Int J Clin Exp Med 2017;10(7):10690-10696
www.ijcem.com /ISSN:1940-5901/IJCEM0051329

Original Article

Effects of rosuvastatin on post-infarction cardiac function and its correlation with serum cytokine level

Xufang Sun[1], Dedong Xu[2], Lingmei Li[3], Baozhong Shan[4]

Departments of [1]Intensive Care Unit, [2]Anesthesiology, [4]Stomatology, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong Province, China; [3]Jinan Health and Family Planning Information Center, Jinan, Shandong Province, China

Received February 20, 2017; Accepted March 17, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: Acute myocardial infarction is necrosis of cardiomyocytes caused by acute and persistent ischemia/hypoxia of coronary artery. Myocardial infarction has rapid onset and can induce heart failure, arrhythmia or even heart rupture. This study aimed to investigate the effect of Rosuvastatin on ventricular reconstruction and cardiac function after infarction, and to analyze its correlation with serum cytokines. C57BL6 mice were recruited to generate myocardial infarction model by coronary artery ligation. Experimental mice were divided into three groups and received saline, 2.5 mg/(kg/d) and 5 mg/(kg/d) Rosuvastatin by gavage. Cardiac function was evaluated by ultrasound examination to analyze LVDS, LVDD, LVFS and LVEF. Heart was collected by surgery and prepared in paraffin-based sections to examine infarction area. ELISA was used to test serum TNF-α, IL-6 and IL-10 expression levels. By analyzing cardiac function indexes including LVDD, LVDS, LVEF and LVFS, high dosage of Rosuvastatin treatment significantly lower LVDD or LVDS, plus higher LVEF and LVFS ($P<0.05$ compared to model group). No significant difference was found regarding cardiac infarction area among all groups. Serum cytokine assay showed that high dosage of Rosuvastatin remarkably decreased TNF-α level and increased IL-6 and IL-10 concentrations ($P<0.05$ compared to model group). Rosuvastatin treatment on myocardial infarction mice improved cardiac functions and alleviated ventricular reconstruction. Rosuvastatin can alleviate cardiomyocyte injury and protect cells via mediating expression of inflammatory cytokine expression.

Keywords: Myocardial infarction, rosuvastatin, cardiac function, ventricular reconstruction, TNF-α, IL-6, IL-10

Introduction

Myocardial infarction has rapid onset and can induce heart failure, arrhythmia or even heart rupture [1]. Myocardial infarction is acute and persistent necrosis of myocardial tissues with ischemia and hypoxia due to rupture of coronary artery atherosclerosis plaque, platelet aggregation and thrombosis formation to block artery cavity. Moreover, rapid increase of myocardial oxygen consumption or coronary artery spasm can also induce acute myocardial infarction [2]. After acute myocardial infarction, cardiomyocytes may develop changes of structure, function and phenotype of heart, forming myocardial reconstruction [3]. Such reconstruction and altered cardiac function post-infarction are closely correlated with heart failure. Therefore, the intervention of myocardial reconstruction after infarction is of critical importance for decreasing mortality of myocardial infarction patients and preventing heart failure [4].

Ventricular reconstruction process after infarction is due to altered gene expression in cardiomyocytes, further causing interaction of intracellular molecules and cell-to-cell interaction, thus manifesting myocardial hypertrophy, apoptosis and fibroblast proliferation, extracellular matrix (ECM) degradation and fiber aggregation at cellular level [5]. Meanwhile, other studies found significantly elevated cell inflammatory factors including TNF-α, IL-6 and IL-10 and matrix metalloproteinase (MMP) in myocardial infarction patients undergoing reconstruction [6]. Therefore, it is proposed that cellular inflammatory factor and MMP expression level might be related with myocardial reconstruction [7].

Rosuvastatin is one selective HMG-CoA reductase inhibitor [8]. Statin drugs have modulatory function for blood lipid level. Previous study found that Rosuvastatin could decrease the risk of myocardial infarction, stroke and coronary artery reconstruction [9]. Various clinical

studies showed that Rosuvastatin effectively improved cardiac function and endothelial function in coronary heart disease and myocardial infarction patients, and modulated blood lipid to inhibit inflammatory response [10, 11]. This study aimed to investigate the effect of Rosuvastatin on cardiac function after infarction and its correlation with serum cytokines such as TNF-α, IL-6 and IL-10.

