Pleiotropic Effects of Atorvastatin in Heart Failure: Role in Oxidative Stress, Inflammation, Endothelial Function, and Exercise Capacity

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Background: Increased oxidative stress, a common feature in chronic heart failure, has been associated with inflammation, endothelial dysfunction, and extracellular matrix degradation. Statins have known anti-inflammatory and anti-oxidant effects; however, their role in chronic heart failure is still controversial.

Methods: This was a prospective study of 38 patients with stable systolic chronic heart failure. Patients received a 4-week placebo course, followed by atorvastatin 20 mg/day for 8 weeks. Oxidative stress, inflammation and remodeling markers, brachial artery flow-mediated vasodilation, and 6-minute walk test were evaluated at baseline, 4, and 8 weeks.

Results: Mean age was 58 ± 12. Mean left ventricular ejection fraction was 27% ± 12%. No significant differences were observed between measurements at baseline and after placebo. Atorvastatin induced a significant decrease of matrix metalloproteinase-9 activity, high-sensitivity C-reactive protein, tumor necrosis factor-α, interleukin-6, and malondialdehyde, and a significant increase of endothelial superoxide dismutase activity when compared with placebo. No differences in tissue inhibitor of matrix metalloproteinase and matrix metalloproteinase-2 activities were observed. Atorvastatin use was associated with an improved flow-dependent brachial vasodilation and exercise capacity in the 6-minute walk test.

Conclusions: In chronic heart failure patients, atorvastatin therapy is associated with a decrease of inflammation and extracellular matrix remodeling, improving both endothelial function and exercise capacity. J Heart Lung Transplant 2008;27:435–41. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Chronic heart failure (CHF) results from different injuries associated with inflammatory processes, increased cytokine release, neurohumoral activation, and oxidative stress.[1–3] In previous reports, our group has described increased plasma levels of lipid peroxidation products and decreased activity of anti-oxidant enzymes in compensated CHF patients, showing a correlation between oxidative stress and the severity of CHF.[3,4] This increase in oxidative stress is often associated with elevated inflammation markers,[5] suggesting a biologic relation between both phenomena, which participate simultaneously in the genesis and progression of CHF.

Statins are widely prescribed in patients with hyperlipidemia and coronary artery disease. Pleiotropic effects of statins have been associated with inhibition of inflammatory cytokine synthesis and reactive oxygen species production,[5–7] inhibition of ventricular remodeling,[8] and increased endothelial nitric oxide production with a decrease in endothelin-1 synthesis, leading to improved endothelial function.[7,9] However despite a favorable safety profile,[10] statins are not currently part of standard therapy for CHF due to the lack of supporting clinical evidence. Our aim is to evaluate the impact of atorvastatin on oxidative stress, inflammation, endothelial function, and clinical functional parameters in compensated CHF patients managed with standard therapy.

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METHODS

Study Population and Intervention

We prospectively included CHF patients with New York Heart Association (NYHA) functional class II to IV, followed-up in our Clinical University Center. Inclusion criteria were:

1. left ventricular ejection fraction (LVEF) of less than 40% as measured by radionuclide-gated scan or echocardiogram;
2. standard pharmacologic treatment, including diuretics, β-blockers, digoxin, and angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (Table 1);
3. stable clinical situation during the last 4 weeks;
4. plasma total cholesterol levels of 200 mg/dl or less;
5. presence of endothelial dysfunction as assessed by flow-dependent vasodilation.

Exclusion criteria were:

1. acute coronary syndrome in the last 6 months;
2. coronary artery bypass graft surgery or coronary angioplasty in the last 6 months;
3. uncontrolled arterial hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 90 mm Hg);
4. hypertrophic cardiomyopathy and congenital cardiopathy;
5. the use of anti-oxidants or statins in the previous 2 months, and
6. the presence of other conditions that affect determination of oxidative stress status, such as renal failure (plasma creatinine > 2.0 mg/dl), autoimmune diseases, neoplasia, advanced liver or pulmonary disease, and acute or chronic inflammation.

