doi: 10.13241/j.cnki.pmb.2017.09.024

阿托伐他汀治疗冠心病的临床疗效及机制研究*

周 云[1,2] 吴 弘[1△] 张 超[2] 缪志静[2] 施珊岚[2]

（1 第二军医大学附属长海医院 心内科 上海 200433；2 上海市宝山区中西医结合医院 心内科 上海 201999）

摘要 目的：探讨阿托伐他汀治疗冠心病的临床疗效及其可能机制。**方法：**按照抽签法将 170 例冠心病患者分为对照组(n=85)及研究组(n=85)，对照组予以常规治疗，研究组在对照组基础上使用阿托伐他汀治疗，比较两组治疗前后血清炎症因子[肿瘤坏死因子-α(TNF-α)、基质金属蛋白酶 -9(MMP-9)、C 反应蛋白(CRP)]水平、氧化应激水平[血清丙二醇(MDA)、超氧化物歧化酶(SOD)水平]、血管内皮功能[血清一氧化氮(NO)、内皮素 -1(ET-1)水平]、血脂水平及心功能的变化。**结果：**治疗后，研究组患者血清 TNF-α、MMP-9、CRP、MDA、ET-1 、总胆固醇(TC)、甘油三脂(TG)、左心室舒张末期内径(LVEDD)、左心室收缩末期内径(LVESD)水平均显著低于对照组，而血清 SOD、NO、高密度脂蛋白(HDL-C)左心室射血分数(LVEF)水平均显著高于对照组，差异有统计学意义(P<0.05)。**结论：**阿托伐他汀可显著提高冠心病患者的心功能，可能与其有效抑制炎症、氧化应激和降低血脂水平有关。

关键词：冠心病；阿托伐他汀；炎症因子；氧化应激；血管内皮功能

中图分类号：R541.4 **文献标识码：**A **文章编号：**1673-6273(2017)09-1692-04

Clinical Effects and Mechanisms of Atorvastatin on the Coronary Heart Disease*

ZHOU Yun[1,2], WU Hong[1△], ZHANG Chao[2], MIAO Zhi-jing[2], SHI Shan-lan[2]

(1 Department of Cardiology, Changhai Hospital Affiliated to Second Military Medical University, Shanghai, 200433, China; 2 Department of Cardiology, Baoshan District Shanghai hospital, Shanghai, 201999, China)

ABSTRACT Objective: To study the clinical effects and mechanisms of atorvastatin on the coronary heart disease. **Methods:** 170 patients with coronary heart disease were divided into the control group (n=85) and research group (n=85) according to the method of lottery. The inflammation factor [tumor necrosis factor-α(TNF-α), matrix metalloproteinases-9 (MMP-9) and c-reactive protein (CRP)] levels, oxidative stress [Malondialdehyde (MDA), superoxide dismutase (SOD)] levels, endothelial function[Serum nitric oxide (NO) and endothelin-1 (ET-1) levels], blood lipids and heart function were compared between two groups before and after treatment. **Results:** After treatment, the serum TNF alpha, MMP-9, CRP, MDA, ET-1, total cholesterol (TC), triglycerides (TG), left ventricular end-diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) levels of research group were significantly lower than those of the control group, but the serum SOD, NO, high-density lipoprotein (HDL-C), left ventricular ejection fraction (LVEF) levels of research group were significantly higher than those of the control group (P<0.05). **Conclusion:** Atorvastatin could significantly improve the cardiac function of patients with coronary heart disease, which might be related to the inhibition of inflammation, oxidative stress and reduction of blood lipid levels.