Materials and methods

Experimental animal grouping

C57BL6 mice (6 weeks old) were recruited as research objects. A total of 48 C57BL6 mice were purchased from Shandong University Laboratory Animal Center, including 24 males and 24 females, with average body weight at 31.6±2.5 g. All experimental mice were divided into myocardial infarction group (N=36) and control/Sham group (N=12). Experimental group received normal diet and food and water ad libitum, and were kept under 25°C with 60±10% relative humidity.

Mice were used for all experiments, and all procedures were approved by the Animal Ethics Committee of Jinan Central Hospital Affiliated to Shandong University.

Generation of mouse myocardial infarction model

All mice were acclimated and weighted. 60 mg/kg hydrate chloral was used for anesthesia via intraperitoneal injection. EKG electrode was connected, and respiratory machine was connected to the tracheal intubation at 100 per min. Chest skin was cut between 3rd and 4th rib of left stenosis, left chest cavity was opened by blunt separation of chest muscle layer. The pericardial sac was opened, and nylon suture was sued to ligate 1/3 of mouse coronary artery. Significant elevation of ST segment on electrode II on EKG indicated successful ligation. In control (Sham) group, nylon suture was used to penetrate cardiac muscle on left descending branch but without ligation, leading to insignificant elevation of ST segment. After surgery, heart was relocated, followed by suture of chest cavity and skins. EKG monitor and respiratory machine were removed after obtaining stable vital signs. 20000 U penicillin was injected intramuscular to prevent infection [12].

Rosuvastatin drug delivery

In those mice with successful surgery, 12 mice in Sham group were recruited as group A (control). The other 36 mice with completed myocardial infarction model generation were randomly divided into group B, C and D (N=12 each). Group C and group D received 2.5 mg/(kg.d) and 5 mg/(kg.d) Rosuvastatin by gavage for 4 week normal feeding. Group A and B mice received equal volume of saline by gavage, for 4-week feeding along with group C and D.

Cardiac function evaluation

Mice were anesthetized by 60 mg/kg hydrate chloral. Long-axial 2-D images of left ventricles adjacent to the stenosis were obtained. Using HPSONOS5500 ultrasound, probe frequency was set at 7.5 MHz and was placed in a vertical line against ventricle septum and posterior wall of left ventricle to obtain echocardiography. Interventricular septum (INS), left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVDS) were measured. Left ventricular ejection fraction (EF) and left ventricular fractional shortening (LVFS) were measured by improved Simpson method [13].

Measurement of myocardial infarction area

All mice used in the experiment were fed for 4 weeks, and were sacrificed by 10% KCl infusion following blood collection (2 mL). The chest cavity was opened to harvest the heart, which was rinsed in pre-cold saline to remove residual blood. Water was drained by filter paper, and was separated for left ventricles using scalpel. All tissues were sectioned horizontally for frozen in liquid nitrogen and for fixation in 10% neutral buffered formalin for paraffin embedding. 5 μm slices were prepared for immunohistochemistry (IHC) and HE staining.

Paraffin-based sections were firstly dried at 30 min at 60°C, and were dewaxed by 15 min xylene immersion. Xylene was removed by gradient ethanol, followed by twice rinsing in distilled water. After drying out, hematoxylin was used for 15 min staining, followed by water rinsing, 1% HCl-ethanol differentiation for 30 s, and 15 min immersion in distilled water. After dry-

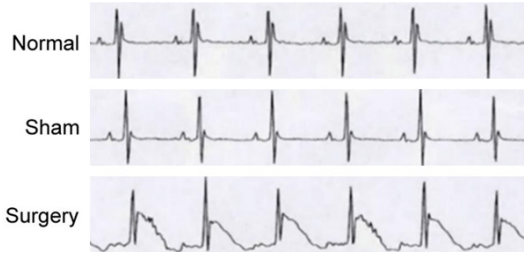

Figure 1. EKG pattern of mouse myocardial infarction model.

ing out, slices were stained in 1% eosin buffer for 3 min, and was carefully dehydrated in gradient ethanol following 70% ethanol. Slices were immersed in xylene-ethanol (1:1) for 5 min, followed by 15 min xylene immersion. And were mounted by resin for observation of infarction area under light field microscope to investigate cell/tissue morphology of infarction area and peripheral regions.

