Conclusion: Atorvastatin might benefit patients with heart failure and diabetes mellitus by improving ventricular electrical stability and decelerating deterioration of renal function.

Introduction

Previous randomized clinical trials have shown that statins reduce cardiovascular events in patients with and/or without coronary artery disease. Statins have been shown to improve endothelial function [1], decrease plasma levels of proinflammatory cytokines [2], and exert antihypertrophic [3,4], antioxidant [5], and antifibrotic [6] effects on myocardium. Furthermore, other reports suggested that statins have beneficial effects on immune function, macrophage metabolism, and cell proliferation irrespective of changes in low-density lipoprotein (LDL) cholesterol concentrations [7].

Recent clinical trials suggested that statins might benefit patients with heart failure [8—13]. Short-term statin therapy improved cardiac function, neurohumoral imbalance, and symptoms in patients with idiopathic dilated cardiomyopathy [8]. Long-term atorvastatin therapy suppressed neurohumoral activation and improved cardiac function in mild to moderate heart failure [9]. Compared with a lower dose, high-dose treatment with atorvastatin in patients with stable coronary disease significantly reduced hospitalization for heart failure [10]. However, it remains unknown how statins impact pathophysiology of heart failure with diabetes mellitus, which is known to have deleterious effects on heart failure [14,15] and coronary artery disease [16].

The aim of this study was to investigate the effects of atorvastatin on pathophysiology of heart failure with diabetes mellitus. The results indicated that atorvastatin might benefit heart failure with diabetes mellitus by improving ventricular electrostability and decelerating the deterioration of renal function.

Subjects and methods

Patient populations

We retrospectively studied patients with symptomatic acute heart failure and diabetes mellitus who were admitted to Aso Iizuka Hospital from January 2003 to December 2005. The criteria for enrollment in the study were the clinical evidence of acute heart failure diagnosed by Framingham criteria [17], and diabetes mellitus diagnosed by the guideline of diabetes mellitus of the Japan Diabetes Society. In those patients, the New York Heart Association (NYHA) functional classification on admission ranged between II and IV. We excluded chronic obstructive pulmonary disease, right heart failure, and patients who had already taken atorvastatin or other statins. All patients were treated for acute heart failure, and were discharged after the improvement of heart failure. We enrolled 128 patients with heart failure and diabetes mellitus. Among them, 80 patients started to receive atorvastatin (10 mg) and the remaining 48 patients did not receive any statins (non-statin group). We followed up both groups for two years. As biochemical biomarkers, we measured plasma brain natriuretic peptide (BNP) and hemoglobin A1c (HbA1c). We calculated estimate of glomerular filtration rate (eGFR) from serum creatinine value and age using Japanese-coefficient-modified MDRD study [18]. As physiological biomarkers, we conducted echocardiography and 24-h Holter monitoring, and the severity of ventricular arrhythmias was evaluated in terms of Lown grade [grade 0: no premature ventricular contraction (PVC); grade I: <30 PVC/h, grade II: >30 PVC/h; grade III: multiform PVC; grade IVa: couplets; grade IVb; ventricular tachycardia runs] [19]. We acquired those biomarkers just before the statin therapy in the statin group and before discharge in the non-statin group, and one and two years after the discharge in both group. Hospitalizations due to worsening heart failure were diagnosed by the Framingham criteria, as described above.

Statistical analysis

Normally distributed variables were expressed as mean ± S.D. Unpaired *t* test or Mann—Whitney *U* test was used to compare the differences in normally distributed variables, respectively, between the statin and non-statin groups. The rate of re-hospitalization due to worsening heart failure between the statin and non-statin groups was compared by Kaplan—Meier analysis. All statistical tests were carried out against the baseline characteristics. Differences were considered significant at a p value of <0.05.

Table 1 Patient characteristics.

	Statin	Non-statin	*P*-value
n	80	48	NS
Male/female	54/26	34/14	NS
Age	65 ± 7	61 ± 5	NS
BMI	22 ± 4	23 ± 3	NS
Current smoker	18 (23%)	10 (20%)	<0.05
Causes of heart failure			
Coronary artery disease	22 (27%)	9 (18%)	NS
Dilated cardiomyopathy	25 (32%)	13 (28%)	NS
Hypertensive heart disease	14 (18%)	10 (21%)	NS
Valvular heart disease	15 (19%)	11 (23%)	NS
Systolic blood pressure (mmHg)	130 ± 17	128 ± 14	NS
Diastolic blood pressure (mmHg)	72 ± 14	68 ± 9	NS
Heart rate (bpm)	82 ± 9	79 ± 5	NS
Medications			
Diuretics	74 (92%)	44 (92%)	NS
β-Blockers	53 (66%)	34 (71%)	NS
ACE inhibitors	75 (94%)	46 (96%)	NS
Angiotensin receptor blocker	3 (4%)	2 (4%)	NS
Sulfonylurea	12 (15%)	8 (17%)	NS

Data are presented as number (%) or mean ± S.D. BMI, body mass index; bpm, beats per minute; ACE, angiotensin-converting enzyme.

