
ORIGINAL RESEARCH

Assessment of arterial stiffness affected by atorvastatin in coronary artery disease using pulse wave velocity

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Abstract

Purpose: Several studies have shown arterial stiffness changes associated with coronary artery disease (CAD). Recently, statins were reported to improve arterial stiffness. The aim of the study was to evaluate the effect of atorvastatin on arterial stiffness in CAD patients using pulse wave velocity (PWV).

Methods: We evaluated 63 patients with hyperlipemia and CAD. Forty-three patients were given 10mg atorvastatin daily and 20 patients were assigned to a low-fat diet. Carotid-femoral PWV (PWV-CF), carotid-radial PWV (PWV-CR) and carotid-distal PWV (PWV-CD) were measured in all patients.

Results: Compared with baseline, PWV-CF, PWV-CR and PWV-CD decreased after therapy in the atorvastatin group (13.22±3.39 & 11.85±2.87; 11.85±2.72 & 10.73±2.31; and 11.04±1.99 & 10.15±1.75, $P<0.05$). There was no difference in the control group (13.29±2.89 & 13.93±2.89; 11.52±2.25 & 12.31±2.22; and 10.46±1.86 & 11.15±1.85, $P>0.05$). After treatment, values of total cholesterol, triglyceride and low density lipoprotein (LDL) cholesterol were reduced in the 2 groups ($P<0.05$).

Conclusions: The study demonstrated that atorvastatin can improve arterial stiffness in CAD patients independent of its lipid-lowering properties.

Arterial stiffness promotes the development of atherosclerosis because it can aggravate the atherosclerotic vascular damage, influence on the cardiac workload, and have direct atherogenic effects.¹ Some studies have demonstrated that arterial stiffness is strongly related to the atherosclerosis at various sites in the vascular tree, and has been as a marker of the risk of coronary artery disease (CAD).² There is an association between elevated arterial stiffness and CAD, and increased arterial stiffness may contribute to increase in incidence of cardiovascular disease.³ Therefore, early assessment and intervention of arterial stiffness are of great importance in reducing the progress of atherosclerosis.

Statins are drugs with potent lipid-lowering effects. Increasing evidence suggests that statins may have a beneficial pleiotropic effect in addition to their lipid-lowering properties.⁴ Nitric oxide (NO), synthesized and released by vascular endothelium, plays an important role in the control of vascular tone and structure.⁵ Statin therapy has been shown to stimulate the synthesis and release of NO, improve endothelial function, inhibit proliferation of smooth muscle cells,

increase plaque stability, and inhibit inflammatory responses and thrombus formation.^{4,5} Recently, statins were reported to improve arterial stiffness and vascular structure.^{6,7}

Pulse wave velocity (PWV) is non-invasive method to assess atherosclerosis accurately. PWV is well correlated to the presence of CAD, and is higher in patients with CAD than in those without CAD.⁸ Recently, it was reported that PWV not only reflects vascular damage but also is a determinant of the number of diseased coronary arteries.⁹ While PWV is an index of arterial stiffness and is inversely related to the arterial distensibility,⁹ a device for measuring PWV has been developed. Measurements of PWV have been used to evaluate arterial stiffness in the healthy and in the diseased heart.¹⁰

Utilizing PWV, this study examined the effect of atorvastatin on arterial stiffness in patients with moderate hyperlipemia and CAD.

Methods

Patients

Patients who visited our hospital from January 2005 to July 2006 with hyperlipidemia and CAD confirmed by previous coronary arteriography were enrolled. All subjects had baseline fasting serum LDL cholesterol level between 3.62 and 6.46 mmol/L, and fasting triglyceride < 4.52 mmol/L. Exclusion criteria included ongoing or previous treatment with lipid-lowering drugs, hypertension, diabetes mellitus, acute coronary syndromes within 6 months, liver or kidney disease and cancer. The Institution's Ethical Committee approved the study, and written informed consent was obtained from all participants.