Key words: Coronary heart disease; Atorvastatin; Inflammation factors; Oxidative stress; Endothelial function

Chinese Library Classification(CLC): R541.4 Document code: A

Article ID: 1673-6273(2017)09-1692-04

前言

冠心病为临床常见的心血管疾病，主要是因冠状动脉粥样硬化诱导官腔出现狭窄，使其血流受到阻滞，诱发心肌血供缺乏所致的心肌功能异常或者器质性病变[1]。相关研究显示炎症反应、氧化应激、血管内皮功能紊乱、血脂代谢异常等在冠心病的发病过程中起着关键作用[2]。他汀类药物是一组调脂药物，广泛应用于临床，对于冠心病患者的病情控制具有重要价值。阿托伐他汀是他汀类的代表药物，具有多种药理作用，目前临床上关于其对冠心病患者血清指标的影响报道并不全面[3]。本研究旨在探讨阿托伐他汀治疗冠心病的临床疗效及对患者血清肿瘤坏死因子 -α(TNF-α)、基质金属蛋白酶 -9(MMP- 9)、C 反应蛋白(CRP)及丙二醇(MDA)水平的影响。

1 材料与方法

1.1 一般资料

选择本院 2014 年 4 月 ~2016 年 2 月收治的冠心病患者 170 例，符合冠心病相关诊断标准[4]，且经临床表现、心电图、冠

* 基金项目：上海市自然科学基金项目(10R13089)

作者简介：周云(1980-)，女，本科，主治医师，研究方向：心内科临床研究，电话：15801893221

△ 通讯作者：吴弘(1969-)，女，医学博士，副主任医师，研究方向：心内科临床研究，电话：15801893221

(收稿日期：2016-11-04 接受日期：2016-11-21)

状造影检查证实为冠心病。纳入轻度冠心病和冠状动脉粥样硬化、无先天性心脏病、无恶性心律失常、肝肾功能正常、近 1 个月未使用任何相关降血脂药物者。排除经冠状动脉介入治疗，冠状动脉狭窄小于 50%或者大于 50%小于 70%、急性心肌梗死、心力衰竭，心功能在Ⅲ级以上、恶性肿瘤、免疫及血液系统疾病、急慢性感染或创伤者。对照组有 45 例男性，有 40 例女性；年龄 43~70 岁，平均(62.48± 1.23)岁。研究组有 43 例男性，有 42 例女性；年龄 45~72 岁，平均(63.24± 1.19)岁。本研究家属与患者均签署知情同意书，且通过本院伦理委员会审核。比较两组性别、年龄等无差异(P>0.05)，有可比性。

1.2 方法

1.2.1 治疗方法 对照组予以阿司匹林、硝酸脂类、β 受体阻滞剂、钙拮抗剂、抗血小板等常规治疗，同时嘱患者行低盐、低脂饮食，增加膳食纤维的食用量。研究组基于对照组结合阿托伐他汀治疗，起始口服 10 mg/d 阿托伐他汀(重庆润康药业有限公司，10 mg/ 片，20140319)，未见明显不适时以 20 mg/d 维持治疗，两组均持续治疗 8 周。

1.2.2 指标测定 两组均于治疗前及治疗结束时采集空腹外周静脉血 4 mL，常规肝素抗凝后，分离血清，置于 -80℃环境中保存备用。① 炎症因子：予以放射免疫法检测 TNF-α、MMP- 9、CRP，试剂盒均来自山西博达制药有限公司。② 氧化应激指标：分别予以黄嘌呤氧化酶法、硫酸巴比妥酸法检测 MDA、超氧化物歧化酶(SOD)，试剂盒分别来自广东康奇力药业有限公司。③ 血管内皮功能：予以酶联免疫双抗体夹心法检测一氧化氮(NO)、内皮素 -1(ET-1)，试剂盒来自华北制药集团华栾有限公司。④ 血脂指标：予以全自动血液分析仪(DxH 800 型，国产)检测低密度脂蛋白(LDL-C)、高密度脂蛋白(HDL-C)、总胆固醇(TC)、甘油三脂(TG)。⑤ 心功能：予以彩色多普勒超声诊断仪(CX30 型，国产)查看患者治疗前及治疗结束时左心室舒张末期内径(LVEDD)、左心室收缩末期内径(LVESD)、左心室射血分数(LVEF)。

1.3 统计学分析

选择 SPSS18.0 行数据统计，计量资料用均数± 标准差($\bar{x}$± s)表示，组间比较用 t 检验，计数资料用[(n)%]表示，组间比较用 x^2 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者治疗前后血清 TNF-α、MM P- 9、CRP 水平的比较