Results

Patient characteristics at baseline

The patient profiles at enrollment are summarized in Tables 1 and 2. As can be seen in Table 1, there were no significant differences in age, gender, or the prevalence of dilated cardiomyopathy, hypertensive heart disease, or valvular heart disease between the non-statin group and statin group just before statin therapy. Medications did not differ either. The frequency of patients taking

Table 2 Patient characteristics (2).

	Statin	Non-statin	*P*-value
Total cholesterol (mg/dl)	227 ± 17	200 ± 10	0.042
LDL cholesterol (mg/dl)	156 ± 11	122 ± 13	0.008
HDL cholesterol (mg/dl)	44 ± 8	47 ± 7	NS
Triglycerides (mg/dl)	129 ± 7	132 ± 11	NS
FBS (mg/dl)	112 ± 7	119 ± 5	NS
HbA1c (%)	6.6 ± 0.7	6.3 ± 0.4	NS
BNP (pg/ml)	128 ± 27	142 ± 36	NS
eGFR (ml/min/1.73 m^2)	62.4 ± 7.9	66.8 ± 4.4	NS
LVEF (%)	35 ± 7	33 ± 5	NS
LVEDD (mm)	56 ± 5	57 ± 7	NS
LVESD (mm)	40 ± 4	42 ± 7	NS
PVC per 24 h	1288 ± 362	1194 ± 443	NS
Lown grade			
I	28 (35%)	15 (31%)	NS
II	43 (54%)	26 (54%)	NS
III	8 (10%)	6 (13%)	NS
IVa/IVb	1 (1%)/0 (0%)	1 (2%)/0 (0%)	NS/NS

Data are presented as mean ± S.D. LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBS, fasting blood glucose; HbA1c, hemoglobin A1c; BNP, brain natriuretic peptide; eGFR, creatinine-based estimate of glomerular filtration rate; LVEF, left ventricular ejection fraction; LVDDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PVC, premature ventricular contraction.

angiotensin receptor blockers or oral hypoglycemic agents also did not differ between the non-statin and statin groups. All patients with hypoglycemic agents took sulfonylurea. There is no patient with insulin-therapy for diabetes mellitus in the present study. As anticipated, the statin group had a higher prevalence of coronary artery disease than the non-statin group.

As shown in Table 2, fasting blood glucose (FBG), HbA1c, BNP, or eGFR did not differ between the two groups. As anticipated, however, total cholesterol and LDL cholesterol were higher in the statin group than in the non-statin group. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), the frequency of PVC and the frequency of patients who had Lown grade I, II, III, or IV did not differ between the two groups. There is no patient with Lown grade 0 in the present study.

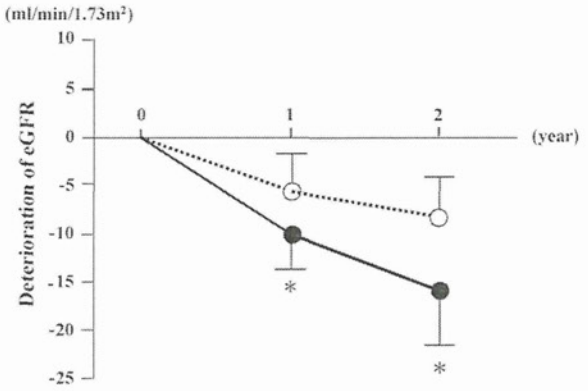

Figure 1 Changes in eGFR at entry, one and two years. Open circle and solid line indicate statin group. Closed circle and dotted line indicate non-statin group. *$p < 0.05$. eGFR, creatinine-based estimate of glomerular filtration rate.

