Published in final edited form as:

J Investig Med. 2004 May ; 52(4): 248–253.

Statin Therapy for Cardiac Hypertrophy and Heart Failure

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Abstract

Cardiac hypertrophy leading to heart failure is a major cause of morbidity and mortality worldwide. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have been shown to inhibit cardiac hypertrophy and improve symptoms of heart failure by cholesterol-independent mechanisms. Statins block the isoprenylation and function of members of the Rho guanine triphosphatase family, such as Rac1 and RhoA. Because Rac1 is a requisite component of reduced nicotinamide adenine dinucleotide phosphate oxidase, which is a major source of reactive oxygen species in cardiovascular cells, the ability of statins to inhibit Rac1-mediated oxidative stress contributes importantly to their inhibitory effects on cardiac hypertrophy. Furthermore, inhibition of RhoA by statins leads to the activation of protein kinase B/Akt and up-regulation of endothelial nitric oxide synthase in the endothelium and the heart. This results in increased angiogenesis and myocardial perfusion, decreased myocardial apoptosis, and improvement in endothelial and cardiac function. Because these effects of statins occur independently of cholesterol lowering, statins may have therapeutic benefits in nonhyperlipidemic patients with cardiac hypertrophy and heart failure.

Keywords

cardiac hypertrophy; heart failure; G proteins; protein kinase Akt; nitric oxide

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or “statins,” are agents that inhibit the rate-limiting enzyme of cholesterol synthesis in the liver, thereby decreasing the hepatic production of cholesterol, increasing the expression of low-density lipoprotein (LDL) receptors, and lowering the circulating levels of LDL cholesterol. Although it is widely accepted that the majority of clinical benefit obtained with statins is a direct result of their lipid-lowering properties, these agents appear to display additional cholesterol-independent or “pleiotropic” effects on various aspects of cardiovascular disease. These effects include improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response in the vascular wall.^{1–4} In normocholesterolemic animals, statin therapy has been shown to protect against stroke,⁵ ischemia-reperfusion injury of the heart,⁶ and vascular inflammatory responses^{7,8} through mechanisms mediated by an increase in endothelium-derived nitric oxide (NO) production.

Many of these cholesterol-independent effects of statins are mediated by their ability to block the synthesis of important isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules. In particular, the inhibition of small guanine

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Presented at the Joint American Federation for Medical Research/American Society for Clinical Investigation Meeting on April 17, 2004, Chicago, IL. Dr. Liao is a recipient of the 2005 AFMR Outstanding Investigator Award.

triphosphate (GTP)-binding proteins, Rho, Ras, and Rac, whose proper membrane localization and function are dependent on isoprenylation,^{9,10} may play an important role in mediating the biologic effects of statins. Although the main impact of statin therapy in cardiovascular disease appears to be predominantly vascular, recent animal and human studies suggest that statins may also have direct beneficial effects on the myocardium. In particular, statins have been shown to attenuate cardiac hypertrophy and improve cardiac function and symptoms in patients with congestive heart failure, irrespective of serum cholesterol levels.^{11–13}

STATINS AND CARDIAC HYPERTROPHY

Cardiac hypertrophy is an adaptive response of the heart to pressure overload. The molecular response to pressure overload is complex and may include modulation of various intracellular signal pathways, such as activation of many protein kinases (mitogen-activated protein kinase and phosphatidylinositol 3 kinase), expression of cardiac fetal genes (atrial natriuretic factor [ANF] and myosin light chain), and increase of protein synthesis. Furthermore, pressure overload leads to the release of secretion and production of vasoactive peptides, such as angiotensin II and endothelin 1, which play pivotal roles in the induction of these hypertrophic responses.^{14,15} Recent studies suggest that the hypertrophic process is also mediated, in part, by an increase in myocardial oxidative stress.^{12,16}