治疗前，两组患者血清 TNF-α、MM P- 9、CRP 水平比较采用均无统计学意义(P>0.05)；治疗后，两组血清 TNF-α、MM P-9、CRP 水平均较治疗前明显降低，且研究组以上指标明显低于对照组，两组比较差异有统计学意义(P<0.05)，见表 1。

表 1 两组患者治疗前后血清 TNF-α、MM P- 9、CRP 水平比较($\bar{x}$± s)

Table 1 Comparison of the serum TNF-α, MM P- 9, CRP levels between the two groups before and after treatment

Groups	n	TNF-α(ng/L)		MMP-9(ng/L)		CRP(mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	85	132.78± 12.28	97.64± 10.23*	99.70± 9.64	67.43± 8.61*	76.73± 8.29	62.17± 6.93*
Research group	85	133.67± 12.85	62.58± 7.81*#	99.35± 9.52	42.50± 6.42*#	76.84± 8.40	49.84± 6.70*#

Note: Compared with before treatment, *P<0.05; compared with control group after treatment, #P<0.05.

2.2 两组患者治疗前后血清 MDA、SOD 水平的比较

治疗前，两组患者血清 MDA、SOD 水平差异均无统计学意义(P>0.05)；治疗后，两组患者血清 MDA 均较治疗前显著降低，且研究组明显低于对照组，而两组 SOD 水平均较治疗前显著升高，且研究组明显高于对照组，两组比较差异有统计学意义(P<0.05)，见表 2。

表 2 两组患者治疗前后血清 MDA、SOD 水平比较($\bar{x}$± s)

Table 2 Comparison of the serum MDA and SOD levels between the two groups before and after treatment($\bar{x}$± s)

Groups	n	MDA(μmol/L)		SOD(μmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	85	13.73± 2.74	10.15± 1.53*	58.51± 8.72	68.79± 9.20*
Research group	85	13.70± 2.62	7.62± 1.21*#	57.60± 8.61	82.65± 9.74*#

Note: Compared with before treatment, * P<0.05; compared with control group after treatment, #P<0.05.

2.3 两组患者治疗前后血清 NO、ET-1 水平的比较

治疗前，两组患者血清 NO、ET-1 水平比较差异均无统计学意义(P>0.05)；治疗后，两组患者血清 NO 均较治疗前明显上升，且研究组显著高于对照组，而两组 ET-1 均较治疗前显著降低，且研究组明显低于对照组，两组比较差异均有统计学意义(P<0.05)，见表 3。

表 3 两组患者治疗前后血清 NO、ET-1 水平的比较($\bar{x}$± s)

Table 3 Comparison of the serum NO and ET-1 levels between the two groups before and after treatment

Groups	n	NO(μmol/L)		ET-1(pg/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	85	40.89± 5.12	50.70± 6.60*	98.54± 9.76	70.42± 8.11*
Research group	85	40.63± 5.27	63.48± 7.21*#	98.41± 9.60	58.23± 7.25*#

Note: Compared with before treatment, * P<0.05; compared with control group after treatment, #P<0.05.

2.4 两组患者治疗前后血脂水平的比较

治疗前，两组患者的血脂水平比较差异均无统计学意义(P>0.05)；治疗后，两组患者血清 HDL-C 水平均较治疗前显著上升，且研究组显著高于对照组，两组患者血清 LDL-C、TC、TG 水平均较治疗前明显降低，且研究组明显低于对照组，两组比较差异均有统计学意义(P<0.05)，见表 4。

表 4 两组患者治疗前后血脂水平比较($\bar{x}\pm s$)

Table 4 Comparison of the serum lipid levels between two groups before and after treatment

Groups	n	LDL-C(mmol/L)		HDL-C(mmol/L)		TC(mmol/L)		TG(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	85	4.17± 0.38	3.75± 0.29*	0.96± 0.18	1.14± 0.25*	6.78± 0.62	5.94± 0.51*	3.15± 0.42	2.32± 0.30*
Research group	85	4.19± 0.36	2.60± 0.24*#	0.97± 0.17	1.26± 0.30*#	6.80± 0.63	4.53± 0.42*#	3.17± 0.40	1.65± 0.25*#

Note: Compared with before treatment, * P<0.05; compared with control group after treatment, #P<0.05.