Effects of atorvastatin on biochemical and physiological biomarkers

Effects of atorvastatin on biochemical biomarkers are summarized in Table 3. Atorvastatin markedly decreased total cholesterol and LDL cholesterol. As a result, LDL cholesterol values at the follow-up period of one year were comparable between the two groups and got lower at two years in the statin group than the non-statin group. BNP was lower at one year and got lower at two years in the statin group than the non-statin group. Systolic blood pressure, LVEF, LVEDD, LVESD, and HbA1c remained not different between the two groups.

As shown in Fig. 1, eGFR decreased more in the non-statin group than in the statin-group (-10.6 ± 2.8 ml/min/1.73 m^2 vs. -6.1 ± 3.3 ml/min/1.73

Table 3 Changes in LDL-C, BNP, LVEF, LV dimension, systolic blood pressure, and HbA1c at one and two years.

	Statin	Non-statin	*P*-value
LDL-C (mg/dl)			
1 year	98 ± 16	116 ± 13	NS
2 years	94 ± 9	112 ± 11	<0.05
BNP (pg/ml)			
1 year	101 ± 12	136 ± 13	<0.05
2 years	76 ± 11	132 ± 13	<0.05
LVEF (%)			
1 year	38 ± 6	35 ± 6	NS
2 years	40 ± 7	38 ± 7	NS
LVEDD/LVESD (mm)			
1 year	57 ± 6/41 ± 4	59 ± 4/44 ± 5	NS/NS
2 years	58 ± 4/42 ± 4	60 ± 7/46 ± 7	NS/NS
Systolic blood pressure (mmHg)			
1 year	118 ± 13	122 ± 15	NS
2 years	116 ± 11	120 ± 13	NS
HbA1c (%)			
1 year	6.4 ± 0.3	6.5 ± 0.4	NS
2 years	6.1 ± 0.4	6.5 ± 0.3	NS

Data are presented as mean ± S.D. LDL-C, low-density lipoprotein cholesterol; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; HbA1c, hemoglobin A1c.

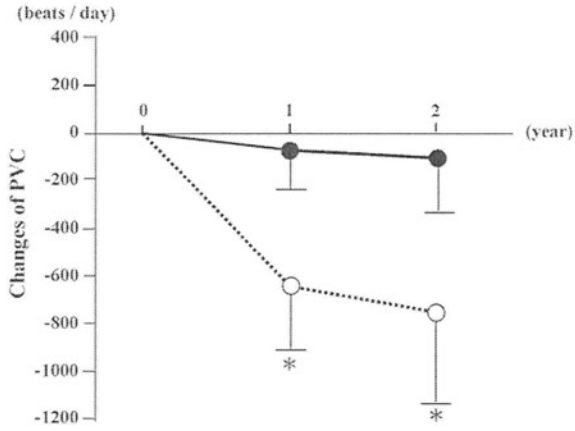

Figure 2 Changes in PVCs at entry, one, and two years. Open circle and solid line indicate statin group. Closed circle and dotted line indicate non-statin group. *$p < 0.05$. PVC, premature ventricular contraction.

m^2, $p < 0.05$) at one year. The difference increased at two years (-16.8 ± 4.1 ml/min/1.73 m^2 vs. -8.3 ± 5.4 ml/min/1.73 m^2, $p < 0.05$). Atorvastatin might have decelerated deterioration of renal function, and thereby might have a potent protective effect on renal function.

Shown in Fig. 2 is the effect of atorvastatin on the frequency of PVCs. Atorvastatin markedly decreased PVCs at one year and two years. There were no changes in PVCs in the non-statin group. Furthermore, the frequency of patients who had Lown grade ≥II was significantly lower in the statin group than in the non-statin group at one year and two years (Fig. 3).

Table 4 Cardiovascular events, hospitalization, and mortality at one and two years.

	Statin	Non-statin	*P*-value
Cardiovascular events			
1 year	5 (6%)	4 (8%)	NS
2 years	8 (10%)	6 (13%)	NS
CHF with hospitalization			
1 year	7 (9%)	8 (17%)	0.003
2 years	16 (20%)	15 (31%)	0.005
All-cause mortality			
1 year	0	0	NS
2 years	0	1	NS

Data are presented as number (%) or mean ± S.D. CHF, congestive heart failure.

Cardiovascular events and hospitalization

No patient died in the statin group, whereas one patient suddenly died in the non-statin group. Treatment with atorvastatin did not significantly reduce cardiovascular events, which was defined as nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, or cardiovascular death (Table 4). However, the frequency of re-hospitalization due to worsening heart failure was significantly reduced in the statin group than in the non-statin group, determined by Kaplan–Meier analysis (Fig. 4). For the patients with atorvastatin, the hazard ratio for re-hospitalization due to worsening heart failure was 0.68 (95% CI, 0.51–0.84) (Fig. 4).