ELISA assay

Blood samples collected from experimental mice were centrifuged to separate serum, which was tested for TNF-α, IL-6 and IL-10 levels by ELISA test kits (Abcam). In brief, 100 μL mouse serum was added into 96-well plate, followed by incubation with 100 μL PBS (pH 7.4) for 4°C overnight incubation. After PBS rinsing, 2% H_2O_2-ethanol solution was used to block endogenous peroxidase activity. Non-specific binding site was blocked by adding 1% BSA solution. With PBS rinsing, rabbit anti-mouse TNF-α, IL-6 and Il-10 antibody (1:1000 dilution) was added for 37°C incubation for 2 h. Excess antibody was washed out, with the addition of biotin labelled goat anti-rabbit secondary antibody (1:200) was added for 37°C incubation for 1.5 h. Excess secondary antibody was washed out, followed by the addition of OPD development substrate for 6 min development at room temperature. 0.2 mM H_2SO_4 was added to stop the reaction. Contents of TNF-α, IL-6 and IL-10 were measured by a microplate reader (Biotek). Immunohistochemistry (IHC) staining was performed following previous methods [9].

Statistical analysis

All data were presented as mean ± standard deviation (SD). SPSS2.0 software was used for data analysis. One-way analysis of variance (ANOVA) was used for between-group comparison. A statistical significance was defined when $P<0.05$.

Results

Generation of mouse myocardial infarction model

Mouse myocardial infarction model was generated by ligation of coronary artery. EKG was used to observe dynamic change of mouse cardiac movement. As shown in **Figure 1**, ST segment on EKG electrode II was significantly elevated in infarction model, whilst Sham group showed no significant difference in EKG pattern compared to normal mice, indicating successful generation of mouse myocardial infarction model.

Effects of rosuvastatin on cardiac function in infarction mice

To evaluate the effect of Rosuvastatin on cardiac function in infraction model mice, ultrasound imaging was used to evaluate cardiac function indexes including LVDD, LVDS, LVEF and LVFS across different groups (**Table 1**). We found significantly higher survival rate of Sham group compared to model control or low dosage group ($P<0.05$) but without significant difference with high dosage group ($P>0.05$). Meanwhile, we found high Rosuvastatin experimental group had significantly lower LVDD and LVDS ($P<0.05$ compared to model control group), whilst LVEF and LVFS were higher ($P<0.05$). These results suggested that Rosuvastatin significantly improved cardiac function of myocardial infarction mice.

Cardiac infarction area

Different groups of mice were fed for four weeks and were sacrificed for harvesting heart tissues, which were horizontally sectioned in paraffin-based slices for HE staining to analyze change of myocardial infarction area, and histopathology manifestation in infarction area. We found that in non-infarction area of myocardial tissues, cells showed clear nuclear staining, complete structure of myocardial striatal, whilst infarction area showed destructed myocardial tissues with significant tissue breakage, complicated with condensed nucleus and platelet-like necrosis (**Figure 2A**). The statistics of infarction areas across all groups (**Figure 2B**)

Table 1. Vascular collagen reconstruction of experimental mice

Group	N	Survival rate	LVDD (mm)	LVDS (mm)	LVEF (%)	LVFS (%)
Sham	12	91.7%	3.75±0.99	2.39±0.61	81.02±3.61	42.39±3.61
Model	12	50.0%*	6.05±1.13*	5.83±1.12*	45.83±4.12*	25.83±4.12*
Low dosage	12	66.7%*	5.45±0.83*	4.65±0.96*	54.65±3.96*	29.65±2.96*
High dosage	12	83.3%#	4.39±0.68#	3.12±0.85#,&	73.12±3.85#,&	38.12±2.85#,&

Note: *, P<0.05 compared to sham group; #, P<0.05 compared to model group; &, P<0.05 compared to low dosage group.

