

A prospective evaluation of the effect of simvastatin on heart rate variability in non-ischemic cardiomyopathy

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Background Modulation of sympathetic tone may contribute to statin-mediated reduction in sudden cardiac death. We examined the effect of simvastatin on heart rate variability (HRV) in patients with non-ischemic dilated cardiomyopathy to evaluate for an antisympathetic effect of statins independent of anti-ischemic properties.

Methods The study was a prospective, open-label, self-controlled trial. Frequency domain analysis of HRV was assessed in 25 patients with non-ischemic dilated cardiomyopathy at baseline and after a 6-week course of simvastatin. The primary end point was the change in 5-minute sitting total spectral power (TSP) as a composite measurement of autonomic nervous system modulation. Secondary end points included the change in respiratory frequency area (RFa) with deep breathing (parasympathetic stress) and in low-frequency area (LFa) with Valsalva (sympathetic stress).

Results Simvastatin had no effect on 5-minute sitting TSP (baseline 1932 ± 1165 vs posttreatment 2570 ± 1877 square milliseconds, $P = .770$), RFa with deep breathing (baseline 19 ± 7 vs posttreatment 14 ± 4 [beat/min]², $P = .31$), or LFa with Valsalva (baseline 26 ± 6 vs posttreatment 32 ± 8 [beat/min]², $P = .342$). Bivariate analysis demonstrated no correlation between low-density lipoprotein (LDL) change and change in TSP or RFa, but did demonstrate an inverse relationship between change in LDL and change in LFa with Valsalva stress ($r = -0.45$ and $P = .041$).

Conclusion Although simvastatin did not change baseline HRV, a modest relationship exists between the extent of LDL reduction and sympathetic responsiveness to stress. (*Am Heart J* 2005;150:478-83.)

The large randomized trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for prevention of adverse events associated with atherosclerotic heart disease have demonstrated a relative reduction in all-cause mortality of 16.5% and a relative reduction in cardiac mortality of 23.5% in 51 353 patients.¹⁻⁵ Two of these trials also reported a 20% reduction in the relative risk of sudden death.¹⁻² De Sutter et al⁶ found that patients with ischemic heart disease post-implantable cardioverter and defibrillator implant have a 35% decrease in recurrences of ventricular arrhythmias on lipid-lowering agents (primarily statins) over a mean follow-up of 490 days. Most

recently, a multivariate analysis of the AVID trial demonstrated that statin therapy was associated with a 40% reduction in the relative hazard for ventricular tachycardia/ventricular fibrillation recurrence in patients with atherosclerotic heart disease who have an implantable cardioverter and defibrillator.⁷ The observed decrease in cardiac arrhythmias and mortality is believed to be primarily due to statin-mediated reduction in ischemic events but some of the benefit may be because of effects on the autonomic nervous system.

Several studies have suggested that statins may modulate autonomic nervous system function. Patients with hyperlipidemia have depressed heart rate variability (HRV) and changes in lipid status may affect HRV.^{8,9} We hypothesized that statins have a sympatholytic effect independent of anti-ischemic effects. Specifically, we evaluated the effect of simvastatin on HRV in patients with non-ischemic dilated cardiomyopathy (DCM). This patient population was chosen in an attempt to study HRV free of a possible confounding effect of the agent on coronary ischemia. In addition, measurement of HRV was chosen because it is a reproducible and valid measure of autonomic nervous system function.¹⁰⁻¹⁵ Furthermore, diminished HRV is associated with increased arrhythmic risk in postinfarction patients,^{16,17} as well as poor prognosis and sudden cardiac death in heart failure and DCM.¹⁸⁻²²

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Methods

The study was a prospective, open-label, 6-week self-controlled trial evaluating the effects of simvastatin on HRV in patients with non-ischemic DCM. Eligible patients were recruited from the Walter Reed Army Medical Center Cardiology Clinic. Eligible patients were identified by their primary providers within the Cardiology Clinic and referred to the principal investigator for possible enrollment in the study. The study protocol was approved by the Department of Clinical Investigation, Walter Reed Army Medical Center. All patients provided written, informed consent before enrollment.