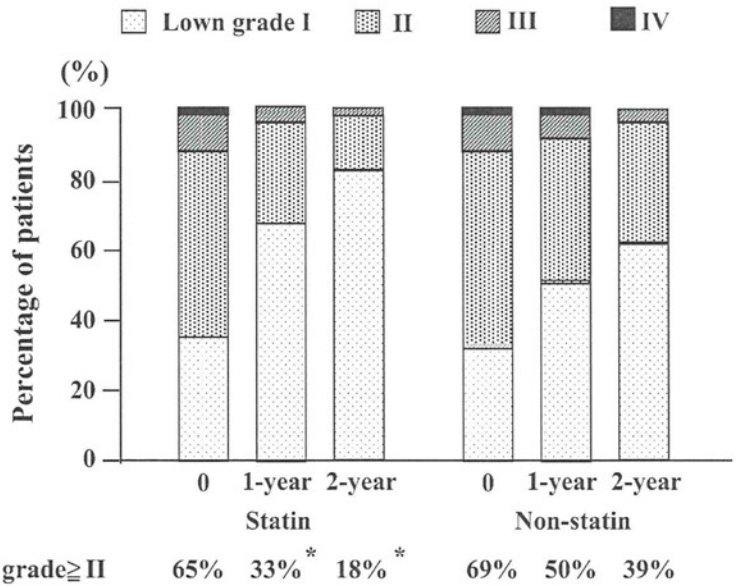

Figure 3 Kaplan–Meier analysis estimates for re-hospitalization due to heart failure. Solid line indicates non-statin group, and dotted line indicates statin-group. *$p < 0.05$.

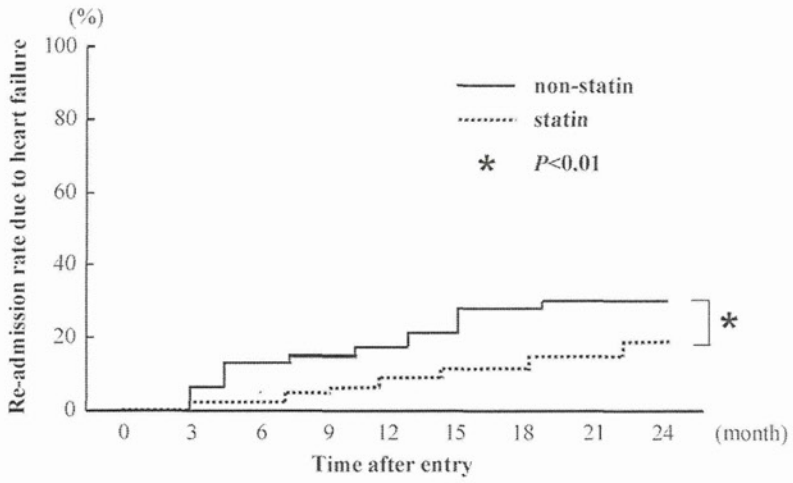

Figure 4 Lown grades at entry, one year, and two years after (grade 0: no PVC; grade I: <30 PVC/h, grade II: >30 PVC/h; grade III: multiform PVC; grade IV: couplets and/or ventricular tachycardia runs). $^{*}p < 0.05$.

Discussion

In the present study, we demonstrated that atorvastatin reduced the frequency of re-hospitalization due to worsening heart failure, BNP, the frequency of PVCs, Lown grade and decelerated deterioration of GFR in the patients with heart failure and diabetes mellitus. These results suggested that atorvastatin might benefit patients with heart failure and diabetes mellitus by improving ventricular electrostability and decelerating deterioration of renal function.

Recent clinical trials and basic studies suggested that statins might benefit patients with heart failure [8—13,20—24]. In the present study, atorvastatin reduced the frequency of re-hospitalization due to worsening heart failure and BNP. These results are comparable to previous studies, which showed that statins might benefit patients with heart failure. Furthermore, the present study suggested that atorvastatin has beneficial effects on the pathophysiology of heart failure with diabetes mellitus, which is known to have deleterious effects on heart failure [14,15]. In the statin group, the LDL cholesterol level was significantly higher than in the non-statin group at entry. Atorvastatin markedly decreased the LDL cholesterol level, and the LDL cholesterol levels at the follow-up period of one year were comparable between the two groups. The LDL cholesterol levels were significantly lower at two years in the statin group than the non-statin group. The statin group had a higher prevalence of coronary atherosclerotic diseases than the non-statin group. These differences of backgrounds between the statin and non-statin groups might be responsible for the results in this study. However, these results indicate that the risks for atherosclerosis and ischemic heart diseases were higher in the statin group than in the non-statin group. Despite those with a background predisposed to coronary heart disease, atorvastatin significantly benefits the patients with heart failure. It is conceivable that atorvastatin might be a novel strategy of treatment for heart failure and diabetes mellitus.

