European Journal of Pharmacology 666 (2011) 135–141

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Cardiovascular Pharmacology

Combined atorvastatin and coenzyme Q10 improve the left ventricular function in isoproterenol-induced heart failure in rat

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ARTICLE INFO

Article history:
Received 7 December 2010
Received in revised form 19 April 2011
Accepted 20 April 2011
Available online 9 May 2011

Keywords:
Atorvastatin
Heart failure
Coenzyme Q10
Isoproterenol

ABSTRACT

The effect of atorvastatin on cardiac remodeling, function, and homodynamic parameters in isoproterenol-induced heart failure was evaluated in the present study. A subcutaneous injection of isoproterenol (5 mg/kg/day) for 10 days was used for the induction of heart failure. Isoproterenol administration produced intensive myocardial necrosis and fibrosis with a significant decrease in the arterial pressure indices, heart rate, contractility ($LVdP/dt_{max}$) and relaxation ($LVdP/dt_{min}$), but an increase in the left ventricular end-diastolic pressure. Rats were randomly assigned to control, treatment with only atorvastatin, and treatment with atorvastatin plus coenzyme Q10. Histopathological analysis showed a marked attenuation of myocyte necrosis and interstitial fibrosis in all atorvastatin treated groups ($P<0.001$). A low dose of atorvastatin (5 mg/kg/day) significantly improved the left ventricular systolic pressure, contractility and relaxation ($P<0.01$). On the contrary, a high dose of atorvastatin (20 mg/kg/day) worsened the isoproterenol-induced left ventricular dysfunction by a further reduction of $LVdP/dt_{max}$ from $+2780\pm94$ to $+1588\pm248$ (mm Hg/s; $P<0.01$) and $LVdP/dt_{min}$ from -2007 ± 190 to -2939 ± 291 (mm Hg/s; $P<0.05$). Co-administration of coenzyme Q10 with atorvastatin reversed the hemodynamic depression and the left ventricular dysfunction to a high level ($P<0.001$). There was a lower level of LVEDPs in the atorvastatin + coenzyme Q10 treated groups (3 ± 1 and 4 ± 1.4 versus 8 ± 3.5 and 14 ± 3.6 mm Hg, respectively), thereby suggesting improvement in the myocardial stiffness by the combined coenzyme Q10 and atorvastatin treatment. The atorvastatin therapy attenuated myocardial necrosis and fibrosis in isoproterenol-induced heart failure. However, a high dose of the drug considerably worsened the left ventricular dysfunction and hemodynamic depression, which was reversed by coenzyme Q10 co-administration.

1. Introduction

Statins possess pleiotropic beneficial effects which are independent of their cholesterol lowering actions. Some of these effects include inhibition of cellular proliferation and migration (Glynn et al., 2008) and improvement of the endothelial function (liu et al., 2009). A large number of clinical trials have established the benefits of statins on coronary heart disease events and strokes (Heart Protection Study Collaborative Group, 2003; Law et al., 2003; Shepherd et al., 1995). Atorvastatin has been shown to decrease mortality (Vrtovec et al., 2008) and improve the left ventricular ejection fraction and symptoms of heart failure (Sola et al., 2006; Yamada et al., 2007). In a recent study of randomized controlled trials of statin versus placebo in patients with heart failure, Lipinski et al. (2009) demonstrated that statins are safe and help to improve left ventricular ejection fraction as well as decrease hospitalization for deteriorating heart failure. However, some other trials have challenged the full beneficial effects of statins (Kjekshus et al., 2007; Silver et al., 2004; Tavazzi et al., 2008). Coenzyme Q10 participates in the electron transport during oxidative phosphorilation in mitochonderia and is involved in the production of ATP (James et al., 2004). Deficiencies of coenzyme Q10 were found in patients with heart failure and the observed level of coenzyme Q10 deficiency was correlated to the severity of the disease (Mortensen, 2003). The use of coenzyme Q10 as part of a maintenance therapy in patients with chronic heart failure was suggested. Statins are also known to reduce coenzyme Q10 levels in plasma and myocardium through inhibition of HMG-CoA reductase. Therefore, treatment with statins may further decrease the existing low levels of