Inclusion criteria included patients aged ≥ 18 years with a non-ischemic DCM with an ejection fraction $\leq 40\%$. Eligible patients were required to be on a stable heart failure medical regimen during the study period and were at goal or maximally tolerated doses of medication for at least 1 month before start of study. Exclusion criteria included patients with documented obstructive coronary artery disease defined as $> 50\%$ epicardial stenosis by coronary angiography or a history of myocardial infarction. Patients with a contraindication or intolerance to statins to include pregnancy, active known liver disease demonstrated by elevations in serum transaminases $> 2\times$ the upper laboratory reference, current treatment with a statin or any lipid-lowering medications, and therapy with medications that interact with simvastatin metabolism to include cyclosporin, macrolide antibiotics, protease inhibitors, nefazadone, or azole antifungal agents were excluded. Also patients with conditions known to alter HRV testing other than non-ischemic DCM¹³ to include diabetes, end-stage renal disease on dialysis, second- or third-degree atrioventricular block, a heart rhythm other than sinus rhythm (eg, atrial fibrillation or paced rhythm), or patients on any antiarrhythmic agent (eg, amiodarone, sotalol) were excluded.

Eligible patients underwent HRV testing using the ANSAR ANS-R-1000 (ANSAR, Philadelphia, Pa) to initiate the study protocol. The ANSAR ANS-R-1000 is a portable noninvasive, real-time HRV monitor that assesses the integrity of the autonomic nervous system. This monitor has a computer-based power spectral density analysis of HRV based on wavelet transforms. The patients are initially monitored for 5 minutes in the baseline state and then undergo challenges to the autonomic nervous system. These challenges include deep breathing to stress the parasympathetic nervous system and Valsalva to stress the sympathetic nervous system. All HRV recordings were performed under standardized conditions to include a 5-minute period of equilibration before the test, standardized test time between 8:00 AM and 1:00 PM to eliminate diurnal variability, continuation of stable chronic medications, and stable congestive heart failure symptoms.

The ANSAR-R-1000 provided the standard short-term recording spectral analysis to include total spectral power (TSP), high-frequency (HF) power, and low-frequency (LF) power. The LF power spectrum is evaluated between 0.04 to 0.15 Hz and reflects sympathetic activity. The HF power spectrum is evaluated between 0.15 and 0.4 Hz and reflects parasympathetic activity.¹⁰

The ANSAR ANS-R-1000 can also adjust for respiratory effects on power spectral analysis of HRV. The ANSAR device performs a spectral analysis of the respiratory signal to develop the respiratory activity spectrum. The respiratory activity spectrum measures the changes in the respiratory cycle, which reflect parasympathetic modulation and influence HRV. The

Table I. Patient characteristics

	Baseline
Patient age	55.4 \pm 14.0
Male	52%
Female	48%
Left ventricular ejection fraction in percentage	28.0 \pm 8.9
New York Heart Association CHF class	1.6 \pm 0.7
Duration of CHF in months	27.0 \pm 47.3
Total cholesterol at baseline	210.6 \pm 37.8
Triglycerides at baseline	177.0 \pm 126.7
HDL at baseline	53.6 \pm 17.5
LDL at baseline	120.6 \pm 31.5
VLDL at baseline	36.3 \pm 17.3
BUN at baseline	15.3 \pm 5.5
Creatinine at baseline	1.0 \pm 0.2
Glucose at baseline	97.8 \pm 20.0
β -Blocker	92%
ACE inhibitor	88%
Digoxin	56%
Lasix	44%
Spironalactone	16%
Angiotensin receptor blocker	12%
Calcium channel blocker	8%

Data are given as mean value with SD unless noted otherwise. CHF, congestive heart failure; VLDL, very low-density lipoprotein; BUN, blood urea nitrogen.

frequency of the peak mode of the respiratory activity spectrum, defined as the fundamental respiratory frequency, provides the center frequency for the HF analysis. A 0.12-Hz-wide window is centered on the fundamental respiratory frequency on the HRV spectrum frequency analysis. This area under the spectral curve within the HF region is defined as the respiratory frequency area (RFA).²³ It reflects parasympathetic activity and corresponds to HF. The ANSAR system also measures the low-frequency area (LFA) in the LF spectrum that remains after subtracting the RFA. It reflects sympathetic activity and corresponds to LF.

After recording baseline measures of HRV, volunteers began treatment with simvastatin 20 mg/d for a 6-week period. Simvastatin 20 mg/d was chosen as the dose used in the Scandinavian Simvastatin Survival Study that demonstrated reduction in cardiovascular mortality.¹ After 6 weeks of simvastatin treatment, repeat HRV testing was performed. Fasting baseline and 6-week serum was assayed for blood urea nitrogen, creatinine, liver-associated enzymes and lipids.

End points

The primary end point was treatment-related change in sitting TSP compared with baseline (representing a composite measurement of parasympathetic and sympathetic-mediated HRV). The secondary end point was treatment-related changes in RFA with deep breathing (parasympathetic activity) and treatment-related changes in LFA with Valsalva (sympathetic activity).

