Assessment of Regional Systolic and Diastolic Functions Affected by Atorvastatin in Coronary Artery Disease Using Tissue Doppler Imaging

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ABSTRACT

Background: Several studies have shown regional left ventricular (LV) systolic and diastolic changes associated with coronary artery disease (CAD). Statins may have beneficial pleiotropic effects in addition to their lipid-lowering properties.

Hypothesis: We hypothesized that atorvastatin can improve regional LV systolic and diastolic functions in CAD patients using tissue Doppler imaging (TDI).

Methods: A total of 63 patients with hyperlipemia and CAD were studied. Forty-three patients were given 10 mg daily of atorvastatin and 20 patients were assigned only a low-fat diet. Tissue Doppler imaging was applied to evaluate LV peak systolic velocity (VS), early diastolic velocity (VE), and late diastolic velocity (VA) in 18 segments. The mean value of LV peak systolic velocity (VS′), the mean value of early diastolic velocity (VE′), and the mean value of late diastolic velocity (VA′), in 18 segments were calculated.

Results: Compared with the baseline, VS′, and VE′, increased significantly after the therapy in the atorvastatin group ($p<0.05$), while there was no change in the control group ($p>0.05$). At 6 mo of therapy, a significant reduction in total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol was observed in the 2 groups ($p<0.05$).

Conclusions: These findings demonstrate that atorvastatin can improve regional LV systolic and diastolic functions in CAD patients independent of its lipid-lowering properties.

Key words: tissue Doppler imaging, atorvastatin, left ventricle, systolic function, diastolic function

Introduction

The ischemia myocardium is always characterized by segmental distribution together with systolic and diastolic dysfunctions. It has been reported that coronary artery disease (CAD) is associated with impaired regional systolic and diastolic left ventricular (LV) functions.[1] Therefore, early discovery and assessment of cardiac dysfunction are of great importance in reducing the deterioration of cardiac function and improving the quality of life.

Statins (HMG-CoA reductase inhibitors) are drugs with potent lipid-lowering effects. This class of drugs, used in primary and secondary prevention of CAD, has been shown to reduce the risk of acute cardiovascular events and to prolong survival. Increasing evidence suggests that statins may have beneficial pleiotropic effects in addition to their lipid-lowering properties.[2] Statins have been shown to improve endothelial function, inhibit proliferation of smooth muscle cells, increase plaque stability, and inhibit inflammatory responses and thrombus formation.[3–5] Recently, statins were reported to improve ischemia-induced LV function.[6]

Tissue Doppler imaging (TDI) is a new echocardiographic technique that uses high-amplitude, and low-frequency ultrasound signals reflected from the myocardium. Tissue Doppler imaging facilitates the quantitative assessment of the regional LV myocardial motion velocity,[7] allows direct measurement of systolic and diastolic functions of the LV,[8] and thus has been used to evaluate ventricular systolic and diastolic functions in the healthy and in the diseased heart.[6,9,10]

Utilizing TDI, this study examined the effect of atorvastatin on myocardial function in patients with moderate hyperlipemia and CAD.

Methods

Subjects

Patients who visited our hospital from January 2005 to July 2006 with hyperlipemia and CAD confirmed by previous coronary arteriography were enrolled. All patients enrolled had a baseline fasting serum low-density lipoprotein (LDL) cholesterol level between 3.62 and 6.46 mmol/L, and a fasting triglyceride <4.52 mmol/L. Exclusion criteria included ongoing or previous treatment

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with lipid-lowering drugs, hypertension, diabetes mellitus, acute coronary syndromes within 6 mo, LV hypertrophy as documented by echocardiography, liver or kidney disease, and cancer. The study protocol was approved by the Institution's Ethical Committee, and all patients gave a written informed consent before they were enrolled in the study.

Study Design

A total of 43 patients were consecutively assigned to 10 mg daily of atorvastatin for 6 mo in addition to a low-fat diet. The control group, comprised of 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.

Echocardiography

All patients were studied using standard echocardiography and TDI at baseline, and at 3 and 6 mo, respectively. The patients were examined in the left lateral decubitis with VIVID 7 equipment (General Electric, Vingmed, Horten, Norway) using a 2.5-MHz probe for image acquisition. One trained technician operated the machine with no prior information about the study. The LV ejection fraction (LVEF) was measured, and TDI was performed to assess the regional function of the LV using apical 4-chamber, 2-chamber, and long-axis views. At least 3 consecutive beats were stored and analyzed offline. A sample volume was placed at the basal, mid-level, and apical segments of each of the LV walls (septum, lateral, inferior, anterior, anteroseptal, and posterior). For visual analysis, the LV was divided into 18 segments, and an 18-segment model was used to assess the regional LV function.