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doi:10.1016/j.ejphar.2011.04.061

coenzyme Q10 in patients with heart failure (McMurray et al., 2010). The above mentioned fact, the role of coenzyme Q10 in ATP production in mitochondria and the importance of mitochondria in myocardial function has provoked the hypothesis that statin-induced CoQ10 deficiency may worsen the cardiac function in patients with heart failure. In addition to a reduction in CoQ10 synthesis, statins also influence other isoprenoid intermediates (farnesyl and geranylgeranyl diphosphates) of mevalonate pathway more potently. By inhibition of mevalonate synthesis, statins prevent geranylgeranylation and farnesylation of Ras, RhoA and Rac1 (Liao, 2004), which are the key mediators of hypertrophic responses (Proud, 2004; Sugden, 2003). In a rat model of cardiac hypertrophy, simvastatin prevented the left ventricular hypertrophy (Indolfi et al., 2002) when induced by a pressure overload. Further, another study reported that simvastatin was even more potent in its reduction of left ventricular dysfunction in comparison to captopril (Luo et al., 1999). Isoproterenol is a synthetic β- adernoceptor agonist that its subcutaneous injection induces heart failure and suppressed cardiac functions because of myocardial hypertrophy and fibrosis (Ojha et al., in press). The present study aims to investigate the effects of atorvastatin on cardiac function, remodeling, and progression to heart failure in isoproterenol induced heart failure in rats. It also aims to examine whether co-administration of atorvastatin with coenzyme Q10 has an impact on these effects.

2. Materials and methods

2.1. Animals

Male Wistar rats (260 ± 20 g) were used in this study. The animals were given food and water ad libitum. They were housed in the Animal House of Tabriz University of Medical Sciences at a controlled ambient temperature of 25 ± 2 °C with 50 ± 10% relative humidity and a 12-h light/12-h dark cycle. The present study was performed in accordance with the Guide for the Care and Use of Laboratory Animals of Tabriz University of Medical Sciences, Tabriz-Iran (National Institutes of Health Publication No 85-23, revised 1985).

2.2. Chemical reagents

Atorvastatin was a generous gift from Sobhan Pharmaceutical Inc (Tehran-Iran). Isoproterenol was bought from Sigma Chemicals Co, while coenzyme Q10 (Ubiquinon) was purchased from Viva Pharmaceutical Inc (Canada). The other reagents were of a commercial analytical grade.

2.3. Induction of myocardial injury

Isoproterenol was dissolved in normal saline and injected subcutaneously to rats (5 mg/kg) daily for 10 consecutive days at an interval of 24 h to induce experimental heart failure (Benjamin et al., 1989).

2.4. Experimental protocol

The animals were randomized into 8 groups consisting of 6 rats each. Rats in group 1 (normal control) received a subcutaneous injection of physiological saline (0.5 ml) and were left untreated for the whole period of the experiment. Rats in group 2 received oral administration of normal saline for 25 days and at the 15th day were subcutaneously injected 5 mg/kg of isoproterenol once at an interval of 24 h for 10 consecutive days. Rats in groups 3 to 5 were pretreated orally, using gastric gavages, with atorvastatin (5, 10 and 20 mg/kg, respectively) for 25 days and at the 15th day were subcutaneously injected 5 mg/kg of isoproterenol once at an interval of 24 h for 10 consecutive days. Rats in group 6 were given coenzyme Q10 (Ubiquinon; 10 mg/kg) orally for 25 days and at the 15th day were subcutaneously injected 5 mg/kg of isoproterenol once at an interval of 24 h for 10 consecutive days. Rats in groups 7 to 8 were pretreated orally with atorvastatin (5 and 20 mg/kg; respectively) plus 10 mg/kg coenzyme Q10 for 25 days and at the 15th day were subcutaneously injected 5 mg/kg of isoproterenol once at an interval of 24 h for 10 consecutive days. All the rats were made to fast overnight. However, they had free access to water at the last administration of the drug.

2.5. Hemodynamic measurements

At the end of the experiment, the animals were anesthetized with sodium pentobarbital (60 mg/kg; i.p). The trachea was cannulated for artificial respiration when the rats no longer responded to external stimuli. Next, the systemic arterial blood pressure was recorded from a catheter inserted into the left carotid artery. A standard limb lead I ECG was monitored continuously throughout the experimental period. The mean arterial blood pressure was calculated from the systolic and diastolic blood pressure traces. The heart rate was calculated from the ECG. To evaluate the cardiac left ventricular function, a Mikro Tip catheter transducer (Millar Instruments, INC) was advanced to the lumen of the left ventricle. This helped to measure the left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), maximum and minimum rates of developed left ventricular pressure ($LVdP/dt_{max}$ and $LVdP/dt_{min}$) and

Table 1
General animal characteristics parameters and tissue weight ratios in the control group and in rats treated with isoproterenol (i.p; Heart failure) or with isoproterenol + atorvastatin or + coenzyme Q10 (orally).