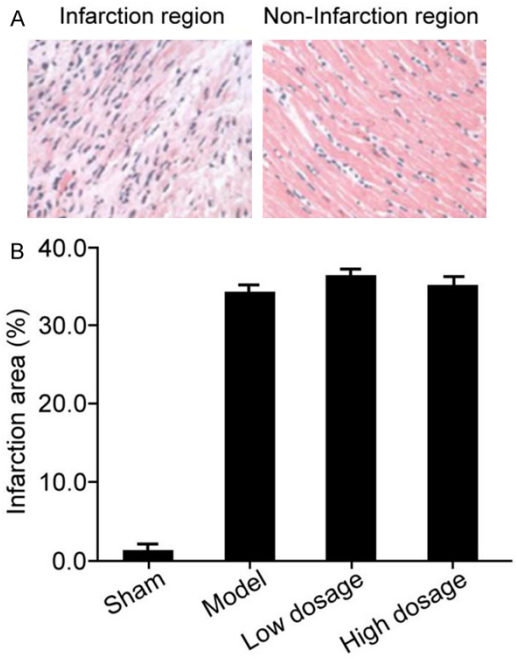

Figure 2. Comparison of myocardial infarction areas across different groups. A: HE staining of mouse myocardial infarction; B: Different infarction arears across groups.

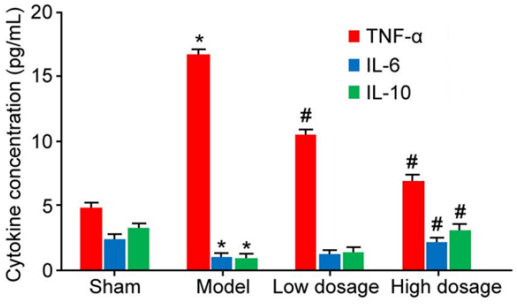

Figure 3. ELISA for mouse serum cytokine levels. *, P<0.05 compared to control group; #, P<0.05 compared to model group.

showed 35.38±2.02% infarction area in high dosage Rosuvastatin group, and 36.42±1.72% in low dosage drug treatment group, both of which were not significantly different from model group (34.26±2.45%, P>0.05).

Serum cytokine content assay

Different groups of mice were fed for four weeks and were sacrificed for separating serum, which was quantified for cytokines including TNF-α, IL-6 and IL-10 using ELISA approach. As shown in **Figure 3**, myocardial infarction mouse had significantly lower serum IL-6 and IL-10 concentration than Sham group (P<0.05), whilst TNF-α concentration was significantly higher. High dosage Rosuvastatin gavage mice showed significantly lower TNF-α expression (P<0.05 compared to model group), and up-regulated IL-6 and Il-10 levels (P<0.05 compared to model group). Low dosage Rosuvastatin gavage showed significantly lower TNF-α expression level (P<0.05 compared to model group), but IL-6 and IL-10 concentration were not significantly changed. These results showed that Rosuvastatin gavage could reverse abnormal expression of cytokines induced by myocardial infarction to certain extents.

Discussion

Myocardial infarction is one severe cardiovascular disease and can induce a series of symptoms including heart failure, arrhythmia or even heart rupture, thus severely threatening patient's health [1]. Some studies believed that a series of gene expression regulation process and cytokine secretion or cellular interaction were accompanied with pathological process of myocardial infarction and heart failure, thus causing structural and functional change of hearts, forming myocardial reconstruction [14]. Study found that Statin drugs can protect cardiac function and reduce risk of myocardial infarction, stroke and coronary artery reconstruction via reducing serum or myocardial tissue inflammatory cytokine secretion, in addition to its blood lipid regulatory functions [15,

16]. This study aimed to construct mouse myocardial infarction model, on which the correlation between Rosuvastatin and post-infarction cardiac function or serum inflammatory cytokines.

