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Potential Autonomic Nervous System Effects of Statins in Heart Failure

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Synopsis

Sympathetic nervous system activation in heart failure, as indexed by elevated norepinephrine levels, higher muscle sympathetic nerve activity and reduced heart rate variability, is associated with pathologic ventricular remodeling, increased arrhythmias, sudden death, and increased mortality. Recent evidence suggests that HMG-CoA reductase inhibitor (statin) therapy may provide survival benefit in heart failure of both ischemic and non-ischemic etiology, and one potential mechanism of benefit of statins in heart failure is modulation of the autonomic nervous system. Animal models of heart failure demonstrate reduced sympathetic activation and improved sympathovagal balance with statin therapy. Initial human studies have reported mixed results. Ongoing translational studies and outcomes trials will help delineate the potentially beneficial effects of statins on the autonomic nervous system in heart failure.

Keywords

statins; autonomic nervous system; heart failure; sympathetic nervous system

Introduction

Heart failure (HF) is a national public health problem with an overall prevalence in the U.S. of approximately 5 million. Despite advances in our understanding of HF pathophysiology and treatment, one out of five patients newly diagnosed with HF will die within one year. Death is often due to gradual worsening of HF (progressive pump dysfunction), although as many as one-half of HF deaths are sudden^{1–3}. Numerous observational studies suggest that statins have survival benefit in HF, reducing all cause mortality as well as arrhythmic deaths⁴. Recent evidence suggests that HMG-CoA reductase inhibitors (statins) may have “pleiotrophic” mechanisms, beyond anti-ischemic or lipid-lowering effects, that are beneficial in HF^{5–9}. Statins may improve endothelial function, reverse myocardial remodeling, inhibit inflammatory cytokines, and potentiate nitric oxide (NO) synthesis. Furthermore, modulation of the autonomic nervous system by statins may be an important, potentially beneficial, mechanism of action in HF.

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The Autonomic Nervous System in Heart Failure

The processes contributing to the progression of systolic HF are complex and inter-related. At the core of the syndrome is impaired cardiac function, associated with ongoing remodeling, inflammation, neurohormonal activation, and impaired autonomic nervous system (ANS) function. Activation of sympathetic drive plays a pivotal role in the progression of HF. Clinical signs and symptoms of the hyperadrenergic state in some HF patients includes tachycardia, vascular constriction, diaphoresis, and oliguria¹⁰. Sympathetic over-activation in HF is characterized by increased levels of circulating norepinephrine as well as increased cardiac and renal norepinephrine spillover^{11, 12}. Both increased neuronal release of norepinephrine and decreased norepinephrine reuptake contribute to the increased cardiac adrenergic drive of HF¹³.

In addition to elevated systemic and cardiac norepinephrine levels, autonomic imbalance in HF has also been indexed by heart rate variability (HRV) analyses. HRV, using time-domain and frequency-domain indices, is a standardized tool for examining autonomic nervous system activity in various disease states such as hypertension, diabetes, coronary artery disease, as well as myocardial dysfunction. Standard time-domain indices include standard deviation of the normal-normal intervals (SDNN) and the square root of the mean squared differences of successive normal-normal intervals (RMSDD). Standard frequency-domain measurements include low frequency (LF) and high frequency (HF)¹⁴. HRV is decreased in systolic HF, and correlates with extent of left ventricular dysfunction. Similar to studies post-myocardial infarction, HF is characterized by a decrease in time-domain indices of HRV, which correlates with severity of left ventricular dysfunction. The relationship between HF severity frequency-domain indices (spectral components) of HRV is more complex, however; HF severity has been correlated with both increased and decreased LF power.^{15, 16 17}

Muscle sympathetic nerve activity (MSNA, bursts/minute) as quantified by direct sympathetic microneurography at the peroneal nerve, has been validated as a tool to study sympathetic nervous system activation in humans with HF^{18–20}, as well as in a variety of other disease processes, including hypertension and obesity²¹. MSNA at rest has consistently been found to be elevated in HF patients when compared to normal controls, and furthermore, life-prolonging therapies for HF patients have also been shown to decrease MSNA^{22, 23}.