2.5 两组患者治疗前后心功能比较

治疗前，两组患者的心功能比较差异无统计学意义(P>0.05)；治疗后，两组患者的 LVEDD、LVESD 水平均较治疗前明显降低，且研究组低于对照组，而两组 LVEF 均显著上升，且研究组高于对照组，两组比较差异均有统计学意义(P<0.05)，见表5。

表 5 两组患者治疗前后心功能比较($\bar{x}\pm s$)

Table 5 Comparison of the cardiac functions between the two groups before and after treatment

Groups	n	LVEDD(mm)		LVESD(mm)		LVEF(%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	85	68.26± 7.51	62.40± 6.47*	53.18± 6.31	49.60± 5.20*	32.38± 4.57	35.90± 5.49*
Research group	85	68.34± 7.68	56.49± 6.21*#	53.24± 6.22	45.41± 5.03*#	32.47± 4.69	39.27± 6.12*#

Note: Compared with before treatment, *P<0.05; compared with control group after treatment, #P<0.05.

3 讨论

冠心病属缺血性心脏病，是中老年人群的多发病，可引起压榨性疼痛、气促、眩晕、寒颤、昏厥等临床表现，严重者可诱发急性心肌梗死、急性心力衰竭，严重时甚至危及患者生命[5]。冠状动脉粥样硬化是冠心病的病变基础，然而粥样硬化形成的机制尚未统一，考虑为多个因素综合所致[6,7]。TNF-α 为机体重要的促炎性因子，可介导炎性细胞的产生聚集、黏附，引发炎症，加速细胞凋亡、坏死，还可促进血管新生[8]。MMP-9 可参与机体炎症反应、血管新生等病理反应，可使动脉粥样硬化的稳定性减弱，促进斑块产生分裂，利于血栓的形成 D[9]。CRP 为炎症反应的急性蛋白，可参与动脉粥样硬化形成的整个过程[10]。阿托伐他汀无需经代谢即可生成药物活性，容易被机体所吸收，其半衰期长，生物利用度高[11]。本研究显示结果显示阿托伐他汀治疗后，患者血清 TNF-α、MMP-9、CRP 水平均显著低于常规治疗者，表明阿托伐他汀存在抗炎作用，能够降低机体炎症介质，控制疾病的进展。

炎症反应能够使氧自由基过度生成，引起氧化应激损伤，诱导脂质过氧化反应，进而参与冠心病的发病过程。MDA 含量能够客观反映机体对于脂质过氧化的能力，SOD 为抗氧化酶，能够使自由基清除，避免细胞损伤，确保机体氧化和抗氧化的平衡[12]。本研究结果显示阿托伐他汀治疗后，患者血清 MDA 更低，且血清 SOD 水平明显高于常规治疗者，表明阿托伐他汀能够使氧化应激损伤减轻，缓解氧化应激引起的心肌受损[13]。此外，研究表明血管内皮功能损伤为冠心病发病的重要环节[14]。NO 为血管内皮的舒张性因子，能够使血管维持正常张力，其活性减弱能够使血管舒张弹性相应下降，降低冠脉的扩张反应[15]。ET-1 为缩血管因子，同冠状动脉的狭窄程度为正比，可间接提示心血管疾病的病情程度和心功能[16]。本研究结果显示阿托伐他汀治疗后，患者血清 NO 水平显著高于常规治疗者，且血清 ET-1 水平更低，提示阿托伐他汀能够纠正血管内皮功能障碍，考虑与其能够使一氧化氮合酶的活性增加，进而促进 NO 的合成、分泌，抑制 ET-1mRNA 的表达，减少 ET-1 合成有关[17]。