Groups **N = 6**	Baseline BW (g)	Δ BW (g)	LV wet to dry weight ratio (g/g)	LV wet to HW ratio (g/g)	Wet HW to BW ratio (g/kg)
Control	262 ± 8	23 ± 1.1	4.24 ± 0.04	0.63 ± 0.03	3.10 ± 0.26
Isoproterenol	269 ± 9	11 ± 0.9[a]	4.62 ± 0.10	0.65 ± 0.02	4.82 ± 0.29
Atorvastatin (5 mg/kg) + isoproterenol	278 ± 12	15 ± 1.3	4.35 ± 0.05	0.69 ± 0.015	4.08 ± 0.09
Atorvastatin (10 mg/kg) + isoproterenol	274 ± 13	14 ± 1.5	4.22 ± 0.37	0.67 ± 0.02	4.02 ± 0.05
Atorvastatin (20 mg/kg) + isoproterenol	282 ± 15	14 ± 1.8	4.25 ± 0.70	0.70 ± 0.03	3.95 ± 0.15
Coenzyme Q10 (10 mg/kg) + isoproterenol	263 ± 7	13 ± 0.8	4.36 ± 0.06	0.69 ± 0.02	4.18 ± 0.20
Atorvastatin (5 mg/kg) + Q10 + isoproterenol	275 ± 9	28 ± 1.5[d]	4.08 ± 0.2[b]	0.66 ± 0.04	3.79 ± 0.09[c]
Atorvastatin (20 mg/kg) + Q10 + isoproterenol	258 ± 13	17 ± 1.1[b]	4.28 ± 0.05	0.65 ± 0.05	4.27 ± 0.18

Data are expressed as mean ± sem. Baseline BW, body weights immediately prior to the drug administration; Δ BW, increase in body weight over treatment period. LV, left ventricle; W, weight; and HW, heart weight.
[a] P<0.01 from respective control value.
[b] P<0.05 from isoproterenol treated group using one way ANOVA with Student–Newman–Keuls post hoc test.
[c] P<0.01 from isoproterenol treated group using one way ANOVA with Student–Newman–Keuls post hoc test.
[d] P<0.001 from isoproterenol treated group using one way ANOVA with Student–Newman–Keuls post hoc test.

Table 2
Effects of atorvastatin alone or in combination with coenzyme Q10 (orally) on hemodynamic and left ventricular functions in rats treated with isoproterenol (i.p).

Groups N = 6	Mean arterial pressure (mm Hg)	Herat rate (bpm)	LVSP (mm Hg)	LVEDP (mm Hg)	LV dP/dt/P (1/s)
Control	86 ± 4.7	333 ± 18	119 ± 6	8 ± 3.1	11 ± 0.9
Isoproterenol	56 ± 3.7[b]	224 ± 33[a]	67 ± 9[a]	11 ± 1.5	5.5 ± 0.6[b]
Atorvastatin (5 mg/kg) + isoproterenol	69 ± 3.2	286 ± 6	127 ± 26[c]	7.6 ± 1.9	7 ± 0.3
Atorvastatin (10 mg/kg) + Isoproterenol	58 ± 4.0	280 ± 17	85 ± 15	8 ± 3.5	6.2 ± 0.8
Atorvastatin (20 mg/kg) + isoproterenol	52 ± 2.5	272 ± 7	57 ± 10	14 ± 3.6	4.9 ± 1.1
Coenzyme Q10 (10 mg/kg) + isoproterenol	61 ± 5.5	267 ± 21	95 ± 9	5.4 ± 1.6	6.6 ± 0.6
Atorvastatin (5 mg/kg) + Q10 + isoproterenol	84 ± 7.0[c]	299 ± 23	114 ± 8	3 ± 1[c]	7.7 ± 1
Atorvastatin (20 mg/kg) + Q10 + isoproterenol	82 ± 13[c, d]	289 ± 19	129 ± 24[c]	4 ± 1.4[c,d]	7.4 ± 0.6

Data are expressed as mean ± sem. LVSP, left ventricular systolic pressure; and LVEDP, left ventricular end diastolic pressure.
[a] P<0.05; from respective control value.
[b] P<0.01 from respective control value.
[c] P<0.05 as compared with isoproterenol treated group.
[d] P<0.01 compared with atorvastatin (20 mg/kg) treated group using one way ANOVA with Student–Newman–Keuls post hoc test.

the rate of pressure change at a fixed right ventricular pressure (LV*d*P/*dt*/P) (Garjani et al., 1995). All the parameters were continuously recorded using a Powerlab system (AD Instruments, Australia).