Impairment, or decreased responsivity, of arterial and cardiopulmonary (sympatho-inhibitory) baroreflexes are seen in HF.²⁴ It is now recognized that baroreflex-mediated mechanisms are not necessarily a cause of the increased sympathetic drive of HF, but may be a consequence of it. Additional potential mechanisms of the sympathetic activation of HF include increased sensitivity of the muscle metaboreceptors and/or mechanoreceptors located in skeletal muscle, alteration of the central endogenous nitric oxide mechanism, augmentation of central angiotensin II, stimulation of reactive oxidant species, or HF – associated sleep disordered breathing. Further, norepinephrine levels at the nerve terminal may be augmented by prejunctional facilitation of neurotransmitter release via beta-2 adrenergic or angiotensin AT1 receptors^{18, 25}.

Sympathetic Activation and Prognosis in Heart Failure

Sympatho-excitation in HF is initially a compensatory mechanism, with inotropic and chronotropic responses of the heart serving to maintain cardiac output, blood pressure, and organ perfusion. However, prolonged sympathetic over-activity may lead to depletion of cardiac norepinephrine stores and decreased beta-adrenoreceptor density, impairing compensatory sympathetic-stimulated inotropy, thus leading to depressed cardiac function¹³,

26, 27. Norepinephrine also has direct, toxic effects on cardiomyocyte viability²⁸ and is a predisposing factor in the development of cardiac arrhythmias²⁹.

Sympathetic nervous system activation is associated with pathologic ventricular remodeling, increased arrhythmias, sudden death, and increased mortality in chronic HF. Supra-normal levels of plasma norepinephrine correlate with progressive HF and sudden death¹¹. Increased cardiac norepinephrine spillover rates also independently predict worse survival in HF³⁰. Cardiac sympathetic nervous system dysfunction, as indexed by reduced cardiac uptake of radiolabelled I-23 metaiodobenzylguanidine (MIBG), also predicts increased mortality in patients with HF and cardiomyopathy³¹.

Multiple studies have linked HRV abnormalities in HF to prognosis. Depressed HRV predicts hemodynamic compromise, sudden death and death from progressive pump dysfunction^{32, 33}. SDNN has been shown to be strongly predictive of mortality in HF; in the UK-HEART study, SDNN < 50msec was associated with >50% mortality compared to only 5.5% in the group with SDNN > 100msec³⁴. Spectral components of HRV also predict HF prognosis; decreased controlled breathing low frequency power in both derivation and validation samples of an Italian study independently predicted a roughly three-fold increased risk for sudden death³³.

Autonomic changes in HF are linked to activation of renin-angiotensin-aldosterone-systems in HF; standard, life-prolonging neurohormonal blockers for HF – including ACEIs, ARBs, beta-blockers, aldosterone antagonists – are all associated with reduced sympathetic activation and improved autonomic balance^{22, 35–39}. Furthermore, improving mechanical function of the ventricles with cardiac resynchronization therapy is also linked to decreased sympathetic nervous system activation as assessed by HRV analysis and sympathetic microneurography. In fact, sympathoinhibition is a characteristic of clinical responders to biventricular pacing^{39–41}.

Statins in Heart Failure

Several observational studies have linked statin therapy in HF to significantly improved survival. The survival benefit associated with statins in HF patients was first reported in an analysis of 551 advanced, systolic HF patients [LVEF 25±7, age 52±13, 77% NYHA III–IV, 45% ischemic etiology] followed at a single university center⁴². Survival without urgent transplantation at one year was 84% in statin-treated and 70% in non-statin-treated patients (HR 0.45, 95% confidence interval [CI] 0.30 to 0.67). The survival advantage associated with statin therapy was observed in both ischemic and non-ischemic HF subjects. Furthermore, statin therapy was not only associated with decreased all-cause mortality, but was also associated with decreased progressive HF death, and sudden death. Multiple subsequent observational studies in various HF populations have also demonstrated significantly improved survival associated with statin use^{43–48}.

Observational studies have also demonstrated decreased arrhythmia risk in patients treated with statins. In an analysis of the DEFibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, statin use was associated with decreased sudden death and decreased appropriate implantable cardioverter-defibrillator (ICD) shocks in non-ischemic HF patients⁴⁹ (Figure 1). In patients with coronary artery disease and ICDs, statin therapy has been associated with significantly decreased re-occurrence of ventricular arrhythmias^{50, 51}. Statin use has also been correlated with decreased incidence of atrial fibrillation⁵². Reduced activation of the sympathetic nervous system may be, in part, responsible for the decreased sudden death and arrhythmias observed with statin therapy.