血脂代谢紊乱是对照冠心病的另一关键因素，与冠心病的进展有着紧密联系[18]。本研究结果显示阿托伐他汀治疗后患者血清 HDL-C 水平显著高于常规治疗者，且血清 LDL-C、TC、TG 水平更低，表明阿托伐他汀能够有效调节脂质代谢，控制疾病的进展，考虑与其能够导致胆固醇的合成受到抑制，促进对 LDL-C 的清除，相应减少 TC、TG 浓度[19]。由于冠状动脉硬化能够使心脏局部组织产生纤维化，导致左心室发生增厚，对于心脏正常的功能形成影响，引起心功能减弱[20]。本研究结果显示：阿托伐他汀治疗后 LVEDD、LVESD 均有降低，且 LVEF 明显升高，表明阿托伐他汀能够抑制心肌肥厚，改善心功能。

综上所述，阿托伐他汀可显著提高冠心病患者的心功能，可能与其有效抑制炎症、氧化应激和降低血脂水平有关。

参 考 文 献(References)

[1] Riazian M, Khorrami E, Alipoor E, et al. Assessment of Apelin Serum Levels in Persistent Atrial Fibrillation and Coronary Artery Disease [J]. Am J Med Sci, 2016, 352(4): 354-359

[2] Xu Tao, Zhang Zhe, Wang Jing-peng, et al. Tanshinone Ⅱ A sulfonate joint atorvastatin cardiac function in patients with coronary heart disease (CHD), oxidative stress, and the influence of the vascular endothelial function [J]. Journal of hebei medicine, 2015, 37 (24):

3695-3698

[3] Chen Yi, Xu Shi-e. Relavalstatin and atorvastatin in patients with coronary heart disease (CHD) lipid effect and safety of comparison [J]. Chinese journal of gerontology, 2014, 36(9): 2389-2390

[4] Gong Jie. Coronary heart disease prevention and control guide [M]. Hubei science and technology press, 2012: 31-33

[5] Chen KJ, Shi DZ, Fu CG, et al. Diagnostic criterion of blood stasis syndrome for coronary heart disease:Activating Blood Circulation Committee of Chinese Association of Integrative Medicine[J]. Chin J Integr Med, 2016, 22(11): 803-804

[6] Fang Ye-qing, Zhang Song-rong, Fang Hong-cheng, et al. In patients with coronary heart disease in endothelial progenitor cells (epcs) change and the correlation of coronary artery lesions[J]. Chinese journal of hardening of the arteries, 2012, 20(9): 814-818

[7] Gao Yang, Lv Bin, Hou Zhi-hui, et al. Coronary heart disease (CHD) combined the characteristics of coronary atherosclerosis in patients with metabolic syndrome [J]. Chinese journal of cardiovascular disease, 2013, 41(11): 935-939

[8] Ji Yuan-yuan, Li Gang, Liu Zhi-yuan, et al. Atorvastatin on coronary heart disease, inflammation factor hs CRP, TNF alpha and IL-6 levels of intervention effect [J]. Chinese journal of biochemical drugs, 2014, 34(7): 147-149

[9] Tian Lei. Atorvastatin associated with trimetazidine treatment of cardiac function in patients with coronary heart disease (CHD), the influence of the inflammatory factors and endothelial function [J]. Journal of hainan medical college, 2016, 22(14): 1489-1492

[10] Yang Hui-cong, Wu A-yang, Lin Jie, et al. CRP in plasma Hcy, LDL, HDL levels, and the research of atherosclerosis [J]. Journal of laboratory medicine and clinical, 2011, 8(20): 2433-2434

[11] Li Su-min, Zhai Ya-dong. Atorvastatin level of blood lipid and inflammatory factors in patients with coronary heart disease[J]. Chinese journal of practical diagnosis and treatment, 2012, 26(7): 694-696

[12] Ye Sheng, Tang Sheng-xing. Oxidative stress on the influence of different types of coronary heart disease and its factor analysis [J]. Journal of practical medical journal, 2015, 31(24): 4151-4152

[13] Ge Jin-wen, Liu Jie-rong, Zhu Hui-bin, et al. Atorvastatin on atherosclerosis rabbit oxidative stress/inflammation[J]. The influence of Chinese journal of hardening of the arteries, 2011, 19(12): 979-983