The mechanism by which atorvastatin benefits patients with heart failure and diabetes mellitus remains unknown. We conjecture three mechanisms: anti-oxidant, anti-inflammatory, and improvement of the sympatho-vagal balance. In patients with heart failure, increased oxidative stress is associated with reduced LV function and severity of heart failure [25,26]. Previous studies suggested that statins inhibited vascular and myocardial oxidative stress by inhibiting rac-induced nicotinamide adenine dinucleotide phosphatase oxidase activity [27,28], and reducing oxidized LDL concentration [9], which is a marker of oxidative stress and a useful predictor of mortality in patients with heart failure [29]. Furthermore, diabetes mellitus increases the risk of heart failure and oxidative stress may contribute to the development of cardiac dysfunction [30]. With regard to the anti-inflammatory effects of atorvastatin, previous studies reported that statins suppressed the inflammatory process in patients with heart failure [8,21,22]. Heart failure is associated with increased levels of proinflammatory cytokines that exert negative inotropic effects and induce apoptosis in cardiac myocytes [31]. Yamada et al. reported that atorvastatin tended to decrease interleukin 6 and high sensitive C-reactive protein in patients with heart failure [9]. Finally, we consider that atorvastatin might improve the imbalance between

the sympathetic and parasympathetic nerve activity and this improvement resulted in the reduction of the frequency of PVCs. A previous study reported that statin therapy restored sympatho-vagal balance in experimental heart failure [23]. We have demonstrated that atorvastatin reduced the oxidative stress in the cardiovascular center of the brainstem [32], in which oxidative stress increased sympathetic nerve activity in hypertensive animal models [33]. These reports suggest that atorvastatin might reduce the oxidative stress in the cardiovascular center, which, in turn, decreases the sympathetic nerve activity, the frequency of PVCs, and Lown grade. Further investigations are needed to clarify the mechanisms.

Renal dysfunction has been known to worsen heart failure [34]. Campese and Park suggested that statin-mediated alterations in inflammatory responses and endothelial function reduced proteinuria and the rate of progression of kidney disease [35]. In the present study, atorvastatin protected the progressive worsening in renal function for two years in the patients with heart failure and diabetes mellitus. These results suggest that atorvastatin might prevent the worsening of heart failure through a renoprotective effect. Additional prospective and randomized trials in the Japanese population are needed to determine whether atorvastatin is truly renoprotective.

Limitations

There are several limitations to the present study. First, the study was retrospective, and observational. The number of patients enrolled is also limited. Second, we were not able to determine whether the beneficial effect of atorvastatin on heart failure with diabetes mellitus is a class effect or not. The results of the present study should be validated by large, prospective, well-controlled, and randomized clinical trials. Third, we did not measure the activity of sympathetic nerve activity, parasympathetic nerve activity, and sympatho-vagal balance using variability of R—R interval and blood pressure analysis. In the present study, we are not able to suggest that the data indicate the improvement of the imbalance between sympathetic and parasympathetic nerve activity by atorvastatin in heart failure with diabetes mellitus.

Conclusion

Atorvastatin might benefit patients with heart failure and diabetes by improving ventricular electrical stability and decelerating deterioration of renal function. Atorvastatin might be a novel strategy of treatment for heart failure and diabetes.

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References

[1] Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC, Alexander RW. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 1995;332:481—7.

[2] Ferro D, Parrotto S, Basili S, Alessandri C, Violi F. Simvastatin inhibits the monocyte expression of proinflammatory cytokines in patients with hypercholesterolemia. J Am Coll Cardiol 2000;36:427—31.

[3] Hayashidani S, Tsutsui H, Shiomi T, Suematsu N, Kinugawa S, Ide T, Wen J, Takeshita A. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation 2002;105:868—73.

[4] Oi S, Haneda T, Osaki J, Kashiwagi Y, Nakamura Y, Kawabe J, Kikuchi K. Lovastatin prevents angiotensin-II-induced cardiac hypertrophy in cultured neonatal rat heart cells. Eur J Pharmacol 1999;376:139—48.