Table 1. Baseline Characteristics of Heart Failure Patients (n = 38)

Characteristic	Value
Age (years, mean ± SD)	58 ± 12
Male, No. (%)	31 (82)
Etiology, No. (%)	
Ischemic	12 (32)
Nonischemic	26 (68)
NYHA functional class, No. (%)	
II	12 (35)
III	20 (59)
IV	2 (6)
Risk factors, No. (%)	
Hypertension	24 (50)
Diabetes mellitus	6 (13)
Smoking	10 (21)
Treatment, No. (%)	
ACEI or ARA II	34 (71)
Beta-blockers	30 (63)
Diuretics	29 (60)
Spironolactone	29 (60)
LVEF (%, mean ± SD)	27 ± 12

ACEI, angiotensin-converting enzyme inhibitor; ARA II, angiotensin II receptor antagonist; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation.

Patients received a 4-week placebo course, followed by 8 weeks of atorvastatin (20 mg/day). Oxidative stress, ventricular remodeling, inflammation markers, endothelial function, and exercise capacity were determined at baseline and after placebo and atorvastatin treatment. Clinical evaluation, and measurement of plasma creatine kinase (CK), and aspartate aminotransferase (AST) levels were performed at 4 and 8 weeks to identify adverse reactions attributable to the treatment.

For baseline evaluation, the Study Group was compared with the results from a cohort of 40 age-matched healthy volunteers. This Control Group did not receive any kind of treatment. All baseline evaluations were performed exactly as described for the Study Group. All patients signed an informed consent approved by our Institutional Review Board and Ethics Committee.

Assessment of Oxidative Stress, Inflammation, Endothelial Function, and Exercise Capacity

Plasma malondialdehyde (MDA) levels, erythrocyte superoxide dismutase, and catalase activities were determined using standard techniques.[3,11] For endothelial (extracellular) superoxide dismutase (ecSOD) measurement, a venous blood sample from the antecubital vein of the non-dominant arm was obtained at baseline. A heparin bolus (5,000 UI) was then injected into the brachial artery of the same arm, and blood samples were drawn from the antecubital vein at fixed intervals of 1, 3, 5, 7, and 10 minutes after the heparin injection.

Extracellular SOD activity was calculated as described by Landmesser et al.[12] Plasma SOD activity was measured as described by Misra and Fridovich.[13] Activities of matrix metalloproteinase (MMP) 2 and 9 were determined by gelatin zymography.[14] Tissue inhibitor of metalloproteinase 1 (TIMP-1) activity was determined by reverse zymography.[15] Inflammation was evaluated measuring plasma levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) using commercially available enzyme-linked immunosorbent assay kits.

For endothelial function assessment, brachial artery flow-mediated endothelial dependent vasodilatation (FDD) was evaluated as described by Celermajer et al.[16] A change below 8% was considered evidence of endothelial dysfunction.[16]

Table 2. Comparison Between Heart Failure Patients and Age-Matched Healthy Individuals

Variable	Patients (n = 38)	Controls (n = 40)	*p*-value*
hsCRP (mg/dL)	3.15 ± 2.65	0.58 ± 2.02	<0.01
TNF-α (mg/dL)	1.2 ± 2.5	0.9 ± 1.2	0.12
IL-6 (mg/dL)	3.6 ± 2.5	1.38 ± 0.38	<0.01
MDA (μM)	1.23 ± 0.55	0.71 ± 0.13	<0.01
Erythrocyte SOD (U/mg Hb)	2.05 ± 1.90	1.04 ± 0.19	0.13
Erythrocyte CAT (U/mg Hb)	108 ± 36	140 ± 12	0.01
ecSOD (U/ml/min)	128 ± 36	204 ± 114	<0.01
MMP-2 (fold over control)	0.95 ± 0.31	1.00 ± 0.51	0.94
MMP-9 (fold over control)	1.41 ± 0.80	1.00 ± 0.38	<0.01
Total cholesterol (mg/dl)	184 ± 36	184 ± 12	0.71
LDL-C (mg/dl)	106 ± 30	107 ± 12	0.99
HDL-C (mg/dl)	44 ± 12	41 ± 6	0.12
Triglycerides (mg/dl)	175 ± 54	181 ± 24	0.06
Plasma AST (U/Liter)	25.1 ± 8.6	24.6 ± 5.1	0.78
Creatine kinase (U/Liter)	101.2 ± 14.8	101.4 ± 17.1	0.85
Creatinine (mg/dl)	1.08 ± 0.37	0.95 ± 0.13	0.31
Uric acid (mg/dl)	7.3 ± 2.46	6.1 ± 1.3	0.06

