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瑞舒伐他汀预处理对心肌缺血再灌注损伤大鼠自噬和凋亡的影响及机制研究 *

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摘要 目的：探讨瑞舒伐他汀预处理对心肌缺血再灌注损伤（MIRI）大鼠自噬因子和凋亡相关基因的影响及作用机制。**方法：**将 60 只 SD 级大鼠纳入研究，遵循随机数字表法分成假手术组、模型组以及预处理组，每组 20 只。模型组以及预处理组大鼠均制备 MIRI 模型，假手术组按照相同的方式开胸，仅穿线不进行冠状动脉的结扎。模型制备前 7d，预处理组予以瑞舒伐他汀 20 mg/（kg·d）灌胃处理，假手术组以及模型组大鼠则予以生理盐水 5 mL/d 处理。比较三组大鼠心肌组织凋亡率、心肌梗死面积、左心室血流动力学参数、自噬因子 P62、Beclin-1 蛋白表达水平以及凋亡相关基因 Bcl-2、Bax 、CytC 蛋白表达水平。**结果：**预处理组及模型组大鼠的心肌组织凋亡率以及心肌梗死面积均高于假手术组，但预处理组低于模型组（均 $P<0.05$）。预处理组及模型组大鼠的左心室舒张末压（LVEDP）均高于假手术组，但预处理组低于模型组（均 $P<0.05$）；预处理组及模型组大鼠的左心室内压最大上升速率（+dp/dtmax）、左心室内压最大下降速率（-dp/dtmax）低于假手术组，但预处理组高于模型组（均 $P<0.05$）。预处理组及模型组大鼠的 P62、Beclin-1 蛋白表达水平均高于假手术组，但预处理组低于模型组（均 $P<0.05$）。预处理组及模型组大鼠 Bcl-2 mRNA 表达水平低于假手术组，但预处理组高于模型组（均 $P<0.05$）；预处理组及模型组大鼠 Bax mRNA 表达水平及 CytC 蛋白表达水平高于假手术组，但预处理组低于模型组（均 $P<0.05$）。**结论：**瑞舒伐他汀预处理可显著减轻 MIRI 大鼠心肌组织受损程度，其主要作用机制可能与瑞舒伐他汀有效抑制心肌细胞自噬因子表达以及调控凋亡相关基因表达有关。

关键词：心肌缺血再灌注；瑞舒伐他汀；自噬因子；凋亡；作用机制

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Study on the Effect and Mechanism of Rosuvastatin Preconditioning on Autophagy and Apoptosis in Rats with Myocardial Ischemia-reperfusion Injury*

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ABSTRACT Objective: To study the effects of rosuvastatin preconditioning on autophagy factors and apoptosis-related genes in myocardial ischemia reperfusion injury (MIRI) rats and to analyze their mechanisms. **Methods:** 60 SD rats were included in the study, and they were randomly divided into sham operation group, model group and pretreatment group, with 20 rats in each group. MIRI models were prepared in both the model group and the pretreatment group. In the sham operation group, thoracotomy was performed in the same way, but only threading was performed without coronary artery ligation. 7d before the model preparation, the pretreatment group was treated with rosuvastatin 20 mg/ (kg·d) by gavage, while the sham operation group and the model group were treated with normal saline 5ml/d. Three groups of rats myocardial tissue apoptosis rate and the myocardial infarction area, left ventricular hemodynamic parameters, the expression of P62, Beclin-1 autophagy related protein, apoptosis-related factor the Bcl-2, Bax and CytC protein were compared. **Results:** The rate of myocardial tissue apoptosis and the area of myocardial infarction in the pretreatment group and the model group were higher than those in the sham operation group, and the pretreatment group was lower than that in the model group (all $P<0.05$). The left ventricular end diastolic pressure (LVEDP) of rats in the pretreatment group and the model group was higher than that in the sham operation group, and the preconditioning group was lower than that in the model group (all $P<0.05$). The levels of maximum rate of pressure rise (+dp/dtmax) and the maximum rate of pressure decline (-dp/dtmax) in the left ventricle in the pretreatment group and model group were lower than those in the sham operation group, and the pretreatment group was higher than that in the model group (all $P<0.05$). Pretreatment group and model group rats P62, Beclin 1 protein expression levels were higher than those in sham operation group, and pretreatment group was lower than the model group (all $P<0.05$). The mRNA expression levels of Bcl-2 in the pretreatment

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group and the model group were lower than those in the sham operation group, and the pretreatment group was higher than that in the model group (all $P<0.05$). The mRNA expression levels of Bax and CytC protein expression levels in the pretreatment group and model group were higher than that in the sham operation group, and the pretreatment group was lower than that in the model group (all $P<0.05$). **Conclusion:** Rosuvastatin pretreatment can significantly reduce the degree of myocardial tissue damage in MIRI rats, and the main mechanism of action may be related to the effective inhibition of the expression of autophagy factors in myocardial cells and the regulation of apoptosis-related gene expression by rosuvastatin.