2.6. Tissue weights

After the hemodynamic measurements, the animals were killed by an overdose of pentobarbital and the hearts were removed and weighed. The tissues were then cut into small pieces for drying at 55 °C until a constant weight was reached. The wet to body weight ratios and the wet to dry weight ratios of the tissues were calculated to assess the degree of congestion.

2.7. Histopathological examination

A separate group of rats (n = 4) treated with isoproterenol and isoproterenol plus atorvastatin (5, 10, and 20 mg/kg) was prepared for the histopathological examination. The cardiac apex was excised and fixed in neutral buffered formalin. The tissues were embedded in paraffin, sectioned at 5 μm and stained with hematoxylin and eosin (H&E) for evaluation of histology, and Gomeri trichrome for distinguishing muscle and interstitial connective tissue. Myocardial fibrosis and necrosis was evaluated in each section of the heart tissue using a morphometric point-counting procedure (Benjamin et al., 1989). Two persons graded the histopathological changes as 1, 2, 3, and 4 for low, moderate, high, and intensive pathological changes, respectively.

2.8. Statistics

Data were presented as mean ± sem. One way ANOVA was used to make comparisons between the groups. If the ANOVA analysis indicated significant differences, a Student–Newman–Keuls post test was performed to compare the mean values between the treatment groups and the control. Any differences between groups were considered significant at P<0.05.

3. Results

3.1. Effects of atorvastatin and coenzyme Q10 on the body and tissue weights

Weight gain, which was greatly reduced (P<0.001) after isoproterenol injection (Table 1), was significantly high (P<0.001 and P<0.05) in the atorvastatin (5 and 20 mg/kg) plus coenzyme Q10 (10 mg/kg) treated groups in comparison to rats treated with only isoproterenol. The left ventricle wet to dry weight ratio, left ventricle to heart weight ratio, as well as heart weight to body weight ratio were determined to assess the extent of heart hypertrophy developed by the injection of isoproterenol (Table 1). All the three ratios were higher in the isoproterenol treated rats. Pre-treatment with atorvastatin or atorvastatin plus coenzyme Q10 produced a slight reduction in the left ventricle wet to dry weight ratio as well as in the heart to body weight ratio in comparison to the isoproterenol treated rats. These reductions were significant (P<0.05; P<0.01 respectively; Table 1) in the group treated with 5 mg/kg atorvastatin plus coenzyme Q10 (10 mg/kg).

3.2. Effects of atorvastatin and coenzyme Q10 on the hemodynamic responses

The mean arterial blood pressure significantly decreased from 86 ± 4.7 mm Hg in normal control to 56 ± 3.7 mm Hg in the isoproterenol treated group (P<0.01; Table 2). There was a slight, but not significant increase in the blood pressure to 69 ± 3.2 and 61 ± 5.5 mm Hg, respectively after treatment with 5 mg/kg atorvastatin or coenzyme Q10 (10 mg/kg). However, compared with both isoproterenol and isoproterenol plus atorvastatin treated rats, co-

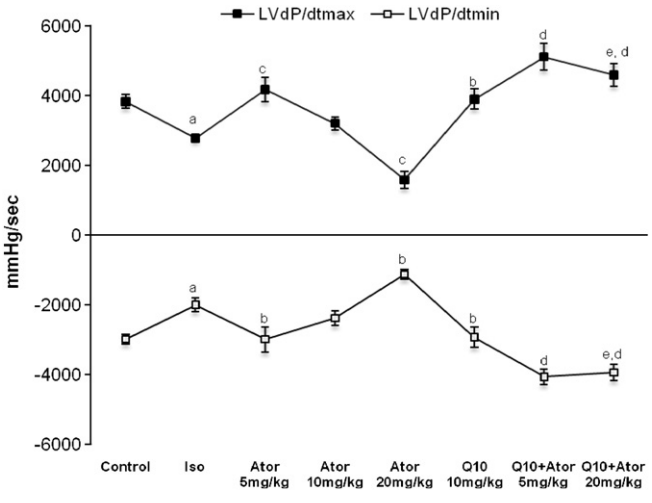

Fig. 1. Left ventricular maximal and minimal rates of pressure increase (LV dP/dt_{max}; LV dP/dt_{min}) in the control group and in the rats treated with isoproterenol (rats with left heart failure), isoproterenol plus atorvastatin, or isoproterenol plus atorvastatin + coenzyme Q10. Iso: isoproterenol; Ator: atorvastatin. Values are mean ± sem (n = 6). [a]P<0.001 from respective control value; [b]P<0.05, [c]P<0.01, [d]P<0.001 as compared with isoproterenol treated group and [e]P<0.001 compared with atorvastatin (20 mg/kg) treated group using one way ANOVA with Student–Newman–Keuls post hoc test.