From the recorded images, peak systolic velocity (VS), early diastolic velocity (VE), and late diastolic velocity (VA) of all segments were measured. All Doppler echocardiographic measurements represented an average of 3 heart cycles. Further, LV VS′, VE′, and VA′ were measured in 18 segments of the 2 groups. The value of VE′/VA′ was calculated as well. Global LV myocardial function was assessed by taking the average of the LV regional measurements.[9]

Laboratory Measurements

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

Statistical Analysis

The data analysis was carried out using the statistical software program (SPSS 11.5, SPSS Inc., Chicago, Ill., USA). Continuous variables are presented as means±standard deviations (SDs). Categorical variables are presented as counts and percentages. Student 2-tail *t*-tests and chi-square tests were used when appropriate; $p<0.05$ was used for statistical significance.

Results

Except 1 patient who withdrew from the study because of experiencing nausea after receiving atorvastatin, others completed the study. Baseline patient characteristics are listed in Table 1. During the study, there were no untoward cardiac events that could have altered the status of the left ventricle.

Table 2 summarizes the lipid values at baseline and at 6 mo of therapy. At 6 mo of therapy, patients receiving atorvastatin had a significant 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 significant changes in the enzymes alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, or creatine kinase.

The LVEF did not change significantly in either of the 2 patient groups at the baseline, and at 3 and 6 mo follow-up (Table 3). During the period of treatment, no significant change was observed in the wall motion, which was initially normal or nearly normal in all patients.

Neither the 6 mo diet therapy in control patients, nor the 3 mo of atorvastatin treatment produced statistically significant changes in parameters measured by the TDI. After 6 mo of treatment, a significant increase in VS and VE in patients receiving atorvastatin was seen. In the 18 LV segments studied, VS and VE in 11 segments increased significantly in patients receiving atorvastatin. At the same time, VS′ and VE′ were also significantly increased. However the VA′ remained unchanged. Due to the increase in VE′, the VE′/VA′ ratio showed a significant increase at 6 mo of therapy (Table 3).

Discussion

In patients with CAD, global and regional LV functions are important indicators of cardiac status, and therapy and prognosis are to a large extent dependent on the LV function.[12] Therefore, precise and reliable assessment of LV function is helpful for the prognosis of cardiac patients.

This study documents that LV systolic and diastolic velocities, as a measure of global LV myocardial function, improves significantly during the 6 mo atorvastatin therapy

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TABLE 1: Baseline patients' characteristics in 2 groups

Variables	No statins (n = 20)	Atorvastatin (n = 42)	p-value
Age (y)	63.30±4.87	61.02 ± 8.97	NS
Male/females	9/11	18/24	NS
Heart rate (beat/min)	69.65±5.71	67.64±7.27	NS
BMI	24.70±3.35	26.13±3.77	NS
Smoking (%)	20.00%	21.43%	NS
SBP (mm Hg)	122.60±9.20	125.88±9.19	NS
DBP (mm Hg)	77.10±8.06	79.48±7.17	NS
Plasma glucose (mmol/L)	5.30±0.50	5.34±0.55	NS
Medication			
Aspirin (%)	95.00%	97.62%	NS
β-blockers (%)	45.00%	45.24%	NS
Nitrates (%)	40.00%	38.10%	NS

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; NS = nonsignificant; SBP = systolic blood pressure.

in patients with hyperlipemia and CAD. In contrast, only an introductory dietary treatment had no effect on tissue VS and VE.

Echocardiography as a noninvasive method is used to evaluate LV function. However, conventional echocardiography has certain limitations, such as its dependence on heart rate and preload. In comparison, TDI as a new echocardiographic technique, is a quantitative analytical technique for ventricular wall movements that can directly determine systolic and diastolic velocities of cardiac tissue. The technique can assess the contraction and relaxation ability of myocardial fibers, and has a sensitive determination of regional ventricular wall dyskinetics.[13] Although TDI is unaffected by heart rate or preload, it reveals changes in myocardial velocities that cannot be detected by the conventional methods used to evaluate LV systolic and diastolic functions.[14] In the study, no differences were observed in either LVEF or the regional wall motion at baseline, as well as after and at 6 mo of therapy in the 2 study groups, so they do not truly reflect the LV function.

Enhanced LV function with time, as assessed by pulsed-wave tissue Doppler velocity, was observed in patients treated with atorvastatin at 6 mo of therapy, while patients not receiving atorvastatin had no significant change in the tissue VS and VE. Considering that there was no change in routine patients' medications of patients during the study, and that no untoward cardiac events occurred, it is likely that the enhanced LV function was the result of the atorvastatin treatment. Since all patients in the 2 groups had a significant decrease in total cholesterol, triglyceride, and LDL cholesterol values, and no significant change in the tissue VS and VE was observed in the control group, it is likely that atorvastatin enhanced the LV systolic and diastolic functions in a manner independent of its lipid-lowering properties.