In the myocardium, Ras, Rho, and Rac are involved in the hypertrophic response.^{17,18} Ras-mediated cardiac hypertrophy has been demonstrated both in vitro¹⁹ and in vivo.²⁰ Transgenic mice that overexpress RhoA in the heart develop loss of systolic function and dilated cardiomyopathy.²¹ However, the development of cardiomyopathy is due to abnormal conduction abnormalities rather than a direct modification of myocardial architecture. This effect of RhoA was unanticipated because, previously, several in vitro studies implicated RhoA in the development of hypertrophy.²² Other studies using cultured cardiomyocytes revealed that the activation of Rac is required in phenylephrine-induced cardiomyocyte hypertrophy. In those studies, transfection of myocytes with a dominant-negative mutant of Rac1 completely inhibited the hypertrophic response to phenylephrine.¹⁶ In addition, transgenic mice that specifically expressed activated Rac1 in the myocardium showed severe cardiac hypertrophy and dilatation.²³

Inhibition of this enzyme by statins leads not only to the reduction of cholesterol biosynthesis in the liver but also to the reduction of the synthesis of several isoprenoid intermediates (Figure 1). Members of the Ras and Rho guanosine triphosphatase family are major substrates for post-translational modification by isoprenylation.^{9,10} Ras translocation from the cytoplasm to the plasma membrane is dependent on farnesylation, whereas Rho translocation is dependent on geranylgeranylation.^{1,24} These studies demonstrate that statins inhibit the development of cardiac hypertrophy through inhibition of Ras and Rho isoprenylation, leading to the accumulation of inactive Ras and Rho in the cytoplasm.^{12,25} Indeed, my colleagues and I have recently shown that Rac1 is a key mediator in the hypertrophic response.¹² Overexpression of a dominant-negative mutant of Rac1 (N17Rac1) and, to a lesser extent, RhoA (N19RhoA) inhibited angiotensin II-induced ANF promoter activity. Cotreatment with statins further decreased ANF promoter activity in cells transfected with N19RhoA and N17Cdc42 but not those transfected with N17Rac1. Similarly, cotreatment with geranylgeranyl pyrophosphate (GGPP) reversed the inhibitory effects of statins, although GGPP could not reverse the inhibitory effect of N17Rac1 on ANF promoter activity.

Recent evidence suggests that reactive oxygen species may be involved in the process of cardiac hypertrophy.^{26,27} Reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is a major source of superoxide in cardiovascular cells.²⁸ In the cardiomyocytes, three of these five components, p40^{PHOX} (PHOX = phagocyte oxidase), p47^{PHOX}, and p67^{PHOX}, exist in the

cytosol, forming a complex. The other two components, p22^{PHOX} and gp91^{PHOX}, are bound to the membranes. Various stimuli lead to the phosphorylation of the cytosolic components, and the entire cytosolic complex then migrates to the membrane. Importantly, not only the core subunits are required for activation but also two low-molecular-weight guanine nucleotide-binding proteins, Rac and Rap. During activation, Rac binds GTP and migrates to the membrane with the core cytosolic complex. Therefore, Rac is critically involved in the activation of cardiovascular NADPH oxidase (Figure 2).

A potent stimulator of cardiac hypertrophy, angiotensin II, increases the activity of vascular oxidase through NADPH oxidase activation.^{28,29} Thrombin, platelet-derived growth factor, and tumor necrosis factor (TNF)- α also stimulate NADPH oxidase-dependent superoxide production in vascular smooth muscle cells.^{30–32} Recent studies of the gp91^{PHOX}-deficient mice demonstrated that angiotensin II treatment increased cardiac hypertrophy and collagen content in wild-type but not gp91^{PHOX}-deficient mice.³³ This evidence further supports the hypothesis that myocardial oxidative stress, in particular NADPH oxidase, plays a crucial role in cardiac hypertrophy. For these reasons, it is likely that statins could inhibit cardiac hypertrophy through an antioxidant mechanism involving inhibition of Rac1 geranylgeranylation. Indeed, statins inhibit angiotensin II-induced oxidative stress and cardiac hypertrophy in rodents.¹² This has been observed in clinical studies in which statins inhibit cardiac hypertrophy in humans with hypercholesterolemia.¹¹