AST, aspartate aminotransaminase; CAT, catalase; ecSOD, extracellular superoxide dismutase; HDL-c, high-density lipoprotein cholesterol; HsCRP, high-sensitive C-reactive protein; IL-6, interleukin 6; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; MMP, matrix metalloproteinase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α.

*Wilcoxon rank-sum test.

Exercise capacity was determined by the 6-minute walk test. At baseline, a practice test was performed for training issues, and then a second test was performed 1 hour later. A trained technician used the standard protocol recommended by the American Thoracic Society to perform all tests.

Statistical Analysis

Results were presented as means ± SD for continuous variables and percentage of all patients for categoric data. Continuous variables were tested for normality using Kolmogorov-Smirnov test. Given the small sample size, non-parametric evaluations were performed (Kruskal-Wallis non-parametric analysis of variance and Dunn's multiple comparison test). The chi-square test was used for categoric data. Significant correlations between continuous variables were evaluated using the Pearson method. A 2-tailed $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS 13.0 software (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

The study included 38 compensated CHF patients. Patient characteristics are detailed in Table 1. Mean age was 58 ± 12 years, 31 (82%) were men, and 7 were women. The CHF etiology was ischemic in 12 cases (32%) and non-ischemic dilated cardiomyopathy in 26 (68%). Six patients (13%) had a history of diabetes mellitus, and 24 (50%) had a history of hypertension. All patients were clinically stable, mostly in NYHA functional class II and III (94%). The mean LVEF was 27% ± 12%. At baseline, CHF patients have increased plasma levels of inflammatory markers, except for TNF- α. Also higher in the Study Group were levels of MMP-9, a surrogate marker for ventricular remodeling, and oxidative stress markers. Simultaneously, lower ecSOD activity was observed in CHF patients compared with a cohort of age-matched healthy volunteers (Table 2).

Effects of Atorvastatin on Oxidative Stress Markers

Atorvastatin therapy decreased significantly both total and low-density lipoprotein (LDL) cholesterol levels, with a moderate effect on triglycerides levels. No significant changes were observed in high-density lipoprotein cholesterol levels (Table 3). The effects of atorvastatin on oxidative stress, remodeling, inflammation, endothelial function, and functional capacity are reported in Table 4. Atorvastatin therapy was associated with a significant increase in ecSOD and erythrocyte SOD activity compared with both baseline and placebo, with a simultaneous decrease in MDA levels. No changes were detected in catalase activity isolated from erythrocytes.

Effects of Atorvastatin on Inflammatory Markers

Treatment with atorvastatin decreased MMP-9 activity, without modifying MMP-2 or TIMP-1 activities. Likewise, atorvastatin treatment was associated with a reduction in plasma inflammation markers hsCRP, IL-6, and TNF-α (Table 4).

Effects of Atorvastatin on Endothelial Function and Exercise Capacity

At baseline, CHF patients showed impaired FDD (4.50% ± 1.85% change from baseline). Atorvastatin significantly improved endothelial function, increasing FDD (Table 4). This improvement was correlated with the fractional change in ecSOD activity ($r^2 = 0.27$, $p < 0.01$; Figure 1). Exercise capacity in the 6-minute walk test was also increased after the atorvastatin course, regardless of baseline functional class.