Several considerations might be important according to this improved systolic and diastolic functions. First, not all patients had used statins medication at the time of enrollment in the study.

Second, in patients with CAD, myocardial ischemia-related impaired LV function was closely associated with systemic endothelial damage/dysfunction and increased thrombogenesis.[8] Statins, as lipid-lowering agents, can not only normalize serum lipid levels but also have beneficial nonlipid effects. It is well known that nitric oxide (NO), synthesized and released by the vascular endothelium, plays an important role in the control of vascular tone and structure, is the primary relaxing factor of blood vessels, and its production is impaired in atherogenic vessels. Statins are mediated by an increase in endothelium-derived NO production, and therefore, statins therapy can act to improve endothelial function through NO-dependent mechanisms independent of their lipid-lowering action in patients with CAD.[15] In addition to improving endothelial function,[3] statins are associated with reducing vascular inflammation and enhancing plaque stability.[4] They may also have an antithrombotic effect and inhibit thrombus formation.[5]

Third, statins enhance endogenous endothelial nitric oxide synthase (eNOS) activity, leading to NO production by the vascular endothelium cells, and promote vasodilatation of capillaries. Thus, they markedly enhance blood-flow recovery in the ischemic tissues. Statins therapy has been found to rapidly improve the vasomotor response to endothelium-dependent agonists and to enhance the coronary blood flow in patients with CAD.[16] Huggins et al.[17] demonstrated that statins therapy increased stenotic segment maximal myocardial blood flow by approximately 45% in patients with hyperlipidemic and ischemic heart disease for 4 mo. Blood-flow recovery correlated with the increasing number of detectable capillaries may augment collateral flow to ischemic tissues.[18] Recently, it was shown that statins may be useful for therapeutic angiogenesis in patients with ischemic disease.[18] Statins therapy can enhance coronary collateral formation in patients with CAD, and the presence of coronary collateral vessels has been associated with improved clinical outcome.[19]

A previous study also reported the effect of statins on LV function. In the study by Bountioukos et al.[6] We examined 32 patients with hyperlipemia, normal LVEF, and without heart disease. After 6 mo of therapy, an improvement in LV function was observed during stress in patients treated with atorvastatin. It should be noted that our results are

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TABLE 2: Lipid levels at baseline and at 6 mo of therapy

	Baseline		6 Mo	
Lipid levels	No statins	Atorvastatin	No statins	Atorvastatin
Total cholesterol (mmol/L)	6.08±0.43	6.25±0.57	5.57±0.42[a]	4.35±0.58[ab]
Triglycerides (mmol/L)	1.94±0.58	1.84±0.72	1.55±0.55[a]	1.38±0.49[a]
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[s]	2.49±0.50[ab]

[a]$p<0.05$, compared with baseline in the same group. [b]$p<0.05$, compared with control group. *Abbreviations*: HDL = high-density lipoproteins; LDL = low-density lipoproteins.

TABLE 3: The LVEF and TDI parameters across time in the 2 study groups

	Baseline		3 Mo		6 Mo	
Variables	No statins	Atorvastatin	No statins	Atorvastatin	No statins	Atorvastatin
LVEF (%)	61.25±3.75	59.90±4.06	60.60±2.98	60.33±3.50	61.05±3.72	60.69±3.80
VS′ (cm/s)	3.45±0.57	3.55±0.55	3.44±0.57	3.69±0.54	3.44±0.51	4.13±0.61[ab]
VE′ (cm/s)	3.32±0.94	3.42±0.83	3.31±0.94	3.57±0.82	3.32±0.90	4.05±0.87[ab]
VA′ (cm/s)	4.28±0.73	4.42±0.69	4.28±0.73	4.44±0.66	4.26±0.73	4.45±0.64
VE′/VA′	0.78±0.19	0.78±0.20	0.77±0.19	0.81±0.20	0.78±0.19	0.92±0.21[ab]

[a]$p<0.05$, compared with baseline in the same group. [b]$p<0.05$, compared with the control group. *Abbreviations*: LVEF = left ventricular ejection fraction; TDI - tissue Doppler imaging; VA = late diastolic velocity; VE = early diastolic velocity; VS = peak systolic velocity.

intrinsically in line with those of the prior studies. In this study, subendocardial hypoperfusion may result in decreased tissue Doppler velocities,[20] and conversely, tissue Doppler velocities are expected to increase after restored subendocardial perfusion.

Conclusion

The present study documented that atorvastatin can improve regional LV systolic and diastolic functions in CAD patients independent of its lipid-lowering properties.

In contrast, the effect was seen at 6 mo but not at 3 mo of therapy, suggesting that prolonged treatment is required to achieve the beneficial effect.

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