[5] Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG-CoA reductase inhibitors. Circulation 1998;97:1129—35.

[6] Dechend R, Fiebeler A, Park JK, Muller DN, Theuer J, Mervaala E, Bieringer M, Gulba D, Dietz R, Luft FC, Haller H. Amelioration of angiotensin II-induced cardiac injury by a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor. Circulation 2001;104:576—81.

[7] Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. Lancet 1996;348:1079—82.

[8] Node K, Fujita M, Kitakaze M, Hori M, Liao JK. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. Circulation 2003;108:839—43.

[9] Yamada T, Node K, Mine T, Morita T, Kioka H, Tsukamoto Y, Tamaki S, Masuda M, Okuda K, Fukunami M. Long-term effect of atorvastatin on neurohumoral activation and cardiac function in patients with chronic heart failure: a prospective randomized controlled study. Am Heart J 2007;153, 1055.e1—e8.

[10] Krum H, McMurray JJ. Statins and chronic heart failure: do we need a large-scale outcome trial? J Am Coll Cardiol 2002;39:1567—73.

[11] Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 2002;8:216—24.

[12] Khush KK, Waters DD, Bittner V, Deedwania PC, Kastelein JJP, Lewis SJ, Wenger NK. Effect of high-dose atorvastatin on hospitalization for heart failure. Circulation 2007;115:576—83.

[13] Kadota S, Matsuda M, Izuhara M, Baba O, Morikawa S, Shioji K, Takeuchi Y, Uegaito T. Long-term effects of early statin therapy for patients with acute myocardial infarc-

tion treated with stent implantation. J Cardiol 2008;51: 171–8.
[14] Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, et al. Study group on diagnosis of the working group on heart failure of the European society of cardiology: the Euroheart Failure survey programme-a survey on the quality of care among patients with heart failure in Europe. Eur Heart J 2003;24:442–63.
[15] Yusuf S, Teo KK, Pogue J, Dyal L, Copland L, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59.
[16] Sassa S, Shimada K, Yoshida K, Tanaka H, Jissho S, Yoshikawa J. Comparison of 64-slice multi-detector computed tomography coronary angiography between asymptomatic, type 2 diabetes mellitus and impaired glucose tolerance patients. J Cardiol 2008;52:133–9.
[17] Eriksson H, Svardsudd K, Larsson B, Ohlson LO, Tibblin G, Welin L, Wilhelmsen L. Risk factors for heart failure in the general population: the study of men born in 1913. Eur Heart J 1989;10:647–56.
[18] Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 2007;11:41–50.
[19] Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–42.
[20] Trochu JN, Mital S, Zhang X, Xu X, Ochoa M, Liao JK, Recchia FA, Hintze TH. Preservation of NO production by statins in the treatment of heart failure. Cardiovasc Res 2003;60:250–8.
[21] Mozaffarian D, Mina mi E, Letterer R, Lawler RL, McDonald GB, Levy WC. The effects of atorvastatin (10 mg) on systemic inflammation in heart failure. Am J Cardiol 2005;96:1699–704.
[22] Sola S, Mir MQ, Lerakis D, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 2006;47:332–7.
[23] Pliquett RU, Cornish KG, Zucker IH. Statin therapy restores sympathovagal balance in experimental heart failure. J Appl Physiol 2003;95:700–4.
[24] Wojnicz R, Wilczek K, Nowalany-Kozielska E, Szygula-Jurkiewicz B, Nowak J, Polonski L, Dyrbuś K, Badziński A, Mercik G, Zembala M, Wodniecki J, Rozek MM. Usefulness of atorvastatin in patients with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels. Am J Cardiol 2006;97:899–904.
[25] Mallat Z, Philip L, Lebret M, Chatel D, Maclouf J, Tedgui A. Elevated levels of 8-iso-prostaglandin F2alpha in pericardial fluid of patients with heart failure: a potential role for in vivo oxidant stress in ventricular dilation and progression to heart failure. Circulation 1998;97:1536–9.
[26] Dhalla AK, Hill MF, Singal PK. Role of oxidative stress in transition of hypertrophy to heart failure. J Am Coll Cardiol 1996;28:506–14.
[27] Li JM, Gall NP, Grieve DJ, Chen M, Shah AM. Activation of NADPH oxidase during progression of cardiac hypertrophy to failure. Hypertension 2002;40:477–84.
[28] Maack C, Kartes T, Kilter H, Schafers HJ, Nickenig G, Bohm M, Laufs U. Oxygen free radical release in human failing myocardium is associated with increased activity of rac1-GTPase and represents a target for statin treatment. Circulation 2003;108:1567–74.
[29] Tsutsui T, Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Ohnishi M, Kinoshita M. Plasma oxidized low-density lipoprotein as a prognostic predictor in patients with chronic congestive heart failure. J Am Coll Cardiol 2002;39:957–62.
[30] Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007;115:3213–23.
[31] Pinsky DJ, Cai B, Yang X, Rodriguez C, Sciacca RR, Cannon PJ. The lethal effects of cytokine-induced nitric oxide on cardiac myocytes are blocked by nitric oxide synthetase antagonism or transforming growth factor beta. J Clin Invest 1995;95:677–85.
[32] Kishi T, Hirooka Y, Shimokawa H, Takeshita A, Sunagawa K. Atorvastatin reduced oxidative stress in the rostral ventrolateral medulla of stroke-prone spontaneously hypertensive rats. Clin Exp Hypertens 2008;30:3–11.
[33] Kishi T, Hirooka Y, Kimura Y, Ito K, Shimokawa H, Takeshita A. Increased reactive oxygen species in rostral ventrolateral medulla to neural mechanisms of hypertension in stroke-prone spontaneously hypertensive rats. Circulation 2004;109:2357–62.
[34] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351: 1296–305.
[35] Campese VM, Park J. HMG-CoA reductase inhibitors and the kidney. Kidney Int 2007;71:1215–22.