Statistical analysis

Sample size calculations assumed a modest effect size of 25% for simvastatin and HRV. This magnitude of change was consistent with reports from retrospective analyses of statins and sudden death. Furthermore, a study of angiotensin-

Table II. Simvastatin effect on HRV parameters

HRV variable	Baseline	Post therapy	P (2-tailed)
TSP sitting	1932.2 ± 1165.1	2570.0 ± 1877.3	.77
HF sitting	515.6 ± 196.3	1416.4 ± 1090.4	.4
LF sitting	1370.5 ± 970.6	1094.8 ± 750.9	.82
LF/HF sitting	2.0 ± 0.3	1.9 ± 0.4	.86
RFa sitting	1.7 ± 0.6	1.7 ± 0.6	.95
LFa sitting	3.1 ± 1.6	2.5 ± 1.1	.77
TSP deep breathing	6135 ± 3064.4	4497.0 ± 1598.2	.34
HF deep breathing	954.6 ± 479.5	692.2 ± 213.2	.44
LF deep breathing	5181.2 ± 2594.7	3804.7 ± 1407.8	.32
LF/HF deep breathing	7.1 ± 0.9	6.4 ± 0.7	.53
RFa deep breathing	19.4 ± 7.0	14.2 ± 4.0	.31
LFa deep breathing	4.2 ± 1.4	5.1 ± 1.8	.54
TSP Valsalva	8048.9 ± 2953.9	10206.3 ± 3394.9	.21
HF Valsalva	1381.1 ± 890.1	1200.4 ± 2503.8	.68
LF Valsalva	6649.3 ± 2185.3	8939.3 ± 2996.3	.14
LF/HF Valsalva	12.7 ± 2.1	11.7 ± 1.5	.46
RFa Valsalva	3.9 ± 2.4	4.8 ± 2.1	.63
LFa Valsalva	26.1 ± 5.9	32.9 ± 8.1	.34

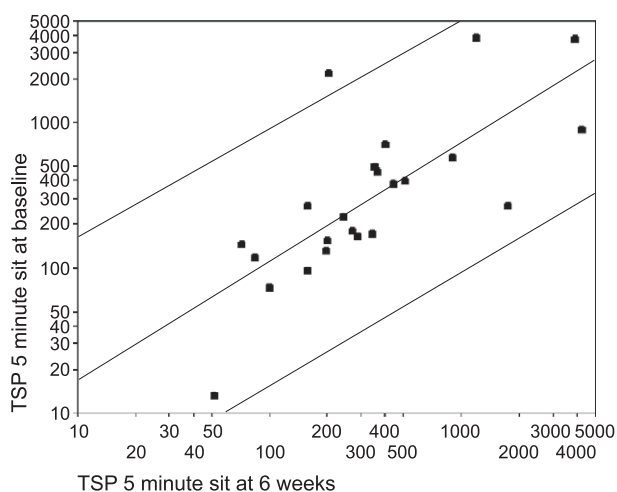
converting enzyme (ACE) inhibitors and HRV in congestive heart failure showed a 50% to 100% improvement from a baseline total heart variability of $2.4 \times 10^{-3} \pm 1.6 \times 10^{-3}$ (beat/min)².²⁴ The null hypothesis was that the mean difference (or change) in HRV within pairs would be 0. The criterion for significance (α) was set at .050. With a 2-tailed test and the proposed sample size of 25 patients, the study had a power of 81.2% to yield a statistically significant result. This computation assumed that the population from which the sample was drawn had a mean difference of 0.6 with a standard deviation of 1.0. This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated in this field of research.

End point data were analyzed using a paired *t* test comparing the mean HRV values at baseline and on-treatment. The change in HRV was compared with the reduction in low-density lipoprotein cholesterol (LDL-C) using bivariate linear regression analysis based upon a modest degree of anticipated interpatient variability in the LDL response to statin therapy. This analysis would indicate whether any relationship between HRV and statins is lipid-dependent or -independent.