Study Design

Forty-three patients were consecutively assigned to 10 mg daily of atorvastatin for 6 months in addition to a low-fat diet. The control group, comprised 20 patients who met the same inclusion and exclusion criteria,

was assigned to only a low-fat diet. The low-fat diet was based on the diet for hyperlipemia recommended by the Expert Panel for CAD.¹¹ During the study period, all patients received routine cardiovascular medications and their smoking status did not change.

PWV

All patients were studied using PWV at baseline, and at 3- and 6-months. The patients were examined supine with Complior SP equipment (Colson, Gargelles-Gonesse, Paris, France) that allowed on-line pulse wave recording and automatic calculation of the time interval between two pulse waves recorded simultaneously. The distance between the two appplanation sites over the carotid artery and femoral artery, over the carotid artery and radial artery or over the carotid artery and distal artery, were measured as a straight line on the surface between the two arteries. Velocity (m/sec) was calculated as transit distance/transit time automatically. The value of Carotid-femoral PWV (PWV-CF), carotid-radial PWV (PWV-CR) and carotid-distal PWV (PWV-CD) were recorded and the average of 10 recording was calculated as well.

Laboratory Measurements

Fasting serum total cholesterol, triglyceride, LDL cholesterol and high-density lipoprotein (HDL) cholesterol were measured at baseline and at 3- and 6-months of therapy. Plasma glucose and alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and creatine kinase were also measured.

Statistical Analysis

Continuous variables are expressed as means \pm SD. Categorical variables are presented as counts and percentages. Student *t* tests and χ^2 tests were used when appropriate. A value of $P < 0.05$ was considered significant. All analyses were performed with SPSS for Windows, version 11.5 (SPSS Inc).

TABLE 1. Baseline characteristic of the patients in 2 groups

	No Statin	Atorvastatin	<i>P</i>
Age, yr	63.30±4.87	61.02±8.97	0.201
Male, %	45	42.86	0.874
Heart rate, beat/min	69.65±5.71	67.64±7.27	0.283
SBP, mmHg	122.60±9.20	125.88±9.19	0.194
DBP, mmHg	77.10±8.06	79.48±7.17	0.246
Smoking category (%)	20.00	21.43	0.813
BMI, kg/m ²	24.70±3.35	26.13±3.77	0.153
Plasma glucose, mmol/L	5.30±0.50	5.34±0.55	0.790
Medication			
Aspirin, %	95.00	97.62	0.832
β blockers, %	45.00	45.24	0.986
Nitrates, %	40.00	38.10	0.886

BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

TABLE 2. Lipid levels at baseline and 6 months of therapy

Lipid levels	Baseline		6 months	
	No Statin	Atorvastatin	No Statin	Atorvastatin
Total cholesterol, mmol/L	6.08±0.43	6.25±0.57	5.57±0.42*	4.35±0.58*+
Triglycerides, mmol/L	1.94±0.58	1.84±0.72	1.55±0.55*	1.38±0.49*
HDL cholesterol, mmol/L	1.28±0.31	1.32±0.33	1.41±0.25	1.42±0.31
LDL cholesterol, mmol/L	4.17±0.40	4.41±0.48	3.54±0.35*	2.49±0.50*+

**P*<0.05, compared with baseline in the same group;

+*P*<0.05, compared with control group

Results

The characteristics of enrolled patients were shown in Table 1. Except for one patient who withdrew from the study because of nausea after receiving atorvastatin, others completed the study. During the study, there were no untoward cardiac events.

Lipid values at baseline and at 6-months of therapy were listed in Table 2. After 6 months of therapy, patients receiving atorvastatin showed a decrease in total cholesterol, triglyceride and LDL cholesterol values. There was a 30.03% ± 9.78% decrease in total cholesterol, a 20.42% ± 25.82% decrease in triglycerides, a 43.08% ± 12.06% decrease in LDL cholesterol, and a 12.82% ± 34.70% increase in HDL cholesterol. Patients receiving only a lipid-lowering diet had a mild decrease in lipid levels, probably because of the type of diet. There were no changes in the en-

zymes alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase or creatine kinase.