STATINS AND HEART FAILURE

The molecular mechanisms of the beneficial effects of statins in heart failure are not completely understood. Heart failure occurs as a result of hemodynamic, metabolic, and neurohormonal abnormalities. Reduced endothelial function is a key pathophysiologic event in heart failure and contributes to the progression from compensated to decompensated heart failure.³⁴ Loss of endothelial function is characterized by down-regulation of NO production and endothelial NO synthase gene expression.^{34–36} The lack of NO contributes to myocardial apoptosis or programmed cell death, a critical event in cardiac remodeling and progression of heart failure.³⁷ The generation of free radicals and higher oxidative stress can cause inactivation of NO in heart failure.³⁸ Statins have been shown to reverse several of the abnormalities seen in association with heart failure. Statins can improve endothelial function and NO production,^{1, 24} inhibit generation of oxygen free radicals,³⁹ and prevent myocyte apoptosis⁴⁰ and may also attenuate vascular inflammation through modulation of the Rho/Rho-kinase pathway.

To determine the efficacy of statins in heart failure, we administered statins to healthy animals and animals with heart failure.⁴⁰ The administration of veratrine, a cholinergic NO-dependent vasodilator, and acetylcholine, an endothelium-dependent vasodilator, resulted in a greater increase in coronary blood flow in statin-treated animals compared with controls. Endothelial NO synthase enzyme expression in the aorta was higher in the statin group compared with controls. Furthermore, basal myocardial oxygen consumption in the statin group was significantly lower than in the control group, suggesting that statins decrease myocardial oxygen consumption and increase myocardial oxygen reserve through an increase in NO production.

To determine if the ability of statin to increase cardiac NO production has beneficial effects in heart failure, my colleagues and I performed additional studies in a canine pacing model of heart failure.⁴¹ The time to the development of end-stage heart failure was longer in the statin group (34 days) compared with the untreated group (29 days). Furthermore, statin-treated dogs had a lower left ventricular (LV) end-diastolic pressure at 4 weeks of pacing compared with the untreated group (18 ± 1 vs 25 ± 1 mm Hg). Endothelium-dependent coronary vasodilation was preserved and myocardial NOS expression was higher in the treated group compared with

the controls. These effects were independent of cholesterol lowering. The findings of this study indicate that statin treatment retards the progression of heart failure, and this may be related to its ability to preserve endothelial function and cardiac NO production.

Because statins can promote angiogenesis,⁴² we investigated whether statins can improve myocardial perfusion and heart failure in Syrian cardiomyopathic hamsters.⁴³ Interestingly, LV fractional shortening decreased from $17 \pm 1\%$ to $9 \pm 2\%$ in the untreated group but did not deteriorate in the statin group ($16 \pm 2\%$ at 6 weeks). Statin-treated animals also exhibited less LV dilatation compared with the untreated group. Myocardial capillary density as a measure of angiogenesis was higher in the statin group compared with the untreated groups, as well as compared with healthy controls. This study demonstrated that the ability of statin to promote new blood vessel formation is not limited to peripheral ischemia but is also seen in heart failure. Indeed, the mechanism is probably due, in part, to the activation of protein kinase Akt, which is stimulated by statins.⁴² The improvement in coronary perfusion may help compensate for the increased demands of a hypertrophied and dilated myocardium and may prevent cardiomyocyte death. These findings suggest that systemic administration of a statin can mimic the effects of local gene transfection into failing hearts on new blood vessel formation and provides a novel mechanism for the benefit of statins in heart failure.