[14] Huang Yu-lin, Xie Fang, Liu Tie-nan. Dynamic observation of atorvastatin influence on vascular endothelial function in pa tients with coronary heart disease [J]. Modern preventive medicine, 2012, 39(2): 514-515

[15] Luo Jun, Zhang Xiang, Wang Shai-hua, et al. Atorvastatin improve vascular endothelial function in patients with coronary heart disease clinical research [J]. Progress in Modern biomedicine, 2011, 11(16): 3162-3165

[16] Wu Ding-ye, Feng Jian, You Hua-yan et al. Cut statin and atorvastatin Rho kinase activity and endothelial function in patients with coronary heart disease (CHD) affect the comparison[J]. Chinese journal of hardening of the arteries, 2013, 21(1): 52-56

[17] Zhu Chun-huai, Zhang Yan-gao. Atorvastatin on homocysteine and endothelial function in patients with senile coronary heart disease [J]. The influence of jiangxi medicine, 2015, 50(10): 996-998

[18] Zhang Rui-qing. Lipid metabolic features a merger with coronary heart disease (CHD) in patients with metabolic syndrome the relationship between extent of coronary stenosis[J]. Chinese journal of gerontology, 2014, 34(21): 6055-6057

[19] Jiang Rrong-jian, Tan Shu, Kong Hong, et al. Atorvastatin blood lipids in patients with coronary heart disease (CHD) and serum level of inflammatory factors[J]. Journal of clinical rational drug use, 2011, 4(28): 18-20

[20] Wang Xing-mei, Li Xiao-yin. Atorvastatin associated with trimetazidine treatment the influence of cardiac function in patients with coronary heart disease[J].Journal of international medical review, 2015, 21 (6): 819-821

（上接第 1715 页）

[12] Pal P, Ray S, Patra SK, et al. Myeloma-associated systemic amyloidosis masquerading as NASH-associated cirrhosis and diabetic microvascular complications [J]. Oxf Med Case Reports, 2015, 2015(4): 258-261

[13] Shanbhogue VV, Hansen S, Frost M, et al. Compromised cortical bone compartment in type 2 diabetes mellitus patients withmicrovascular disease[J]. Eur J Endocrinol, 2016, 174(2): 115-124

[14] Wu D, Xuan Y, RuanY, et al. Prevalence of macro- and microvascular complications in patients with type 2 diabetes and kidney disease with or without albuminuria in a single Chinese Diabetes Centre[J]. Diab Vasc Dis Res, 2016, 13(1): 21-30

[15] Lundwall K, Jörneskog G, Jacobson SH, et al. Paricalcitol, Microvascular and Endothelial Function in Non-Diabetic Chronic Kidney Disease: A Randomized Tria[J]. Am J Nephrol, 2015, 42(4): 265-273

[16] Cohen R, Pechy F, Petry T, et al. Bariatric and metabolic surgery and microvascular complications of type 2 diabetes mellitus[J]. J Bras Nefrol, 2015, 37(3): 399-409

[17] Cunha-Vaz JG. Diabetic retinopathy: need for more research to understand the relative role of neuropathy and microvascular disease[J]. Ophthalmic Res, 2015, 54(3): 109-111

[18] Kwak SH, Park KS. Genetic Studies on Diabetic Microvascular Complications: Focusing on Genome-Wide Association Studies [J]. Endocrinol Metab(Seoul), 2015, 30(2): 147-158

[19] Bijkerk R, Duijs JM, Khairoun M, et al. Circulating microRNAs associate with diabetic nephropathy and systemicmicrovascular damage and normalize after simultaneous pancreas-kidney transplantation[J]. Am J Transplant, 2015, 15(4): 1081-1090

[20] Sucato V, Evola S, Quagliana A, et al. Comparison of coronary artery flow impairment in diabetic and hypertensive patients with stable microvascular angina [J]. Eur Rev Med Pharmacol Sci, 2014, 18(23): 3687-3689