Results

Patient characteristics

The patient characteristics are shown in Table I. A total of 26 patients were initially enrolled; 25 patients completed the protocol. One patient was unable to complete the study after requiring implantation of a dual chamber pacemaker for second-degree atrioventricular block. The average age of the patients was 55 years with an average left ventricular ejection fraction of 28%. The mean New York Heart Association congestive heart failure class was 1.6, including 44% with class 2 or worse heart failure. The etiology of the DCM was idiopathic in

Figure 1

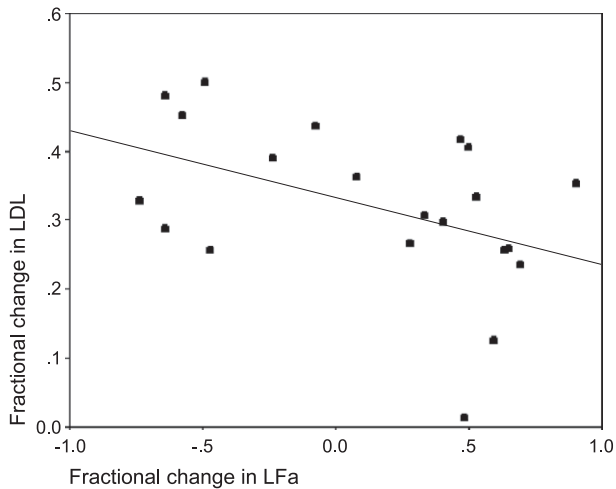
Scatterplot with linear regression fit line and 95% CIs for primary end point evaluating simvastatin effect on TSP ($r = 0.73$ and $P = .87$) (values in square milliseconds).

19 patients, familial in 2, valvular in 1, viral in 1, postpartum in 1, and hypertension in 1. Medical therapy was appropriate for the degree of left ventricular dysfunction including β -blockers in 92%, ACE inhibitors in 88%, digoxin and lasix in 44% (each), and an angiotensin receptor blocker in 12%.

Statin effects on lipids

Baseline lipids were consistent with a selected population that does not require statin therapy with a

Figure 2



Bivariate correlation analysis demonstrating an inverse relationship between change in LDL and change in LFa with Valsalva stress ($r = -0.45$ and $P = .04$) (values in $[\text{beat}/\text{min}]^2$).

mean high-density lipoprotein (HDL) of 54 ± 18 , mean LDL of 120 ± 32 , and mean triglycerides of 176 ± 127 . Simvastatin led to an expected effect on the lipid parameters with a statistically significant 33% decrease in LDL, 2% increase in HDL, and a 27% decrease in triglycerides ($P < .0001$).

Statin effects on heart rate and blood pressure

Mean heart rate at baseline was 66.9 ± 2.5 beat/min and was unchanged at 6-week follow-up. Mean blood pressure was $125.6/71.5 \pm 4.6/2.3$ mm Hg at baseline with a significant decrease to $111.6/67.4 \pm 5.3/1.8$ mm Hg at baseline ($P = .005$ for systolic and $P = .023$ for diastolic).

Simvastatin effects on HRV parameters

Spectral analysis measures at baseline and after therapy are presented in Table II. There was no effect of simvastatin on the primary study end point of 5-minute sitting TSP (baseline 1932 ± 1165 vs posttreatment 2570 ± 1877 square milliseconds, $P = .770$). Two outlier values (TSP >29000 square milliseconds) were then removed from the primary end point analysis to determine if the extreme values masked an effect of simvastatin on TSP. The paired sample analysis of TSP at baseline and after 6 weeks of simvastatin therapy again demonstrated no significant effect of therapy on TSP with $P = .873$ (Figure 1). Similarly, the secondary end points of RFa with deep breathing (baseline 19 ± 7 vs posttreatment 14 ± 4 $[\text{beat}/\text{min}]^2$, $P = .31$) or LFa with Valsalva (baseline 26 ± 6 vs posttreatment 32 ± 8 $[\text{beat}/\text{min}]^2$, $P = .342$) were unchanged with simvastatin. Post hoc

analyses included simvastatin effects in higher risk subgroups as defined by congestive heart failure class ≥ 2 and in patients with low baseline HRV (TSP $<$ study group mean) demonstrated no effect of simvastatin on HRV parameters.

Bivariate analysis demonstrated no correlation between LDL change and change in TSP and RFa. Bivariate analysis showed an inverse relationship between change in LDL and change in LFa with Valsalva stress ($r = -0.45$ and $P = .025$). Three outlier values ($>700\%$ change in LFa) were then removed from the analysis to determine if the relationship was only secondary to the extreme values. Repeat bivariate analysis confirmed the inverse relationship between change in LDL and change in LFa with stress ($r = -0.45$ and $P = .041$) (Figure 2).

Discussion

This study showed no significant effect of simvastatin 20 mg daily on HRV when prescribed to patients with non-ischemic DCM with average cholesterol values. In addition, simvastatin did not demonstrate a lipid-lowering independent effect on frequency domain HRV parameters to sympathetic and parasympathetic challenges. These data suggest that the reduction in sudden death associated with simvastatin use is from mechanisms other than lipid-independent modulation of the sympathetic nervous system. However, per our study design, we cannot exclude statin-mediated modulation of the sympathetic nervous system because of anti-ischemic effects in patients with atherosclerotic coronary artery disease.