As shown in Figure 1, a decrease in PWV-CF, PWV-CR and PWV-CD in patients receiving atorvastatin was seen after 6 months of treatment (*P*<0.05). There was no correlation between the percentage change in PWV-CF, PWV-CR, PWV-CD and that of serum LDL cholesterol level (*r*=0.523, *P*>0.05; *r*=0.194, *P*>0.05; or *r*=0.327, *P*>0.05). Also, there was no relationship between the percentage change in PWV and that of total cholesterol, triglyceride and HDL cholesterol. However, neither the 6 month diet therapy in control patients, nor the 3 months of atorvastatin treatment produced changes in parameters measured by the PWV.

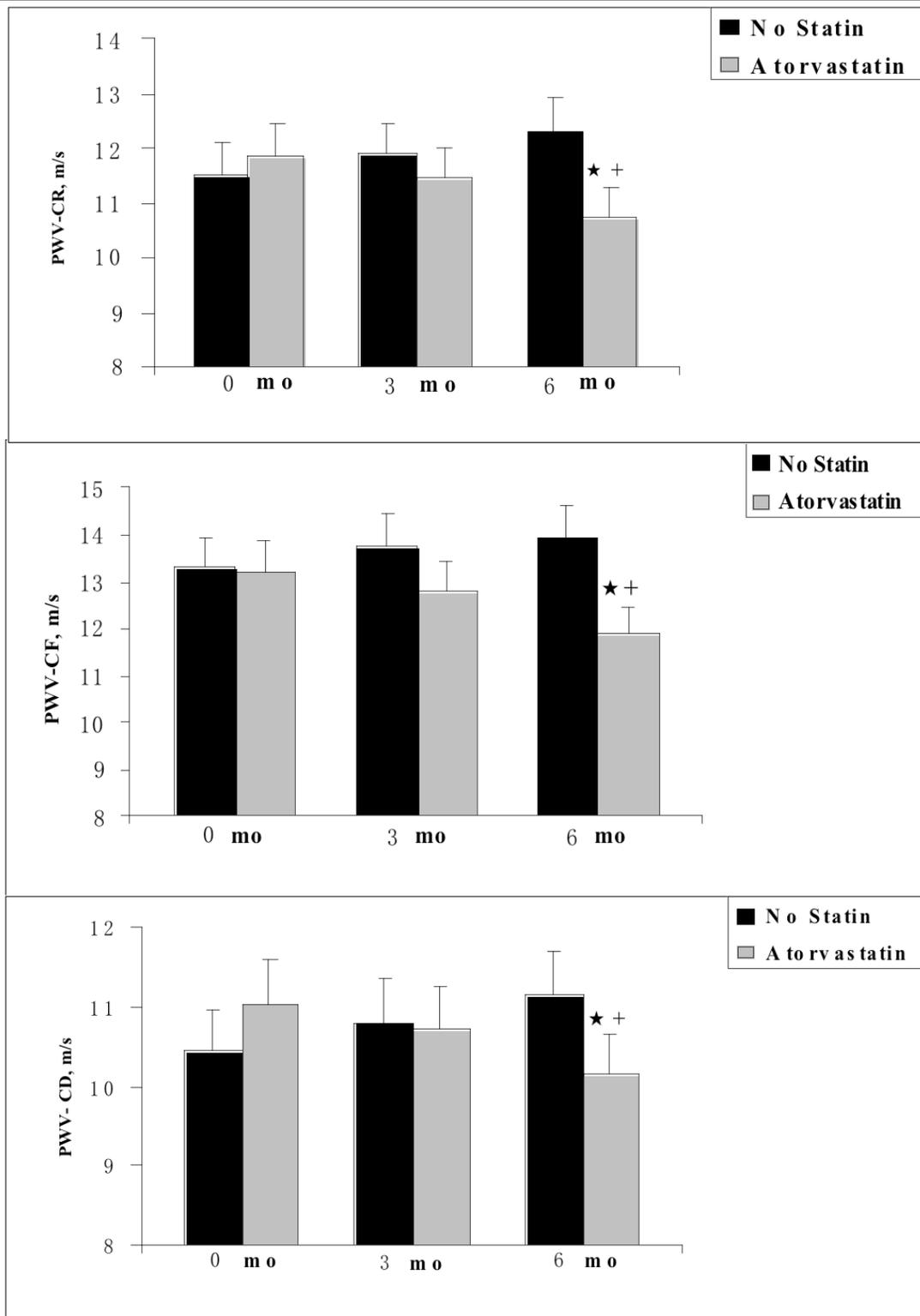


FIGURE 1. . Compared with baseline, PWV-CF, PWV-CR and PWV-CD decreased after the therapy in the atorvastatin group ($P<0.05$). There was no difference in the control group. Compared with control group, decrease in PWV in patients receiving atorvastatin was seen after 6 months.

Discussion

Decreased arterial stiffness with time, as assessed by PWV, was observed in patients treated with atorvastatin after 6-months therapy. Patients not receiving atorvastatin had no change. We have documented the value of PWV, as an assessment of arterial stiffness, to demonstrate the improvement after 6 months atorvastatin therapy.

These results are compatible with previous studies. In an experimental study, pitavastatin reduced aortic stiffness through anti-atherogenic effects.⁶ Shige et al¹² also reported that simvastatin improved peripheral PWV. In the study by Hongo et al⁷ 93 patients with hyperlipemia and CAD were examined. After 3 months therapy, a decrease of PWV was observed during stress in patients treated with fluvastatin. This improvement was further enhanced for the follow-up period. On the coronary, PWV was progressively increased in the contrast group.

Arterial stiffness promotes the development of coronary atherosclerosis, it is an important cause of cardiovascular complications and a major contributor to atherosclerosis. Many studies have shown the existence of a relationship between arterial stiffness and the risk of CAD.^{2,3} Furthermore, the severity of atherosclerosis in the coronary bed was found to be correlated positively with arterial stiffness.