Table 3. Changes in Lipid Profile using Atorvastatin in Heart Failure Patients

Variable	Baseline (n = 38)	Placebo (n = 38)	Atorvastatin (n = 38)	*p*-value*
Total cholesterol, mg/dl	184 ± 37	178 ± 18	138 ± 30	<0.01
LDL cholesterol, mg/dl	106 ± 30	117 ± 42	65 ± 30	<0.01
HDL cholesterol, mg/dl	44 ± 12	41 ± 12	43 ± 6	0.5
Triglycerides, mg/dl	175 ± 54	185 ± 18	139 ± 18	<0.01

LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

*Kruskal-Wallis test.

Table 4. Effect of Atorvastatin in Oxidative Stress Markers, Remodeling, Inflammation, Endothelial Function and Exercise Capacity in Heart Failure Patients

Variable	Baseline* (n = 38)	Placebo* (n = 38)	Atorvastatin (n = 38)	*p*-value†
ecSOD (U/ml/min)	128 ± 36	103 ± 48	191 ± 66	<0.01
Erythrocyte SOD, U/mg Hb	2.05 ± 1.90	2.32 ± 2.22	3.30 ± 2.89	0.03
Erythrocyte CAT, U/mg Hb	108 ± 36	106 ± 12	111 ± 42	NS
MDA (μM)	1.23 ± 0.55	1.18 ± 0.43	1.03 ± 0.43	0.04
MMP-2 (fold over control)	0.95 ± 0.31	1.03 ± 0.31	0.92 ± 0.37	0.6
MMP-9 (fold over control)	1.41 ± 0.80	1.30 ± 0.43	0.96 ± 0.43	<0.01
TIMP-1 (fold over control)	1.17 ± 0.42	1.16 ± 0.21	1.22 ± 0.31	0.4
hsCRP, mg/dl	3.15 ± 2.59	3.44 ± 3.08	2.08 ± 1.97	0.05
TNF-α, mg/dl	1.2 ± 2.4	1.4 ± 2.4	0.9 ± 1.8	<0.01
IL-6, mg/dl	3.6 ± 2.4	4.3 ± 3.0	2.5 ± 1.8	<0.01
Vasodilation				
Endothelium-dependent‡	4.50 ± 1.85	5.03 ± 1.97	6.73 ± 2.77	<0.01
Endothelium-independent‡	14.9 ± 7.4	16.3 ± 6.6	15.6 ± 5.4	0.6
6-min walk test, m	431 ± 136	428 ± 92	470 ± 111	0.03

CAT, catalase; ecSOD, extracellular superoxide dismutase; hsCRP, high-sensitive C-reactive protein; IL-6, interleukin 6; MDA, malondialdehyde; MMP, matrix metalloproteinase; SOD, superoxide dismutase; TIMP-1, tissue inhibitor of MMP-1; TNF-α, tumor necrosis factor-α.

*Wilcoxon rank-sum test baseline vs placebo non-significant.

†Kruskal-Wallis test.

‡Percentage change from baseline.

Safety

No serious adverse effects were reported associated with placebo or atorvastatin therapy. After atorvastatin use, a minor asymptomatic elevation in CK levels was observed. AST activity remained within normal limits (Table 5).

DISCUSSION

Clinical trials have demonstrated the role of statins in the prevention of cardiovascular events in moderate- and high-risk patients, even in those with a normal LDL cholesterol level.[17–19] However, CHF patients have been systematically excluded from most statin clinical trials, partly due to concerns regarding safety of lipid-lowering therapy in CHF.[7] Earlier observational studies suggested that low cholesterol was related to a higher mortality rate in CHF.[8] However, low cholesterol is a marker for hepatic dysfunction and malnutrition, which is often present in end-stage disease. In fact, patients in these studies with lower cholesterol tended to have lower sodium, albumin, LVEF, and cardiac output at the time of referral.[20,21] Thus, the observed excessive mortality rate could be related to a more advanced disease rather than a deleterious effect of low cholesterol itself.