Key words: Myocardial ischemia reperfusion; Rosuvastatin; Autophagy factor; Apoptosis; Mechanism of action

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前言

心肌缺血再灌注损伤（Myocardial ischemia reperfusio，MIRI）属于临床上较为多见的病理生理表现之一，自由基大量生成，心肌功能受损，血管内皮细胞功能紊乱以及一氧化氮增加等因素均可能影响了 MIRI 的发生、发展[1,2]。随着近年来相关研究的不断深入，越来越多的学者发现细胞凋亡可能在 MIRI 的发病过程中起着不可忽视的作用[3-5]。有相关研究证实，通过抑制心肌细胞的凋亡，可在一定程度上改善 MIRI 的预后[6]。此外，MIRI 是急性心肌梗死致死及致残的重要病因，由此可见，如何有效减轻 MIRI 对治疗缺血性心脏疾病具有极其重要的意义。瑞舒伐他汀不仅具有调血脂，改善动脉粥样硬化的作用，同时可发挥抗炎、抑制细胞凋亡以及调控机体免疫功能等作用[7-9]。然而，关于其在 MIRI 中的治疗机制尚不完全明确。鉴于此，本文通过研究瑞舒伐他汀预处理对 MIRI 大鼠自噬和凋亡相关基因的影响并分析其作用机制，旨在明确瑞舒伐他汀治疗 MIRI 的具体作用机制。

1 材料与方法

1.1 实验动物

将 60 只 SD 级大鼠纳入研究，遵循随机数字表法分成假手术组、模型组及预处理组，每组 20 只。大鼠体质量为 200～250 g，平均（227.34±11.24）g，均由北京维通利华实验动物技术有限公司提供，动物合格证号 SYXK（京）2017-0033。

1.2 实验方法

（1）预处理方式：造模前 7d，假手术组与模型组大鼠均予以生理盐水 5 mL/（kg·d）处理，预处理组则予以瑞舒伐他汀 20 mg/（kg·d）灌胃处理。（2）造模：采用乙醚对大鼠进行麻醉，取仰位固定在手术台上。开胸部位选择左侧 3～4 肋间，彻底暴露心脏，明确冠状动脉左前降支部位后采用 0 号线对左冠脉实施结扎处理，30 min 后二次开胸，通过剪断丝线的方式保证血流再通，复灌 120 min。假手术组仅穿线，不予以结扎。所有大鼠术前禁食、禁水，麻醉完成后实施气管插管，连接动物呼吸机维持呼吸。开放尾静脉输液，实时监测心电图、心率以及中心动脉压。造模成功标准：松开结扎线恢复冠状动脉血量，缺血部位心肌颜色恢复，抬高的 ST 段下降。（3）检测各组大鼠的左心室血流动力学参数，包括左心室舒张末压（Left ventricular end diastolic pressure，LVEDP）、左心室内压最大上升速率（+dp/dtmax）、左心室内压最大下降速率（-dp/dtmax）。

1.3 心肌细胞凋亡检测

采集三组大鼠的心尖组织，予以石蜡包埋处理，切片后采用 TUNEL 凋亡检测试剂盒完成心肌细胞凋亡情况的检测。凋亡细胞核于显微镜下成像蓝色，每张 TUNEL 阳性切片随机选取 5 个高倍视野，计算凋亡率 = 凋亡细胞数÷ 100×100%。

1.4 心肌梗死面积检测

大鼠造模 24h 后通过主动脉注入剂量为 20 g/L 的伊文氏蓝，留取整个心脏，清洗后制成薄片，采用 TTC 染色，完成心肌梗死面积的检测。心肌梗死面积 = 心脏梗死范围 / 缺血区面积（呈白色）×100%。

1.5 P62、Beclin-1、CytC 表达水平检测

获取各组大鼠的心肌组织，以 BCA 蛋白试剂盒测定蛋白浓度。分别取 100 μg 的蛋白样品实施电泳，分离及转模处理。以 5%脱脂奶粉封闭，4℃条件下过夜，分别加入兔抗鼠 P62，Beclin-1、CytC 以及 β-actin 多克隆抗体以及相应的二抗完成杂交。洗膜后加入免疫印迹化学发光试剂，随后实施放射自显影。借助 Quantity One-v 4.6.6 软件完成图像的分析，分别计算 P62、Beclin-1、CytC 蛋白相对表达量。