¹³ However, direct measurement of arterial stiffness requires invasive techniques unsuitable for routine clinical use. In comparison, PWV is a simple, reproducible, and non-invasive method that does not require specialized techniques. PWV is a computerized oscillometric method, which is strongly correlated to direct measurement of arterial distensibility, and can assess both the central elastic and peripheral muscular arterial stiffness. The distensibility of both large and small arterial systems serves as a cushion to buffer the pulsatile pressure and flow.⁸ A reduced buffering capacity because of atherosclerosis leads to a more rapid PWV. Thus, the measurement of PWV is suitable, especially for assessing damage in follow-up studies. Previous

cross-sectional studies have reported the accuracy and variability of this automatic device for measuring arterial stiffness.^{9,10,14} In this study, we investigated the association between arterial stiffness and atorvastatin therapy in three vessel beds through the values of PWV-CF, PWV-CR and PWV-CD.

Statins have beneficial non-lipid effects.⁶ Statin therapy can improve endothelial function through increase in endothelium-derived NO production independent of their lipid-lowering properties in patients with CAD.⁵ Park et al⁸ found that endothelial damage/dysfunction produces vasoconstriction, which reduces arterial compliance and elasticity, and increases arterial stiffness. Umeji et al⁶ also showed that statin's anti-inflammatory action might contribute to the favorable effects on arterial stiffness. Further, statins contribute directly to favorable vascular structural changes. Statins improve the elasticity of central arterial and peripheral arterial component, change diameter of arteries and, thus remodel the vascular wall,¹⁵ which would be expected to directly improve PWV. Considering that there were decreases in total cholesterol, triglyceride, and LDL cholesterol values in the 2 groups, but no change in PWV-CF, PWV-CR and PWV-CD in patients receiving diet-only intervention, it is likely that atorvastatin decreased arterial stiffness in a manner independent of its lipid-lowering properties.

Some potential limitations of this study merit consideration. This study was performed in a small group of selected subjects. Also, the effect was seen at 6- but not at 3-months of therapy, suggesting that prolonged treatment is required to achieve the beneficial effect.

In the present study, we documented that atorvastatin improved both the central and peripheral arterial stiffness in CAD patients independent of its lipid-lowering properties.

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