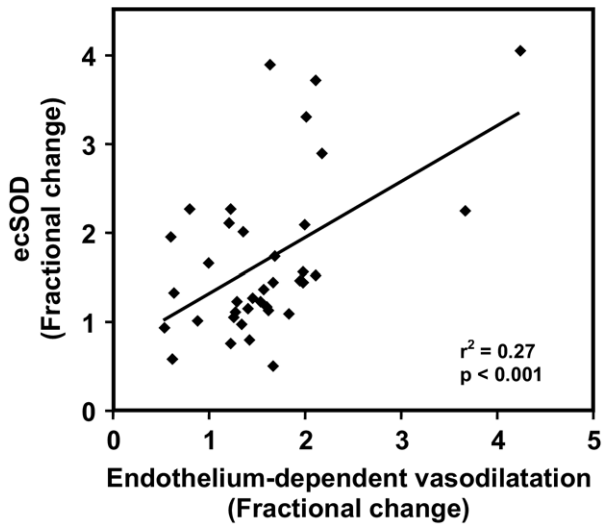

Figure 1. Correlation between fractional change in endothelial (extracellular) superoxide dismutase (ecSOD) activity and endothelium-dependent vasodilatation after atorvastatin therapy in heart failure patients.

Several small trials evaluated the role of statin in CHF patients already receiving standard therapy, showing lower mortality and morbidity and improved ventricular function, regardless of the etiology of the disease.[22–24] Other non-randomized clinical trials, such as the Prospective Amlodipin Survival Evaluation and the Antiarrhythmics Versus Implantable Defibrillators trials have demonstrated a mortality benefit in patients with either ischemic or non-ischemic CHF treated with statins.[25,26]

These findings have been reinforced by post hoc analysis of other large CHF trials. The Sudden Cardiac Death in Heart Failure trial included 2,521 patients at NYHA functional class II to III with LVEF of 35% or less. Patients were followed up for a median of 45.5 months. Statin use was reported in 965 (38%) at baseline and 1,187 (41%) at the end of follow-up. Mortality risk was significantly lower in patients taking statins as part of their regular medications (hazard ratio, 0.70; 95% con-

Table 5. Evaluation of Adverse Effects Induced by Atorvastatin Treatment

Variable	Baseline (n = 38)	Placebo (n = 38)	Atorvastatin (n = 38)	*p*-value
Laboratory				
Plasma AST (U/Liter)	25.1 ± 8.6	23.9 ± 6.2	25.7 ± 8.0	0.97*
Creatine kinase (U/Liter)	101.2 ± 14.8	115.5 ± 11.1	117.1 ± 18.5	0.01*
Adverse effects n (%)				0.70
Any adverse effect	0 (0)	1 (2.6)	2 (5.2)	
Adverse effect leading to Discontinuation of study drug	0 (0)	0 (0)	0 (0)	
Skeletal muscle adverse effects, No. (%)				0.97†
Myalgia	0 (0)	0 (0)	1 (0)	
Rabdomyolysis	0	0	0	
Other adverse effects with incidence <10%, No. (%)				0.67†
Headache	2 (5.2)	2 (5.2)	3 (7.9)	
Diarrhea	0 (0)	0 (0)	2 (5.2)	

AST, aspartate aminotransferase.
*Kruskal-Wallis test.
†Chi-Square test.

fidence interval, 0.58–0.83).[27] Of interest was that statin benefit was similar in ischemic cardiac disease and non-ischemic cardiac disease patients, suggesting a non-anti-arrhythmic benefit derived from statin use.

A large randomized trial designed to evaluate the impact of rosuvastatin on survival of ischemic CHF patients has recently been published. The Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA Group) trial failed to show a significant effect on the primary outcome of death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke in an older population at higher risk for competing events.[28] However, although these results are negative, they are far from conclusive. In fact, this study showed a significant reduction in hospitalizations for cardiovascular causes in the statin-treated patients, with favorable trends for both non-fatal myocardial infarction and non-fatal stroke and without a significant increase in any adverse effect. Thus, the question about the role of statins in CHF therapy remains yet unanswered.

Our results emphasize the potential beneficial effects of the addition of atorvastatin to standard CHF therapy owing to its ability to decrease both inflammatory and oxidative stress markers and improve FDD and exercise capacity. The underlying mechanisms associated with the observed improvement and the potential impact in long-term evolution of the disease has not been fully assessed yet. However, a growing body of evidence regarding these pleiotropic effects deserves careful consideration.