administration of atorvastatin with Q10 (10 mg/kg) caused a significant elevation in mean arterial pressure ($P<0.05$; Table 2) closer to normal values. The intraventricular pressures were measured to determine the degree of the left ventricular responses to the isoproterenol injection. Isoproterenol reduced the left ventricular systolic pressure (LVSP) from 119 ± 6 to 67 ± 9 mm Hg ($P<0.05$). A low dose of atorvastatin (5 mg/kg) significantly increased the LVSP to 127 ± 26 ($P<0.05$), while a high dose (20 mg/kg) decreased it to 57 ± 10 mm Hg (Table 2).

There was an increase of 38% in the LVEDP in the isoproterenol received rats, thereby indicating left ventricular dysfunction. All the three doses of atorvastatin (5, 10, and 20 mg/kg) had no significant effect on this elevation. However; the value was the highest in the group treated with the high dose (20 mg/kg) of atorvastatin (14 ± 3.6 mm Hg). Administration of atorvastatin with doses of 5 and 20 mg/kg with coenzyme Q10 improved the left ventricular function by lowering the left ventricular end diastolic pressure from 11 ± 1.5 mm Hg to 3 ± 1 and 4 ± 1.4 mm Hg, respectively in rats with heart failure (Table 2; $P<0.05$). Except a significant ($P<0.05$) reduction of heart rate in isoproterenol injected rats, this parameter was not altered significantly by any treatments (Table 2).

When compared with the normal control, the rats with left ventricular dysfunction (isoproterenol group) demonstrated a fall in the values of the left ventricular maximal and minimal rates of pressure (LV dP/dt_{max}; LV dP/dt_{min}, $P<0.05$: Fig. 1) as well as a lower rate of pressure change at a fixed ventricular pressure (LV $dP/dt/P$, $P<0.01$; Table 2). Similar to LVSP changes, these indices of myocardial contractility showed a marked improvement ($P<0.01$) by the low dose of atorvastatin alone (5 mg/kg) and coenzyme Q10 alone (10 mg/kg). On contrary, the high dose of atorvastatin (20 mg/kg) worsened the isoproterenol-induced left ventricular dysfunction by a further and very significant ($P<0.01$; Fig. 1) reduction of contractility (LV dP/dt_{max}) and relaxation (LV dP/dt_{min}). Co-administration of coenzyme Q10 reversed these reductions very highly ($P<0.001$; Fig. 1) when compared with the isoproterenol and isoproterenol plus atorvastatin (20 mg/kg) treated groups.

3.3. Histopathological examination of the cardiac tissues

In the normal control group, the myocardial fibers were arranged regularly with clear striations. No apparent degeneration or necrosis was observed (Fig. 2). Histological sections of the isoproterenol treated hearts showed widespread subendocardial necrosis, hypertrophia, and abundant fibroblastic hyperplasia with capillary dilatation and leukocyte infiltration (Figs. 2 and 3). All the three doses of atorvastatin significantly prevented inflammatory responses and