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Cilnidipine Inhibits the Sympathetic Nerve Activity and Improves Baroreflex Sensitivity in Patients with Hypertension

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N-type calcium channel blocker, cilnidipine, is reported not to increase the heart rate in spite of the strong depressor effect. However, it has not been determined whether cilnidipine has the sympatho-inhibitory effects or not. Moreover, the effect of cilnidipine on the baroreflex control has not been determined. The aim of this study was to determine the effect of cilnidipine on sympathetic and parasympathetic nerve activity, and baroreflex sensitivity. We studied five hypertensive patients treated with 10 mg cilnidipine (10-mg group) and five hypertensive patients treated with 20 mg cilnidipine (20-mg group). Before the treatment and 6 months after the treatment, we measured the blood pressure, spontaneous baroreflex sensitivity (BRS), heart rate variability (HRV), and blood pressure variability (BPV). After 6 months, systolic blood pressure (SBP) and the low-frequency component of systolic BPV expressed in normalized units (LFnuSBP), as the parameter of sympathetic nerve activity, was significantly decreased in both groups, and the suppressive effects were stronger in the 20-mg group than in the 10-mg group. The high-frequency component of HRV expressed in normalized units, as the parameter of parasympathetic nerve activity, and BRS were significantly increased in 20-mg group, but not significant in 10-mg group. These results suggest that 6 months treatment with cilnidipine for hypertension has the sympatho-inhibtory effect, and that high-dose cilnidipine improves the parasympathetic nerve activity and baroreflex control in patients with hypertension.

Keywords N-type calcium channels blocker, hypertension, sympathetic nerve activity, baroreflex sensitivity

Introduction

Hypertension is an established risk factor in the prognosis of cardiovascular diseases and organ damage. It may be feasible for patients with hypertension or at high cardiovascular risk to receive a blood pressure-lowering medication in order to achieve a

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reduction of stroke and cardiovascular complications (1). Ca channel blocker is widely used as the blood pressure-lowering agents. However, it has been reported that Ca channels blocker increases heart rate with lowering blood pressure. Among the Ca channels blockers, cilnidipine is known not to increase the heart rate and plasma norepinehrine concentrations in spite of the strong blood pressure lowering effects (2–4). Cilnidipine is a long-acting dihydropyridine calcium channel blocker by inhibiting L-type calcium channels directly associated with vascular tone, and N-type calcium channels related to sympathetic nervous activity (5–7). Whereas cilnidipine inhibits N-type calcium channels, it has not been well established whether cilnidipine decreases the sympathetic nerve activity and increases the parasympathetic nerve activity in the patients with hypertension.