As other authors had shown, the clinically stable CHF patients included in our study showed substantially elevated inflammatory markers at baseline compared with healthy subjects. Statin therapy decreased plasma inflammation markers such as hsCRP and TNF-α. This effect could be related with the ability of statins to inhibit isoprenylation and the activation of members of the Rho family, blocking pro-inflammatory transduction pathways.[8] In a study published by Node et al, 63 patients were randomly assigned to simvastatin or placebo for 14 weeks. They observed an improvement in LVEF and FDD and a decrease of TNF-α and IL-6 plasma levels.[10] This decrease in soluble levels of several inflammatory markers suggest a role of statins in blunting the inflammatory response associated with CHF.[9,22]

Concomitantly with increased inflammatory markers, CHF patients show higher levels of oxidative stress markers at baseline compared with healthy individuals.[3,4] In our group, however, MDA plasma levels at baseline showed no differences with healthy subjects, probably due to less advanced stage of disease in our cohort. Baseline ecSOD levels were comparatively lower in CHF patients than in healthy controls and increased significantly after statin treatment. Of interest was that the extracellular isoform of SOD is physically attached to the endothelium and seems to play a pivotal role in the physiologic response to hyperemia and other related stimuli.[12] It has been suggested that the positive effect of statin use in FDD could be related with its a ability to increase ecSOD activity.[29]

Both increased oxidative stress and increased inflammatory markers are associated with CHF progression manifested by adverse ventricular remodeling. In animal models of CHF, reactive oxygen species increase inflammatory markers such as hsCRP and TNF-α. In human CHF studies, both markers have been associated with increased rates of mortality and morbidity due to major cardiovascular events.[30,31] In experimental models of ischemic CHF, fluvastatin has shown to decrease left ventricular dilatation, myocyte hypertrophy, inter-

stitial fibrosis, and death.[32] Similar findings have been described in a mice model of non-ischemic CHF in Dahl salt-sensitive rats, in which pravastatin use did not attenuate heart hypertrophy but avoided transition to decompensated heart failure, preventing the increase of both MMP-2 and MMP-9, and avoiding an increase in oxidative stress in the ventricular milieu induced by the salt-rich diet.[33] Moreover, Nakaya et al[34] found that in patients with myocardial infarction, treatment with pravastatin improved left ventricular end-diastolic volume index and decreased MMP-2 plasma levels.

In our group, baseline soluble markers of ventricular remodeling were significantly higher than those of healthy subjects. Up-regulation of MMP-9 is common in failing myocardium, independent of the underlying disease,[35] as was seen in our group of patients. MMPs may alter myocardial extracellular matrix and contribute to adverse ventricular remodeling in progressive CHF.[36,37] Changes in MMP-2 are also described in several in vivo and in vitro studies of CHF[38]; however, no such changes were observed in our cohort. Both MMPs are up-regulated in CHF, but the transcriptional control is different for each one. Whereas MMP-2 is constitutively active in tissues at substantial levels,[39] MMP-9 is mostly inactive in baseline conditions. In addition, the MMP-9 promoter has a nuclear factor-κB binding site, which can up-regulate its synthesis in response to several stimuli such as oxidative stress and inflammation,[40] explaining the selective elevation of MMP-9 seen in our patients.

In summary, short-term treatment with atorvastatin in CHF patients results in favorable biochemical changes characterized by a decrease in inflammatory and soluble remodeling markers, improving both anti-oxidant activity and endothelial function. Even more important, these changes seem to be associated with increased exercise capacity. Although design and sample size limits the generalization of these results, a considerable amount of evidence suggests a beneficial effect of statins in CHF. Results from ongoing large randomized trials such as the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico – Insufficienza cardiaca) trial and the Rosuvastatin Impact on Ventricular Remodeling Cytokines and Neurohormones (UNIVERSE) trial should be awaited to conclusively establish their role in standard therapy for CHF.

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