To translate these findings to the clinical setting, my colleagues and I performed a prospective double-blind, placebo-controlled study on 51 patients with symptomatic, nonischemic, dilated cardiomyopathy. Patients were randomly divided into two groups receiving statin ($n = 24$) or placebo ($n = 39$) for 14 weeks.¹³ Although patients receiving statins exhibited a modest reduction in serum cholesterol level compared with patients receiving placebo (130 ± 13 mg/dL vs 147 ± 14 mg/dL), these patients demonstrated a remarkable improvement in exercise endurance, as exhibited by a lower New York Heart Association functional class, compared with patients receiving placebo (2.04 ± 0.06 vs 2.39 ± 0.07 ; $p < .01$). This corresponded to improved LV ejection fraction in the statin group (33 ± 4 to $41 \pm 4\%$; $p < .01$) but not in the placebo group. The improvements in their exercise endurance and heart function were in addition to the improvements already observed with two current treatments for heart failure, β -blocker and angiotensin-converting enzyme inhibitors. Furthermore, plasma concentrations of TNF- α , interleukin-6, and brain natriuretic peptide were lower in the statin group compared with the placebo group. This study indicates that short-term statin therapy improves cardiac function, neurohormonal imbalance, and symptoms associated with idiopathic dilated cardiomyopathy and suggest that statins may have therapeutic benefits in patients with heart failure, irrespective of serum cholesterol levels or atherosclerotic heart disease.

CLINICAL IMPLICATIONS

Strong experimental evidence and some recent clinical studies indicate that statins can prevent cardiac hypertrophy, irrespective of serum cholesterol levels. This effect is most likely mediated by inhibition of Rac1 isoprenylation and includes a reduction in myocardial oxidative stress, suggesting a novel pharmacologic approach to treating cardiac hypertrophy. However, caution should always be exercised when attempting to extrapolate results obtained from animal studies to the clinical setting. Thus, further studies in nonhyperlipidemic patients with cardiac hypertrophy are warranted with statin therapy to determine whether these effects are truly cholesterol independent. Similarly, statins reduce the incidence of heart failure in patients with coronary artery disease.^{44,45} However, this may be due in large part to a reduction in recurrent coronary events via cholesterol reduction and subsequent beneficial effects on LV remodeling. Nevertheless, our findings that short-term statin therapy improves cardiac function should pave the way for further large-scale clinical trials to evaluate the long-term clinical benefits of statin therapy in normocholesterolemic patients with nonischemic, dilated cardiomyopathy.

Acknowledgements

Supported in part by grants from the National Institutes of Health (HL52233) and the American Heart Association Bugher Foundation Award. Dr. Liao is an established investigator of the American Heart Association.

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FIGURE 1.

Cholesterol biosynthesis. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is a rate-limiting enzyme, and this blockade (statins) leads to the reduction of other isoprenoid intermediates such as mevalonate, farnesyl pyrophosphate (PP), and geranylgeranyl PP, as well as intracellular cholesterol. BMP = bone morphogenetic protein; eNOS = endothelial nitric oxide synthesis; ET = endothelin; NAD(P)H = reduced nicotinamide adenine dinucleotide (phosphate); PAI = plasminogen activator inhibitor; PI3 = phosphatidylinositol 3; t-PA = tissue plasminogen activator.

FIGURE 2.

Reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The core enzyme comprises five components: p40^{PHOX} (PHOX = phagocyte oxidase), p47^{PHOX}, p67^{PHOX}, p22^{PHOX}, and gp91^{PHOX}. In the resting cell (*left panel*), three of these five components, p40^{PHOX}, p47^{PHOX}, and p67^{PHOX}, exist in the cytosol as a complex. The other two components, p22^{PHOX} and gp91^{PHOX}, are located in the membranes. Following stimulation by angiotensin II (Ang II), thrombin, platelet-derived growth factor, and tumor necrosis factor- α (*right panel*), the cytosolic component becomes heavily phosphorylated, and the entire cytosolic complex migrates to the membrane. Activation requires the participation, not only of the core subunits but also of two low-molecular-weight guanine nucleotide-binding proteins, Rac and Rap. During activation, Rac binds guanosine triphosphate and migrates to the membrane, along with the core cytosolic complex. NADP = nicotinamide adenine dinucleotide phosphate.