1.6 RT-PCR 法检测 Bcl-2、Bax mRNA 表达水平

其中 PCR 引物以及参照物引物序列见表 1。采用 TRIzol 试剂进行 RNA 的提取，并逆转录合成 cDNA。取 PCR 扩增产物 5 μL，通过 1.5%的琼脂糖凝胶电泳 30 min 后，于紫外透射仪下观察结果，并通过 Gene tools 软件完成电泳条带的灰度扫描，以各个基因和 β-actin 电泳带的灰度值的比值表示基因的 mRNA 表达水平，并以目的基因灰度值和同一样本的 β-actin 灰度值比值作为统计参数。

1.7 统计学处理

上述数据应用 SPSS 22.0 软件分析，计量资料的表示通过（$\bar{x}\pm s$）实现，实施 t 检验，多组间对比实施单因素方差分析，将 $P<0.05$ 记作差异有统计学意义。

2 结果

2.1 三组大鼠心肌组织凋亡率以及心肌梗死面积对比

预处理组及模型组大鼠的心肌组织凋亡率以及心肌梗死面积均高于假手术组，但预处理组低于模型组（均 $P<0.05$），见表 2。

2.2 三组大鼠左心室血流动力学参数对比

预处理组及模型组大鼠的 LVEDP 均高于假手术组，但预处理组低于模型组（均 $P<0.05$）；预处理组及模型组大鼠的 +dp/dtmax、-dp/dtmax 低于假手术组，但预处理组高于模型组（均 $P<0.05$），见表 3。

表 1 Bcl-2、Bax 引物序列、退火温度以及反应产物长度

Table 1 Primer sequence of Bcl-2, Bax, annealing temperature and length of reaction products

Gene	Primer sequence		Annealing temperature(℃)	Length of reaction products(bp)
Bcl-2	Upstream primer	5'-CTGGTGGACAACATCGA-3'	55	123
	Downstream primers	5'-GGAGAAATCAAACAGAGGC-3'		
Bax	Upstream primer	5'-CTGAGGCGCTCCAGGCACCA-3'	56	510
	Downstream primers	5'-CTCTTAATGTCACGCGATTTC-3'		

表 2 三组大鼠心肌组织凋亡率以及心肌梗死面积对比($\bar{x}\pm s$)

Table 2 Comparison of myocardial tissue apoptosis rate and myocardial infarction area in three groups($\bar{x}\pm s$)

Groups	n	Apoptosis rate(%)	Myocardial infarction area(mm2)
Sham operation group	20	2.39±0.48	0.00±0.00
Model group	20	30.52±4.85#	44.28±5.93#
Pretreatment group	20	15.02±2.01#*	23.49±4.21#*
F	-	24.835	33.956
P	-	0.000	0.000

Note: compared with sham operation group, #*P*<0.05; compared with model group, **P*<0.05.

表 3 三组大鼠左心室血流动力学参数对比($\bar{x}\pm s$)

Table 3 Comparison of left ventricular hemodynamic parameters in three groups of rats($\bar{x}\pm s$)

Groups	n	LVEDP(mmHg)	+dp/dtmax(mmHg/s)	-dp/dtmax(mmHg/s)
Sham operation group	20	5.56±0.97	4905.82±197.57	3844.72±112.39
Model group	20	14.02±1.18#	3445.79±143.75#	2587.78±90.48#
Pretreatment group	20	8.45±1.02#*	4126.74±160.87#*	3241.65±104.85#*
F	-	13.924	8.475	7.285
P	-	0.000	0.000	0.000

Note: compared with sham operation group, #*P*<0.05; compared with model group, **P*<0.05.

2.3 三组大鼠自噬因子 P62、Beclin-1 蛋白表达水平对比

预处理组及模型组大鼠的 P62、Beclin-1 蛋白表达水平均高于假手术组，但预处理组低于模型组(均 $P<0.05$)，见表 4。

表 4 三组大鼠自噬因子 P62、Beclin-1 蛋白表达水平对比($\bar{x}\pm s$)

Table 4 Comparison of the expression of P62 and Beclin-1 in three groups of rats

Groups	n	P62	Beclin-1
Sham operation group	20	0.16±0.03	0.12±0.05
Model group	20	0.73±0.08#	0.85±0.06#
Pretreatment group	20	0.51±0.04#*	0.60±0.04#*
F	-	20.165	18.754
P	-	0.000	0.000

Note: compared with sham operation group, #*P*<0.05; compared with model group, **P*<0.05.