Statins' Effect on the Autonomic Nervous System in HF: Animal Studies

Improvement in autonomic nervous system function with statin treatment has been demonstrated in animal models of HF. Pliquett et al. studied autonomic function in rabbits with pacing-induced HF compared to normal control rabbits, focusing on HRV⁵³. Rabbits with HF had significantly reduced HRV, as assessed by SDNN and power spectral analysis compared to non-HF controls. However, HF rabbits fed simvastatin for three weeks had higher HRV than HF rabbits not treated with simvastatin. HRV increased incrementally with simvastatin dose; the HF rabbits fed the highest dose (3mg/kg/day) had HRV similar to non-HF controls, both in terms of SDNN, low frequency power, high frequency power, and total power.

Pliquett et al. also investigated the effects of statin therapy on baroreceptor sensitivity, renal sympathetic nerve activity, and plasma norepinephrine levels in rabbits with pacing-induced HF⁹. Plasma norepinephrine levels were elevated in HF rabbits, compared to controls; however, norepinephrine levels were significantly lower in HF rabbits who received moderate to high dose simvastatin compared to non-statin treated HF animals. Renal sympathetic nerve activity (RSNA), directly measured by surgically implanted electrodes, also confirmed lower sympathoexcitation in those HF rabbits treated with simvastatin. The statin-treated HF animals had lower resting RSNA, as well as lower RSNA response to smoke inhalation and sodium nitroprusside injection compared to HF animals not on statins (Figure 2). Furthermore, baroreflex responses in terms of heart rate and RSNA were depressed in HF rabbits treated with vehicle but restored to near-normal in HF rabbits treated with 1.5 – 3.0 mg/kg/day of simvastatin. Cholesterol levels were unchanged by simvastatin in both studies, suggesting a cholesterol-independent, or pleiotropic, effect of statins on autonomic function.

Statins' Effect on the Autonomic Nervous System: Human Studies

Statin-associated improvements in autonomic function have been observed in non-HF disease states such as coronary artery disease and hyperlipidemia. In a study of patients with previous myocardial infarction referred for cardiac catheterization, patients treated with statins had higher SDNN; furthermore, statin use was an independent predictor of higher HRV on multivariate analysis⁵⁴. In a prospective study of 40 hyperlipidemic subjects with and without coronary artery disease, atorvastatin 20 mg/day for a two year period resulted in significant improvement in time- and frequency- domain indices of HRV, including SDNN, RMSSD, low frequency, and high frequency power compared to controls. LDL level after atorvastatin treatment did not correlate with indices of HRV⁵⁵. In a third study of 37 subjects with combined hyperlipidemia, both atorvastatin and fenofibrate improved time- and frequency-domain indices of HRV⁵⁶.

More recently, the effect of statins on autonomic tone in human subjects with HF has been examined. Three studies have investigated the effect of statins on sympathovagal balance as indexed by HRV, with mixed findings. One small, single-arm study of simvastatin 20 mg/day for six weeks in 25 patients with dilated, non-ischemic cardiomyopathy found no treatment-related change in HRV, as indexed by 5 minute sitting total spectral power, respiratory frequency area with deep breathing (parasympathetic stress) or low-frequency area with Valsalva (sympathetic stress)⁵⁷. Another study of 21 patients with stable, systolic HF (EF < 45%) randomized patients to three months of atorvastatin 40 mg/day vs. placebo. Atorvastatin therapy had no significant effect on time-domain indices of HRV, including SDNN and RMSSD. Atorvastatin therapy impacted frequency domain measures of HRV, with decreased low frequency power and decreased low frequency to high frequency ratio after 3-month treatment period compared to no change seen in controls. The authors concluded that this represented a modest improvement in sympatho-vagal balance, indicating a potential reduction in sympathetic activity.⁵⁸

The largest study to date evaluated 80 NYHA III, systolic HF patients with hyperlipidemia randomized to atorvastatin 10 mg vs. placebo for three months⁵⁹. Those randomized to atorvastatin, compared to controls, showed significant increase in the HRV time-domain indices of SDNN and RMSSD, as assessed by five-minute high resolution ECG at baseline and after three months of treatment (Figure 3). Statin therapy was also associated with decreased QT interval variability and decreased corrected QT interval. Cholesterol lowering was not correlated with changes in HRV or repolarization, again suggesting a mechanism of action of statins not associated with lipid-lowering.