Analysis of spontaneous heart rate and blood pressure variability offers insights into different features of autonomic control of circulation (8), including the arterial baroreflex regulation (9). In this context, heart rate spectral powers in the so-called high-frequency (HF; 0.15–0.40 Hz) and low-frequency (LF; 0.04–0.15 Hz) regions and blood pressure spectra powers in the LF regions have been repeatedly reported to provide relevant information (8, 10–12). The LF power of blood pressure was reported to be increased in parallel with the sympathetic nerve activation (13). Furthermore, the baroreflex control is one of the key mechanisms responsible for the short-term control of blood pressure. Impairment of this reflex has been found in a number of conditions, such as aging (14), heart failure (15), post-myocardial infarction (16), and the impairment of baroreflex sensitivity (BRS) is known as the predictive factor of mortality in hypertension (17). Baroreflex sensitivity was originally assessed by intra-arterial measurement of the change in pulse interval following a pharmacologically induced change in blood pressure. However, for some time now, noninvasive monitoring of blood pressure using finger plethysmography has been available (18), and is an accepted method for tracking beat-to-beat changes in blood pressure (19). Added to this, a further method for measuring BRS has been developed, which assesses spontaneous changes in blood pressure and pulse interval, and does not require pharmacological manipulation of blood pressure-spectral analysis (20,21). However, it has not been determined whether the cilnidipine improves the impaired BRS or not.

Therefore, the aim of the present study was to evaluate the effect of cilnidipine on the sympathetic nerve activity, parasympathetic nerve activity, and BRS in the patients with hypertension. We evaluated the sympathetic and parasympathetic nerve activity using the analysis of systolic blood pressure and heart rate variability, and BRS was measured by the spontaneous sequence method.

Materials and Methods

Subjects

The present study was conducted prospectively on 10 outpatients with hypertension (5 males and 5 females; mean age: 58.6 years; range 44–74 years) whose blood pressure was over 140/90 mmHg. No patients were currently receiving anti-hypertensive medication and all of them were newly diagnosed. Patients with the secondary hypertension were excluded. All studies were performed between 9 and 11 a.m., with each subject examined at the same time of day on each visit to reduce the possible influence of circadian variation in BRS. This study was performed in a quiet room, and every effort was made to keep stimuli to a minimum during the study period. Each subject gave informed

consent to the experimental procedures, which was approved by the ethics committee of our institution.

Measurement of Blood Pressure and Heart Rate

Subjects lay supine, and were rested for a minimum of 15 minutes prior to assessment. Each subject then underwent periods of blood pressure and heart rate monitoring. Blood pressure monitoring was performed using the TaskForce Monitor 3040i (CNSystems, Graz, Austria). The cuff was attached to a finger of the left hand and supported at heart level. Electrocardiogram electrodes were attached to the chest. After a minimum period of 5 minutes, and once a reading of blood pressure and heart rate had stabilized, three consecutive, 5-minute recordings were made of the blood pressure and electrocardiogram tracing. Noninvasive brachial blood pressure readings were taken with an appropriate-sized cuff.

Spectral Analysis for Systolic Blood Pressure and Heart Rate

Spectral analysis was performed using an adaptive auto-regressive model to provide power spectra for both systolic blood pressure (SBP) and R-R interval (RRI). Low Frequency power of SBP was computed by integrating the spectra between 0.04 and 0.15 Hz, and HF power of RRI was computed by integrating the spectra between 0.15–0.40 Hz. Parasympathetic nerve activity was represented by the normalized unit of HF component of RRI (HFnuRRI), and sympathetic nerve activity was represented by the normalized unit of LF component of SBP (LFnuSBP).

Measurement of Baroreflex Sensitivity by Spontaneous Sequence Method

Sequence analysis detected sequences of three or more beats in which there was either an increase in SBP and pulse interval (Up sequence) or a decrease in SBP and pulse interval (Down sequence). Baroreflex sensitivity was estimated as the mean slope of the up sequences (UP BRS), the down sequences (Down BRS), and also the mean slope of all sequences (Sequence BRS) (20,21). Previous reports showed that this protocol measures BRS accurately in animals compared to standard pharmacological techniques (20,21).

Administration of Cilnidipine

Cilnidipine was administered at a dosage of 10–20 mg (10-mg group and 20-mg group) once daily after breakfast according to the guidelines of the treatment with hypertension of the Japanese Society of Hypertension (JSH2004). All the patients were placed on monotherapy with cilnidipine.

Statistical Analysis

All values were expressed as the mean ± SEM. The student's paired *t*-test was used to analyze the changes of variables between pre- and post-treatment with cilnidipine. Differences in variables between the groups were analyzed by one-way ANOVA. A value of $p < 0.05$ was considered statistically significant.