2.4 三组大鼠 Bcl-2、Bax mRNA 表达水平及 CytC 蛋白表达水平对比

预处理组及模型组大鼠 Bcl-2 mRNA 表达水平低于假手术组，但预处理组高于模型组(均 $P<0.05$)；预处理组及模型组大鼠 Bax mRNA 表达水平及 CytC 蛋白表达水平高于假手术组，但预处理组低于模型组(均 $P<0.05$)，见表 5。

3 讨论

近年来相关研究证实[10-12]，MIRI 导致的心肌损伤主要是多途径以及多信号通路共同介导的一个复杂病理过程，且由心肌细胞过氧化引起的氧自由基大量堆积以及心肌细胞凋亡和能力代谢障碍等均可能对心肌产生进一步损伤。有研究报道指出[13-15]，心肌细胞凋亡是心肌组织学损伤的最终发病环节，且在心肌纤维化、心力衰竭以及心室重塑等发生过程中起着至关重要的作用。由此可见，能否有效抑制心肌细胞凋亡可作为评估 MIRI 预后的关键。瑞舒伐他汀可通过对甲基戊酸的生成产生

表 5 三组大鼠 Bcl-2、Bax mRNA 表达水平及 CytC 蛋白表达水平对比($\bar{x}\pm s$)

Table 5 Comparison of Bcl-2, Bax mRNA expression levels and cytc protein expression levels in three groups of rats($\bar{x}\pm s$)

Groups	n	Bcl-2 mRNA	Bax mRNA	CytC
Sham operation group	20	0.46±0.06	0.24±0.03	0.13±0.01
Model group	20	0.12±0.02#	0.64±0.08#	0.55±0.03#
Pretreatment group	20	0.23±0.04#*	0.43±0.02#*	0.36±0.02#*
F	-	14.295	11.075	15.867
P	-	0.000	0.000	0.000

Note: compared with sham operation group, #$P<0.05$; compared with model group, *$P<0.05$.

抑制作用,从而减少胆固醇的合成,进一步发挥降血脂作用[16-18]。瑞舒伐他汀具有抗氧化以及抗炎性因子等多种作用,有利于为血管内皮提供保护作用,预防心脑血管事件的发生[19-21]。

本文结果表明，预处理组及模型组大鼠的心肌组织凋亡率、心肌梗死面积、LVEDP 均高于假手术组,但预处理组低于模型组，预处理组及模型组大鼠的 +dp/dtmax、-dp/dtmax 低于假手术组,但预处理组高于模型组,说明瑞舒伐他汀预处理可显著减轻 MIRI 大鼠的心肌损伤。究其原因,可能是由于炎症因子可通过影响过氧化物合成、分泌,损害线粒体,促进细胞外基质改变等途径促进细胞凋亡的发生,而瑞舒伐他汀作为他汀类药物之一,具有抗氧化作用,同时可通过激活 PI3K/Akt/eNOS 通路,进一步对心肌细胞的凋亡产生抑制作用[22-24]。另有相关研究报道证实[25-27],他汀类药物可有效抑制炎症介质的释放,减轻氧化应激,进一步降低 MIRI 损伤,且该类药物的抗炎关键可能和降低环氧酶活性密切相关。P62 可与自噬相关蛋白 - 微管相关蛋白连链 3 蛋白结合,在自噬调节中起到重要作用,属于自噬表达标志蛋白之一。Beclin-1 属于自噬发生的始动因子,其可通过Ⅲ型 PI3K 复合物对自噬体形成起到调控作用，因此其表达水平可直接预示自噬程度。本文结果显示,预处理组及模型组大鼠的 P62、Beclin-1 蛋白表达水平均高于假手术组,但预处理组低于模型组，提示瑞舒伐他汀可有效抑制 MIRI 大鼠的心肌细胞自噬,而这可能是瑞舒伐他汀减轻心肌损伤的可能机制之一。另外,预处理组及模型组大鼠 Bcl-2 mRNA 表达水平低于假手术组,但预处理组高于模型组;预处理组及模型组大鼠 Bax mRNA 表达水平及 CytC 蛋白表达水平高于假手术组,但预处理组低于模型组，提示瑞舒伐他汀可显著降低 MIRI 导致的心肌细胞凋亡,具有较好的心肌保护作用。其中 Bcl-2 具有抑制细胞凋亡的作用,而 Bax 可促进细胞凋亡,两者平衡状态直接影响细胞凋亡。CytC 是线粒体凋亡的关键步骤,可与凋亡蛋白酶激活因子结合,最终活化 caspase-3,活化的 caspase-3 可通过激活 DNA 裂解酶以及增强核因子活性等途径导致细胞内的多种蛋白酶复合体破坏,进一步促进细胞凋亡发生[28-30]。

综上所述，瑞舒伐他汀预处理在减轻 MIRI 大鼠心肌组织受损方面效果显著,其主要作用机制可能与抑制心肌细胞自噬因子表达和调控凋亡相关基因表达密切相关。

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