Mouse myocardial infarction model was successfully generated by coronary artery ligation surgery, and was divided into different groups following different gavage drugs delivery. Colored ultrasound was used to analyze cardiac function indexes including LVDD, LVDS, LVEF and LVFS. LVDD and LVDS parameters can be used to evaluate thickness of left ventricles, thus indirectly reflecting post-infarction reconstruction of left ventricles, whilst LVEF and LVFS can be used to evaluate cardiac function. Results showed that high dosage Rosuvastatin group mice had significantly lower LVDD or LVDS than model group, whilst LVEF and LVFS were higher. These results indicated that Rosuvastatin drug delivery can alleviate left ventricular reconstruction after infarction to improve cardiac function. Meanwhile, ELISA analysis was used to compare serum cytokine levels across different groups. High dosage Rosuvastatin group had significantly lower TNF-α and higher IL-6/IL-10 concentrations compared to model group.

Study found significantly elevated expression level of inflammatory cytokines including TNF-α, IL-6 and IL-10 and MMP in infarction patients undergoing myocardial reconstruction [17, 18]. It is thus proposed that inflammatory cytokine and MMP expression change might be related with myocardial reconstruction process. Up-regulation of pro-inflammatory factor may induce further damage of cardiomyocytes, causing my-ocardial fibrosis or even apoptosis [19]. IL-6 and IL-10 are important body protective cytokines. Previous studies showed decreased IL-6 or IL-10 expression in myocardial infarction patients, whilst TNF-α up-regulation could aggravate cell inflammation [20, 21]. After treatment using Rosuvastatin, IL-10 and IL-6 concentrations were increased, thus suppressing inflammation of myocardial tissues, and protecting cardiomyocytes.

Rosuvastatin is one selective HMG-CoA reductase inhibitor and can suppress reductase activity [8]. How does Rosuvastatin regulate inflammatory factor expression in injured myocardial tissues is still unclear yet. Some scholars found that Rosuvastatin treatment could increase SERCA protein expression, thus proposing that Rosuvastatin could change expression of cellular inflammatory factors via mediating calcium modulating proteins [22], although detailed mechanism still require further experiments.

Conclusion

Treatment using Rosuvastatin on myocardial infarction mice significantly improves cardiac function and alleviates ventricular reconstruction. Rosuvastatin can alleviate cardiomyocyte injury and protect myocardial tissues via modulating expression of cellular inflammatory factors.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Baozhong Shan, Department of Stomatology, Jinan Central Hospital Affiliated to Shandong University, No. 105, Jiefang Road, Jinan, Shandong Province, China. Tel: +86-0531-85695114; Fax: +86-0531-85695114; E-mail: baozhongshandop@163.com

References

[1] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ and Mendis S. Third universal definition of myocardial infarction. Circulation 2012; 126: 2020-35.

[2] Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surak-

ka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D and Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet 2012; 380: 572-80.

[3] van den Borne SW, Diez J, Blankesteijn WM, Verjans J, Hofstra L and Narula J. Myocardial remodeling after infarction: the role of myofibroblasts. Nat Rev Cardiol 2010; 7: 30-7.

[4] Abbate A, Kontos MC, Grizzard JD, Biondi-Zoccai GG, Van Tassell BW, Robati R, Roach LM, Arena RA, Roberts CS, Varma A, Gelwix CC, Salloum FN, Hastillo A, Dinarello CA and Vetrovec GW; VCU-ART Investigators. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (virginia commonwealth university anakinra remodeling trial [VCU-ART] pilot study). Am J Cardiol 2010; 105: 1371-1377, e1.

[5] Nahrendorf M, Pittet MJ and Swirski FK. Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. Circulation 2010; 121: 2437-45.

[6] Anzai T. Post-infarction inflammation and left ventricular remodeling: a double-edged sword. Circ J 2013; 77: 580-7.

[7] van Nieuwenhoven FA and Turner NA. The role of cardiac fibroblasts in the transition from inflammation to fibrosis following myocardial infarction. Vascul Pharmacol 2013; 58: 182-8.

[8] Zhang Z, Li S, Cui M, Gao X, Sun D, Qin X, Narsinh K, Li C, Jia H, Li C, Han Y, Wang H and Cao F. Rosuvastatin enhances the therapeutic efficacy of adipose-derived mesenchymal stem cells for myocardial infarction via PI3K/Akt and MEK/ERK pathways. Basic Res Cardiol 2013; 108: 333.

