respectively, and HR decreased slightly from 125.2±21.3 ms to 102.5±4.94 ms by stimulation of SAN-FP, while HR was not affected by stimulating AVN-FP. The effect of stimulating cervical vagus trunk on reducing HR was partially expressed with SAN-FP ablation and totally eliminated by SAN-FP+AVN-FP combined ablation. (2) The ERP and increased ERP dispersion of atrial and pulmonaries were significantly by stimulating SAN-FP and abolished by ablating SAN-FP, while no big difference of ERP and ERP dispersion in atrial and pulomonaries was recorded when stimulation and ablation was exerted on AVN-FP; (3) Pacing at right atrial with 600 bpm, the AF was induced 60% and 18.4% by stimulating right and left cervical vagus trunk as well as 15.29% and 2.25% by stimulating SAN-FP and AVN-FP. However, with the stimulating at right and left cervical vagus trunk, the inducibility of AF was reduced to 16.8% and 6% when SAN-FP had ablated and even to 0% when AVN-FP had ablated.

Conclusion We concluded that sinus node function was adjusted mainly by stimulating at right cervical vagus trunk through AVN-FP. The shorted ERP and increased ERP dispersion of atrial and pulmonary as well as AF were induced by stimulating cervical vagus trunk mainly coordinated with AVN-FP. Our study strongly suggested that AVN-FP is a very important coordinator in relation to parasympathetic dominant AF.

e0070 ATORVASTATIN SUPPRESSES INFLAMMATORY RESPONSE INDUCED BY OXLDL THROUGH INHIBITION OF ERK PHOSPHORYLATION, IκB? DEGRADATION AND COX-2 EXPRESSION IN MURINE MACROPHAGES

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Objective Macrophages crosstalk with oxidised low-density lipoprotein (oxLDL), play a critical role in the initiation, progression and subsequent stability of atherosclerotic plaques. Statins, inhibitors of HMG CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, reduce the expression of inflammatory proteins in addition to their lipid-lowering action. However, the effect and the detailed anti-inflammation mechanisms of statins in macrophages induced by oxLDL remain unclear. In the present study, we investigated the effect of atorvastatin on inflammatory response upon oxLDL stimulation in murine macrophages and analysed the underlying mechanisms.

Methods Raw 264.7 macrophages were cultured and pre-treated with varying doses of atorvastatin in the absence or presence of 40 μg/ml oxLDL. The morphology of the cells was observed and the expression of inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) and tumour necrosis factor (TNF) was assayed by real-time PCR. The expression of Cyclooxygenases -2(COX-2) was performed by real-time PCR and Western blotting. MAPK phosphorylation and IκBa degradation were determined by Western blotting. After pre-incubation with atorvastatin or PD98059, inhibitor of ERK1/2 MAPK, the expression of COX-2 was also detected by real-time PCR and Western blotting.

Results Our findings have shown that exposure of RAW264.7 cells to oxLDL, substantially changed the morphology of the cells and increased the mRNA expression of proinflammatory cytokines and chemokines including TNFa and MCP-1, approximately to 14-fold, 10-fold, respectively while pretreatment with atorvastatin resulted in a significant inhibition of the oxLDL-induced morphological alteration and inflammatory cytokines expression in a dose-dependent fashion. Further investigation of the molecular mechanism revealed that oxLDL upregulated the transcription and protein expression of COX-2 in a time-dependent manner. Moreover, the activation of ERK pathway and IκBa degradation contribute to this effect.

Conclusions Taken together, the anti-inflammatory effect of atorvastatin is mediated through the inhibition of proinflammatory COX-2. Furthermore, suppression of ERK phosphorylation and IκBa degradation is involved in this regulation. Our findings provide novel evidence that statins suppress inflammatory response in murine macrophages induced by oxLDL, exert its anti-atherogenic actions via against inflammation beyond cholesterol-lowering effect.

e0071 EFFECT OF FLUVASTATIN ON MYOCARDIAL INTERSTITIAL FIBROSIS AND CARDIAC FUNCTION IN DIABETIC RATS

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Objective To investigate effect of fluvastatin on myocardial interstitial fibrosis and cardiac function in diabetic rats.

Methods 24 male SD rats were randomly divided into three groups: normal control (n=8), untreated and STZ-induced diabetic rats (n=8) and diabetic rats treated with fluvastatin (n=8). DM was induced in male SD rats with a single intraperitoneal (i.p.) injection of streptozotocin 50 mg/kg dissolved in 20 mM citrate buffer (pH 4.5) overnight. Tail vein blood glucose was measured 72 h later and those with plasma glucose levels ≥16.7 mmol/l were considered to be diabetic. Control rats were injected 1 ml/kg body weight of 20 mM citrate buffer (pH 4.5) vehicle, and diabetic rats were treated with fluvastatin (10 mg/kg administered orally, n=8). Fluvastatin were dissolved in sterile water, and administered every day via stomach tube. These rats were housed for 12 weeks with daily general checking. After 12 weeks intervention, miniature cardiac catheter was inserted into the left ventricle to conduct haemodynamic examination. Then, myocardium tissues were collected, collagen content was detected by picro-sirius red staining, immunohistochemistry was used to detect protein expression of fibronectin, real-time RT-PCR was used to detect the mRNA expression of CTGF and Western blotting was used to detect the protein expression of CTGF. RhoA activity in LV myocardial tissue of rats was determined by pull down assay.

Results By the end of the experiment, the left ventricular systolic pressure (LVSP)(97±12 mm Hg vs 131±21 mm Hg) and maximum rate of left ventricular (LV) pressure rise and fall (+dP/dt max and -dP/dt max) (4410±332 mm Hg/s vs 6465±442 mm Hg/s and −4326±365 mm Hg/s vs-6432±426 mm Hg/s) were significantly lower and left ventricular end diastolic pressure (LVEDP) (16.2±3.2 mm Hg vs 4.8±1.2 mm Hg) were significantly higher in the diabetic group compared to the control group (all $p<0.01$). Moreover, in LV myocardial tissue of diabetic rats the collagen content (4.2%±0.36% vs 6.4%±0.33%, $p<0.01$), fibronectin (3.12±0.30 vs 0.95±0.33, $p<0.01$), mRNA and protein expression of CTGF (0.86±0.10 vs 1.37±0.24 and 0.48±0.13 vs 1.26±0.22, $p<0.01$) and the activity of RhoA (1.72±0.21 vs 1.1±0.1, $p<0.01$) were all significantly increased compared to the control rats. Administration of fluvastatin obviously improved the cardiac function of diabetic rats, attenuated fibronectin expression, mRNA and protein expression of CTGF and the activity of RhoA in LV myocardium of diabetic rats.

Conclusions Our data demonstrate that fluvastatin attenuates cardiac dysfunction and myocardial interstitial fibrosis of diabetic rat by inhibiting activity of RhoA to down-regulate the over-expression of CTGF, and Rho/Rho-kinase pathway may be an important target in the treatment of diabetic cardiomyopathy.