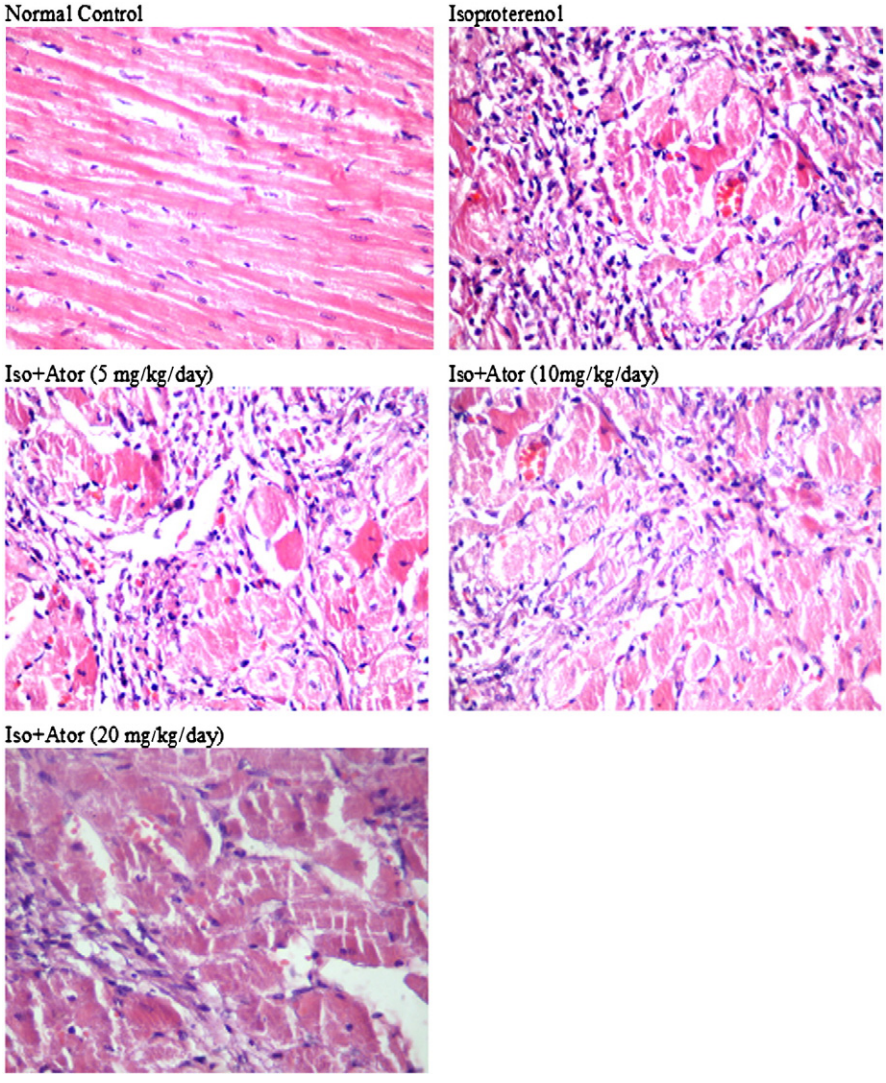

Fig. 2. Photomicrographs of sections of rat cardiac apexes. Heart tissue of a rat treated with isoproterenol shows intensive fibrosis, cardiomyocyte necrosis, and focal mononuclear cell infiltration. Pretreatment with atorvastatin demonstrates a marked improvement. Iso: isoproterenol; Ator: atorvastatin. H&E (40 M).

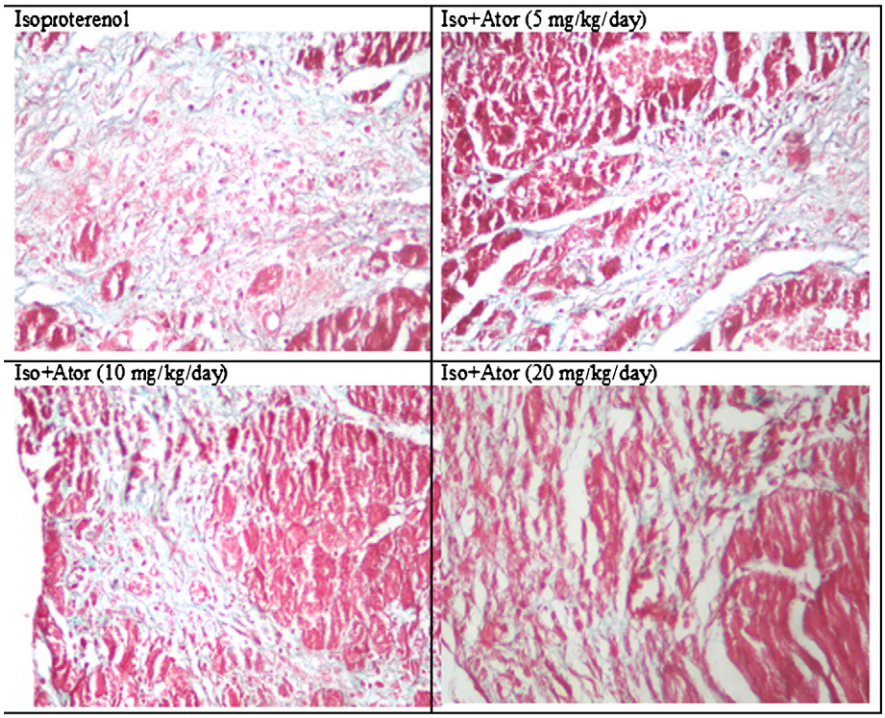

Fig. 3. Heart tissue of a rat treated with isoproterenol shows an intensive fibrosis and angiogenesis. Pretreatment with atorvastatin significantly prevented the fibrosis. Iso: isoproterenol; Ator: atorvastatin. Gomeri's one-step Trichrom method (40 M).

myocardial necrosis and fibrosis. Atorvastatin with doses of 5, 10, and 20 mg/kg/day reduced the isopreterenol-induced fibrosis dose dependently by 25% ($P<0.05$), 50% ($P<0.01$), and 75% ($P<0.001$), respectively as shown in Fig. 4.

