 7.6 mg/L in day 28 in the group receiving 20 mg/day atorvastatin (P <0.01). The effect of atorvastatin on CRP observed in this study was in agreement with previous studies (14, 15). In addition, our data indicated that the mean IL-10 concentrations increased from 16.0 ng/L at baseline to 22.3 ng/L at day 28 of atorvastatin (20 mg/day) treatment (P <0.001). However, no such change in IL-10 was observed in the placebo group (P >0.05). In addition, we observed a significant negative correlation between CRP and IL-10 after therapy in both the group receiving 20 mg/day atorvastatin (r = −0.384; P <0.01) and the placebo group (r = −0.323; P <0.01). No significant changes in hepatic enzyme concentrations were observed in either group (data not shown).

The results of numerous investigations have suggested that administration of statins could modify CRP and other proinflammatory cytokine concentrations with a concurrent decrease in cardiovascular events. In the present study, we demonstrated that atorvastatin (20 mg/day) given at the time of admission in patients with unstable angina not only reduced LDL-cholesterol and CRP concentrations within 4 weeks, which was in agreement with previous studies (14, 15), but also significantly increased the concentration of the antiinflammatory cytokine IL-10. This is of a great interest, particularly in ACS, because it may translate to a balance of pro- and antiinflammatory responses in the body and signal early onset of vascular endothelial benefit after short-term atorvastatin therapy.

Dynamic instability of a coronary atherosclerotic plaque is now seen as the foundation for the development of the clinical syndromes we recognize as UA and myocardial infarction. A complex intravascular inflammatory response is an integral component of this dynamic instability (20). Compared with patients who have chronic stable angina, patients with ACS have coronary plaques with more extensive macrophage-rich areas (21). A previous study demonstrated that serum IL-10 concentrations were significantly lower in patients with UA compared with patients with stable angina, suggesting that decreased serum IL-10 concentrations are associated with clinical instability (8). Recent data also indicated that increased serum concentrations of the antiinflammatory cytokine IL-10 were associated with a significantly improved outcome for patients with ACS (10).

It is well established that IL-10 is secreted by activated monocytes/macrophages and lymphocytes. Previous data have shown that IL-10 has multifaceted antiinflammatory effects and inhibits many cellular process that could play an important role in plaque progression and rupture, or thrombosis, including inhibition of the prototypic proinflammatory transcription nuclear factor-κB, leading to suppression of cytokine production (22), inhibition of matrix-degrading metalloproteinases (23), reduction in tissue factor expression (24), inhibition of apoptosis of macrophages and monocytes after infection (25), and promotion of the phenotypic switch of lymphocytes into the Th2 phenotype (26). These data further support the concept that the balance between pro- and antiinflammatory cytokines may be a major determinant of patients with ACS. Therefore, enhancing antiinflammatory cytokines may be a promising approach for therapy of acute coronary diseases.

It has been demonstrated that patients with ACS and abnormalities of serum lipid and CRP concentrations often have endothelial vasodilator dysfunction, which may contribute to cardiovascular events (27). The lowering of LDL-cholesterol concentrations by statins appears to be a sufficient explanation for the benefits seen in those studies. In vitro studies have shown that LDL-cholesterol and, in particular, its oxidized derivative are injurious to the endothelium. Furthermore, a statin-induced decrease in LDL-cholesterol concentrations in patients with coronary artery disease has been associated with beneficial effects on the coronary endothelium via decreases in inflammatory markers, such as CRP (28). However, our data demonstrated that statins increase concentrations of the antiinflammatory cytokine IL-10, suggesting that statins have multiple effects on inflammatory response, including enhancement of the antiinflammatory effects.

The clinical meaning of our present results must be considered cautiously. The data did not demonstrate that atorvastatin directly influences the production of IL-10. It might also be that unstable atherosclerotic plaques by some mechanism suppress IL-10. Atorvastatin-induced stabilization of atherosclerosis might then allow the enhanced production of IL-10, compared with the placebo group, without direct effects on the IL-10–producing cells. Regarding our study design, limitations included that we did not evaluate a dose-dependent effect of atorvastatin on IL-10 and we did not measure the changes of endothelial function after 4 weeks of atorvastatin treatment. Moreover, the fact that cardiovascular events were not

evaluated in our small study sample is also a potential limitation.

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Pediatric Reference Intervals for Seven Common Coagulation Assays,

Michele M. Flanders,[1] Ronda A. Crist,[2] William L. Roberts,[1,3] and George M. Rodgers[1,3,4]* ([1] ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT; [2] ARUP Laboratories, Salt Lake City, UT; [3] Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, UT; [4] Department of Medicine, University of Utah Health Sciences Center, Salt Lake City, UT; * address correspondence to this author at: Division of Hematology, University of Utah Health Sciences Center, 50 North Medical Dr., Salt Lake City, UT 84132; fax 801-585-5469, e-mail george.rodgers@hsc.utah.edu)

Accurate interpretation of pediatric coagulation tests is complicated by the fact that reference intervals for many assays differ from those for adults. In 1992, Andrew et al. (1) reported childhood coagulation reference intervals for ages 1–5, 6–10, and 11–16 years with a minimum of 4 and maximum of 7 individuals at each age, with 20–50 per age group. These results have served as the basis for most pediatric coagulation reference intervals for over a decade. However, with the development of newer reagents, methodologies, and instruments to measure coagulation analytes, results from this study, which was limited by its small size, may be less relevant.

In 2002, we initiated a project to collect blood and urine samples from healthy children 7–17 years of age, with the goal of establishing pediatric reference intervals for many laboratory tests (2). The purpose of this study was to determine pediatric reference intervals for 7 coagulation tests associated with common bleeding disorders.

Samples were drawn for reference interval studies from 902 healthy children, ages 7–17 years. All were healthy, had no history of bleeding or thrombotic disorders, and were taking no medications for at least 2 weeks before specimen collection. Informed consent was obtained from parents, and the study was approved by the University of Utah Institutional Review Board. Samples used to establish adult reference intervals were purchased from George