[9] Kim JW, Yun KH, Kim EK, Kim YC, Joe DY, Ko JS, Rhee SJ, Lee EM, Yoo NJ, Kim NH, Oh SK and Jeong JW. Effect of high dose rosuvastatin loading before primary percutaneous coronary intervention on infarct size in patients with st-segment elevation myocardial infarction. Korean Circ J 2014; 44: 76-81.

[10] Wang W, Zhang Y, Gao M, Wang J and Hou Y. Effect of rosuvastatin on atrial structural remodeling in rabbits with myocardial infarction. Biomed Rep 2015; 3: 78-82.

[11] Takayama T, Hiro T and Higuchi Y. Aggressive lipid-lowering therapy using rosuvastatin improves endothelial dysfunction in patients with coronary artery disease. Journal of The American College Of Cardiology 2015; 65.

[12] Gao Y, Gao J, Chen C, Wang H, Guo J and Wu R. Cardioprotective effect of polydatin on ventricular remodeling after myocardial infarction in coronary artery ligation rats. Planta Med 2015; 81: 568-77.

[13] Ishiguchi H, Kobayashi S and Kouno M. Fixation of the disturbing ryanodine receptor by dantrolene restores cardiac dysfunction and suppreses ventricular arrhythmia in mice myocardial infarction model. J Card Fail 2016; 22: S212-S213.

[14] Shi S, Liang J, Liu T, Yuan X, Ruan B, Sun L, Tang Y, Yang B, Hu D and Huang C. Depression increases sympathetic activity and exacerbates myocardial remodeling after myocardial infarction: evidence from an animal experiment. PLoS One 2014; 9: e101734.

[15] Chang G, Zhang P, Ye L, Lu K, Wang Y, Duan Q, Zheng A, Qin S and Zhang D. Protective effects of sitagliptin on myocardial injury and cardiac function in an ischemia/reperfusion rat model. Eur J Pharmacol 2013; 718: 105-13.

[16] Zhang Y, Yuan H, Sun Y, Wang Y and Wang A. The effects of ethanol on angiogenesis after myocardial infarction, and preservation of angiogenesis with rosuvastatin after heavy drinking. Alcohol 2016; 54: 27-32.

[17] Kandalam V, Basu R, Abraham T, Wang X, Soloway PD, Jaworski DM, Oudit GY and Kassiri Z. TIMP2 deficiency accelerates adverse post-myocardial infarction remodeling because of enhanced MT1-MMP activity despite lack of MMP2 activation. Circ Res 2010; 106: 796-808.

[18] Anderson DR, Poterucha JT, Mikuls TR, Duryee MJ, Garvin RP, Klassen LW, Shurmur SW and Thiele GM. IL-6 and its receptors in coronary artery disease and acute myocardial infarction. Cytokine 2013; 62: 395-400.

[19] Seropian IM, Toldo S, Van Tassell BW and Abbate A. Anti-inflammatory strategies for ventricular remodeling following ST-segment elevation acute myocardial infarction. J Am Coll Cardiol 2014; 63: 1593-603.

[20] Kobara M, Noda K, Kitamura M, Okamoto A, Shiraishi T, Toba H, Matsubara H and Nakata T.

Antibody against interleukin-6 receptor attenuates left ventricular remodelling after myocardial infarction in mice. Cardiovasc Res 2010; 87: 424-30.

[21] Liu H, Luiten PG, Eisel UL, Dejongste MJ and Schoemaker RG. Depression after myocardial infarction: TNF-alpha-induced alterations of the blood-brain barrier and its putative therapeutic implications. Neurosci Biobehav Rev 2013; 37: 561-72.

[22] Qiu Z, Zhang W, Fan F, Li H, Wu C, Ye Y, Du Q, Li Z, Hu X, Zhao G, Sun A, Bao Z and Ge J. Rosuvastatin-attenuated heart failure in aged spontaneously hypertensive rats via PKCalpha/beta2 signal pathway. J Cell Mol Med 2012; 16: 3052-61.