4. Discussion

A subcutaneous injection of isoproterenol (5 mg/kg) administered for 10 days resulted in cardiac hypertrophy, myocyte necrosis, fibroblast proliferation, and connective tissue accumulation with decreased myocardial compliance and inhibition of diastolic and systolic functions. This was very similar to the homodynamic and pathological changes seen in human chronic heart failure.

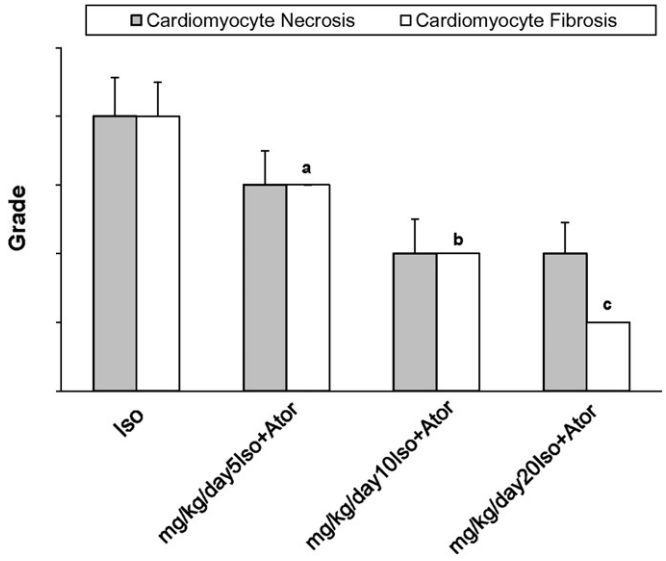

Fig. 4. Grading of histopathological changes in the rat's cardiac apex tissues. Grades 1, 2, 3, and 4 show low, moderate, high and intensive pathological changes, respectively. Iso: isoproterenol; Ator: atorvastatin. Values are mean ± sem ($n=4$). [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$ as compared with isoproterenol treated group using one way ANOVA with Student–Newman–Keuls post hoc test.

The effect of statins on myocardial hypertrophy and fibrosis has been reported in several animal studies (Chang et al., 2009; Saka et al., 2006; Zhou et al., 2008). However, there was some controversy among the previous studies, possibly because of differences in the animal models, statins, lipophilicity, duration of treatments, doses, and experimental protocols. Loch et al. (2006) reported that rosuvastatin attenuates hypertension induced cardiovascular remodeling in the DOCA-salt hypertensive rats without affecting the blood pressure. Conversely, another study showed that the rosuvastatin treatment in LNAME-induced hypertensive rats improved the peripheral vascular resistance with no effect on the collagen content (Susic et al., 2003). Recently, Chang et al. (2009) reported that rosuvastatin therapy does not improve the left ventricular hypertrophy in hypertensive rats with established ventricular hypertrophy, but attenuates myocardial fibrosis and left ventricular stiffness. A study by Sola et al. (2006) showed that the left ventricular systolic function in patients with non-ischemic heart failure was improved after the atorvastatin treatment, in parallel with decreasing left ventricular remodeling and serum inflammation markers. Similarly, it was observed that atorvastatin produced favorable effects on lung remodeling and right ventricular hypertrophy and dysfunction associated with heart failure in rats (Jiang et al., 2010).

In addition, several clinical trials were published on the effects of statins in chronic heart failure. The published Treating to New Targets (TNT) study involving patients with stable coronary disease investigated the efficacy of 80 mg versus 10 mg atorvastatin. The TNT study excluded patients with a left ventricular ejection fraction lower than 30%. However, a pre-specified secondary outcome of the TNT trials was the incidence of hospitalization with a primary diagnosis of CHF. It was observed that 3.3% of the patients on atorvastatin 10 mg vs. 2.4% of the patients on atorvastatin 80 mg were hospitalized with a primary diagnosis of congestive heart failure, thereby representing a