An additional study evaluated the effects of fluvastatin in 29 ischemic HF patients with hyperlipidemia on heart rate recovery, defined as the difference between the heart rate at peak exercise and the first and third minutes of recovery⁶⁰. Decreased heart rate recovery after exercise in HF is associated with high mortality, and is thought to represent an abnormal withdrawal of vagal tone⁶¹. After 3 months of fluvastatin therapy, heart rate recovery was significantly augmented at both one and three minutes after symptom-limited maximum exercise test. The authors concluded that augmentation of heart rate recovery may have represented lessened sympathetic or increased parasympathetic tone associated with statin therapy.

Preliminary reports demonstrate an effect of statins in lowering MSNA in HF. In a single-arm study of 5 HF patients treated with simvastatin 40 mg QD for one month, resting MSNA was significantly lower post – treatment compared to pre-treatment (65 ± 6 vs. 77 ± 2 bursts/100 beats)⁶². In another study of 8 HF subjects already on statin therapy, MSNA increased significantly 8 weeks after discontinuation of statin but returned to baseline 4 weeks after statin therapy was restarted. There was no significant effect of statins on plasma norepinephrine levels.⁶³

Potential Mechanisms for Statins' Modulation of the Autonomic Nervous System

There are several potential mechanisms for the beneficial effects of statins on autonomic nervous system function in HF. Both angiotensin II and nitric oxide have been implicated in the modulation of sympathetic tone by statins in HF. Gao et al. first demonstrated that there is intense free radical stress in the autonomic areas of the brain in the HF state, characterized by upregulation of angiotensin receptors and NADPH oxidase subunits in the rostral ventrolateral medulla as well as NADPH-dependent superoxide anion production⁶⁴. This group subsequently linked autonomic improvement to an effect of simvastatin on inhibition of central angiotensin II and the superoxide pathway⁶⁵. In this study of pacing-induced HF in rabbits, the heightened blood pressure and renal sympathetic nerve activity responses to intracerebral angiotensin II injection seen in CHF animals was abolished by simvastatin therapy. Importantly, simvastatin therapy was also seen to decrease mRNA and protein expression of angiotensin receptor and NADPH oxidase subunits and to inhibit production of superoxide (O_2^-) in the rostral ventrolateral medulla of CHF rabbits.

Investigations in hyperlipidemia have shed light on a potential molecular component for statins' effects on autonomic function. In a cross-over study of HRV in 30 patients with hyperlipidemia, pravastatin therapy resulted in an increase in HF power, an index of parasympathetic responsiveness. Increased HF power correlated with increased expression of α -subunit of the heterotrimeric G-protein, $G\alpha_{i2}$, a molecular component of the parasympathetic signaling component in the heart. Interestingly, simvastatin did not change HRV or $G\alpha_{i2}$ expression, which the authors attributed differences in hydrophobicity between the two statins⁶⁶.

Conclusions

There is increasing evidence that the non-lipid-lowering, “pleiotrophic” effects of statins may prove beneficial to patients with both ischemic and non-ischemic heart failure. Statins’ ability to decrease sympathetic activation and restore autonomic balance has clearly been demonstrated in animal models of heart failure. Preliminary human studies also suggest a positive effect of statins on sympathovagal balance. Additional investigation is required to further delineate the optimal type of statin, dosage, and course of therapy to improve autonomic function and improve outcomes in heart failure.

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Figure 1.

The Kaplan-Meier estimates of arrhythmic sudden death plus resuscitated cardiac arrest among patients treated with statins and those not taking statins in the 458 patients enrolled in the DEFINITE trial. From Goldberger JJ, Subacius H, Schaechter A, et al. Effects of statin therapy on arrhythmic events and survival in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol.* Sep 19 2006;48(6):1228–1233, with permission.

Figure 2.

Original recording of arterial pressure (AP), heart rate (HR), and renal sympathetic nerve activity (RSNA) in 1 conscious heart failure animal (top) and 1 conscious heart failure animal treated with simvastatin (bottom) for 3 weeks. At arrows, an injection of SNP was given intravenously. From Pliquett RU, Cornish KG, Peuler JD, Zucker IH. Simvastatin normalizes autonomic neural control in experimental heart failure. *Circulation*. May 20 2003;107(19): 2493–2498, with permission.

Figure 3.

Heart rate variability parameters in the statin and control groups at baseline and after 3 months of the study (the results are presented as mean + SD). From Vrtovec B, Okrajsek R, Golcnik A, Ferjan M, Starc V, Radovancevic B. Atorvastatin Therapy Increases Heart Rate Variability, Decreases QT Variability, and Shortens QTc Interval Duration in Patients With Advanced Chronic Heart Failure. *Journal of Cardiac Failure*. 2005;11(9):684, with permission.