Effect of simvastatin on left ventricular mass in hypercholesterolemic rabbits

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摘要

Abstract

Epidemiological studies showed that hypercholesterolemia is associated with higher left ventricular mass. Endothelin signaling is activated in hyperlipidemic animals and may contribute to progressive ventricular hypertrophy. Simvastatin has been shown to inhibit endothelin-1. However, the behavior of simvastatin on ventricular hypertrophy in hyperlipidemic animals is not well understood. In this study, we evaluated the hemodynamic, biochemical, and morphological responses to simvastatin in cholesterol-fed (1%) rabbits. The left ventricular weight increased 8 wk after cholesterol feeding compared with that in normocholesterolemic rabbits. Simvastatin at a clinical therapeutic dose (1.2 mg x kg(-1) x day(-1)) significantly decreased left ventricular weight by 14% and left ventricular myocyte sizes by 14% as isolated by enzymatic dissociation. Hypercholesterolemia upregulated ventricular preproendothelin-1 mRNA as assessed by real-time quantitative RT-PCR and elevated production of cardiac endothelin-1 concentration. The increased endothelin-1 responses can be inhibited after simvastatin administration. Left ventricular mass indexed by body weight positively correlated with tissue endothelin-1 levels (P = 0.0003). In Langendorff-perfused rabbit hearts, hyperlipidemia led to significant QT prolongation compared with normocholesterolemia, which can be reversed by administering simvastatin. In contrast, simvastatin-induced beneficial effects were reversed by the addition of mevalonate. The addition of bosentan, a nonspecific endothelin receptor blocker, improved the response in hypercholesterolemic rabbits and did not have additional beneficial effects in simvastatin-treated rabbits. The results of the present study suggest that the antihypertropic and electrocardiographic effects of simvastatin at a clinical therapeutic dose are mediated through inhibition of tissue endothelin-1 expression, which is linked to mevalonate metabolism, and result in an amelioration of cardiomyocyte hypertrophy development by an atherogenic diet.