26% decreased hospitalization rate for congestive heart failure in the high dose atorvastatin group (LaRosa et al., 2005). A similar recent randomized trial conducted by Strandberg et al. (2009) demonstrated that atorvastatin 80 mg was more efficient in comparison to simvastatin 20 to 40 mg in preventing hospitalization for heart failure in patients with previous myocardial infarction. Thus, these trials suggest that the incidence of new onset congestive heart failure in patients with coronary disease can be reduced with atorvastatin therapy. In the present study, administration of atorvastatin in all doses of 5, 10, and 20 mg/kg/day for 25 days clearly and dose dependently improved myocardial injury, necrosis and massive fibrosis in the isoproterenol treated rats. However, atorvastatin had contradictory effects on the left ventricular function. Isoproterenol administration significantly decreased the arterial pressure indices, heart rate, contractility ($LVdP/dt_{max}$) and relaxation ($LVdP/dt_{min}$), and increased the left ventricular end-diastolic pressure. Pre-treatment with a low dose of atorvastatin (5 mg/kg) favorably modulated almost every studied parameter in the isoproterenol induced left ventricular dysfunction. However, a high dose of the drug (20 mg/kg) considerably worsened both the systolic and the diastolic parameters.

Myocardial hypertrophy and fibrosis are the major pathological components of chronic heart failure. Undeniably, the blocking of cardiac hypertrophy and fibroblast proliferation is effective for treating cardiac dysfunction in chronic heart failure. Statins inhibit the rate-limiting step of the mevalonate pathway (Goldstein and Brown, 1990), which is essential for the synthesis of various compounds, including cholesterol and a number of non-steroid isoprenylator intermediates, such as farnesyl and granylgrany diphosphate or other phosphorylated products. There are small GTP-binding proteins including Ras, Rho and Rab amongst the isoprenylated proteins which are involved in proliferation, apoptosis, vascular NADPH oxidase, and endothelial No synthesis. In fact, inhibition of isoprenoid synthesis by statins might explain their beneficial effects on cardiac hypertrophy and fibrosis in heart failure.

However, mevalonate is not just a precursor for isoprenoids. It can also be converted to coenzyme Q10. In the heart, coenzyme Q10 is most abundant. Further, it represents an essential component of the mitochondrial respiratory chain, and is a lipid-soluble antioxidant. Reduced ATP synthesis has been demonstrated in the isolated cardiac mitochondria from failing animal and human hearts (Pepe et al., 2007). It is evident that the diminished mitochondrial energy metabolism in the failing heart mostly involves failure in the activity of the electron transport chain and the free radical scavenging proteins. Thus, coenzyme Q10 may act beneficially in the pathophysiology of advancing heart failure.

Statins have been shown to decrease the level of coenzyme Q10 in the blood of patients with cardiovascular disease (Mortensen et al., 1997; Rundek et al., 2004; Watts, 1993). De Pinieux et al. (1996) reported coenzyme Q10 depletion in patients treated with statins in association with elevated lactate to pyruvate ratios and mitochondrial dysfunction. This depletion could be principally important in heart failures, where the coenzyme Q10 levels are already low.

In the present study, coenzyme Q10 significantly improved the hemodynamic parameters and the left ventricular functions in isoproterenol induced heart failures in rats. Furthermore, animals treated with atorvastatin plus coenzyme Q10 exhibited an obvious improvement in weight gain and physical activity. The beneficial effects of the combination treatment of coenzyme Q10 and atorvastatin were clearly observed with respect to myocardial hypertrophy assessed as left ventricular congestion and heart weight to body weight ratio as well as left ventricular contractility and relaxation. Left ventricular end diastolic pressure was also lower in the atorvastatin + coenzyme Q10 group, thereby suggesting improvement in the myocardial stiffness. Coenzyme Q10 supplementation in isoproterenol injected rats with worsening systolic and diastolic functions by the high dose of (20 mg/kg) atorvastatin improved the cardiac performance. Beneficial effects of atorvastatin in heart failure may relate to its pleotropiuc actions including improved myocardial anti-necrotic and anti-fibrotic effects and anti-inflammatory processes. However, in failing hearts these beneficial effects might be encountered by detrimental effects of coenzyme Q10 depletion, particularly if such depletion is strengthened by a high dose of statins.

Despite the beneficial anti-hypertrophic and anti-fibrotic effects of atorvastatin in heart failure, high doses of the drug may cause a further decrease in the already low levels of coenzyme Q10 in patients with chronic heart failure. This could possibly exaggerate the left ventricular depression. Thus, coenzyme Q10 supplementation could counter this probable side effect by replacing the endogenous levels as well as producing a synergistic action on oxidative stress.

Acknowledgments

The present study was supported by a grant from the Research Vice Chancellors of Tabriz University of Medical Sciences; Tabriz, Iran.

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