Prior studies evaluating statin effects on HRV have been primarily performed in patients with ischemic heart disease or significant hyperlipidemia. An earlier trial had demonstrated decreased HRV in patients with stable angina,²⁵ but more recent trials have shown increases in HRV in post-myocardial infarction patients²⁶ and in patients with hyperlipidemia with and without concomitant ischemic heart disease.^{27,28} Whether these observations occurred from reductions in coronary ischemia, reduced serum cholesterol levels, or a direct drug effect has not been validated.

The lack of direct simvastatin effect on resting HRV parameters seen in our population suggests that an effect on autonomic modulation is a primarily lipid-lowering effect. However, a potential statin-specific effect may have been minimized by the high use of β -blockers and ACE inhibitors in this study and their attendant effects on HRV. In addition, there are possible differential effects on autonomic nervous system function within the statin class. Welzig and colleagues²⁸ found that pravastatin but not simvastatin increased parasympathetic modulation in a hyperlipidemic population requiring statin therapy. Their finding correlated with an increased expression of $G\alpha_{i2}$ (a molecular component of the parasympathetic signaling pathway in

the heart) seen only in the pravastatin-treated arm. They suggested that the differential effect on $G\alpha_{i2}$ expression could be explained by differences in hydrophobicity. The hydrophilic pravastatin requires an active transporter that is absent in nonliver cells, whereas hydrophobic statins simvastatin can passively diffuse across cardiac cells and decrease $G\alpha_{i2}$ expression.

Although this study showed that resting HRV parameters were unrelated to changes in LDL, a modest relationship between change in LDL and change in LFa with the Valsalva challenge was demonstrated. An increase in sympathetic tone because of decreasing LDL with subsequent decreased LFa with Valsalva challenge is unlikely given the lack of effect on baseline TSP and LF/LFa as well as the decrease in systolic blood pressure at follow-up. This finding likely suggests decreased LDL tempers sympathetic modulation to stress. This explanation is consistent with other known lipid-lowering effects. As sympathetic activation is a known risk factor for ventricular arrhythmias,^{29,30} it suggests one potential mechanism for the decrease in sudden cardiac death associated with statins. The modulation of sympathetic tone with lipid lowering may be explained by the effects of statins on nitric oxide. Statins are known to increase nitric oxide levels through anti-LDL effects and through induction of the transcription activation of the nitric oxide synthase gene.³¹⁻³³ Furthermore, nitric oxide may attenuate cardiovascular end-organ responses to sympathetic stimulation.³⁴⁻³⁶ Although biologically plausible, this finding is considered hypothesis-generating and in need of prospective confirmation because the effect of lipid lowering on sympathetic modulation was not a prespecified end point of the study.

Interestingly, our study group had a significant 14 mm Hg decrease in systolic blood pressure and 4 mm Hg decrease in diastolic blood pressure. We believe this finding is most likely related to the simvastatin effects on endothelial nitric oxide synthase and direct improvement in endothelial function. Statins have been demonstrated to reduce blood pressure through improvement in endothelial function in patients with hypertension, hyperlipidemia, and postrenal transplant.³⁷⁻⁴⁶ Although our population was neither hypertensive or hyperlipidemic at baseline, patients with heart failure have been shown to have impaired endothelial function secondary to a decrease in nitric oxide synthesis.⁴⁷

Study limitations

Although this study argues against a moderate effect of statins on HRV, a smaller effect size, of unclear clinical relevance, cannot be excluded. Furthermore, our population had primarily mild to moderate heart failure and mildly decreased HRV parameters at baseline. To evaluate for a possible effect in sicker patients, we performed subgroup analysis on patients with heart failure \geq New York Heart Association class 2 and

separately on patients with TSP \leq our mean population TSP with no effect seen on baseline HRV parameters with simvastatin use. However, we cannot exclude an effect on HRV with statin use in populations with more severe heart failure or more severely depressed HRV.

The trial was not randomized, but the use of a self-controlled design was chosen to control for confounding inpatient factors that may influence HRV. Lastly, although this study used open-label therapy, HRV end point analysis is an objective, computer-derived measurement.

Conclusion

In a population of patients without ischemic heart disease or hyperlipidemia, simvastatin did not lead to overall change in baseline HRV. Statin-mediated LDL reduction was associated with a tempered sympathetic modulation to stress. This latter finding, which requires prospective confirmation, could impart a reduced susceptibility to arrhythmic events.

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