doi: 10.13241/j.cnki.pmb.2024.02.002

右美托咪定上调 HIF-1α 抑制 NLRP3 炎性体的激活减轻糖尿病小鼠心肌缺血再灌注损伤 *

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摘要 目的:探讨右美托咪定(DEX)对糖尿病小鼠心肌缺血再灌注损伤的保护作用及可能分子机制。**方法:**将 60 只 8 周龄的 SPF 级 C57BL 小鼠高脂喂养 6 周,第 7 周通过腹腔注射链脲佐菌素(STZ)45 mg/kg/ 天,1 次 / 天,连续 5 天,建立 2 型糖尿病模型,建模后采用随机数字表法分为假手术组(sham 组)、缺血再灌注组(I/R 组)、缺氧诱导因子 -1α(HIF-1α)抑制剂 2ME2 组(2ME2 组)、DEX 组、DEX+2ME2 组(DM 组),每组 12 只。假手术组仅切开皮肤后缝合,其余四组开胸结扎冠状动脉左前降支,缺血 60 min 后松开结扎线结,再灌注 120 min 建立缺血再灌注损伤模型。于再灌注 120 min 时抽取小鼠腹主动脉血,ELISA 检测血清肌钙蛋白 I(cTnI)、白介素 -1β(IL-1β)、肿瘤坏死因子 -α(TNF-α)的浓度,随后处死小鼠,分离左心室,HE 染色观察心肌组织形态结构,Western blot 检测 HIF-1α、nod 样受体蛋白 3(NLRP3)的表达量,再灌注 24 h 时超声心动图评估心功能。**结果:**与 sham 组相比,I/R 组、2ME2 组、DEX 组、DM 组 cTnI、IL-1β,TNF-α 浓度明显升高,心肌组织结构紊乱,心肌纤维断裂增加,心肌细胞明显肿胀,炎性细胞浸润增加,心肌组织 NLRP3 表达量显著增加,每搏量(SV)、射血分数(EF)%、短轴缩短率(FS)%明显下降($P<0.05$);与 I/R 组相比,DEX 组、DM 组 HIF-1α 表达量明显增加,NLRP3 表达明显降低,cTnI、IL-1β,TNF-α 浓度明显下降,心肌组织结构明显改善,炎性细胞浸润明显减少,SV,EF、FS 明显升高($P<0.05$);与 DEX 组相比,DM 组 HIF-1α 表达量明显降低,NLRP3 表达量明显增加,cTnI、IL-1β、TNF-α 浓度明显增加,心肌组织结构紊乱,心肌纤维断裂增加,心肌细胞明显肿胀,炎性细胞浸润增加,SV,EF、FS 明显降低($P<0.05$)。**结论:**DEX 可能通过上调心肌组织 HIF-1α 的表达,抑制 NLRP3 炎性体的激活,减轻心脏炎症反应,改善糖尿病小鼠心肌缺血再灌注损伤。

关键词:右美托咪定;2 型糖尿病;心肌;缺血再灌注损伤;缺氧诱导因子 -1α;nod 样受体蛋白 3

中图分类号:R-33;R587.2;R541.4;R614 **文献标识码:**A **文章编号:**1673-6273(2024)02-206-05

Dexmedetomidine Alleviates Myocardial Ischemia-reperfusion Injury in Diabetic Mice by up-regulating HIF-1α and Inhibiting the Activation of NLRP3 Inflammasome*

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ABSTRACT Objective: To investigate the protective effect of dexmedetomidine (DEX) on myocardial ischemia-reperfusion injury in diabetic mice and its possible molecular mechanism. **Methods:** Sixty 8-week-old SPF C57BL mice were fed with high fat for 6 weeks. At the 7th week, the type 2 diabetes model was established by intraperitoneal injection of streptozotocin (STZ) 45 mg/kg/d once a day for 5 days. After modeling, the mice were randomly divided into sham operation group (sham group), ischemia-reperfusion group(I/R group), hypoxia-inducible factor-1α (HIF-1α) inhibitor 2ME2 group (2ME2 group), DEX group and DEX+2ME2 group (DM group), with 12 mice in each group. In sham group, the skin was only cut and sutured. In the other four groups, the left anterior descending coronary artery was ligated through thoracotomy, and the ligating wire was released after 60 minutes of ischemia, followed by 120 minutes of reperfusion to establish the ischemia-reperfusion injury model. Blood samples were collected from the abdominal aorta at 120 min of reperfusion for determination of serum concentrations of troponin I (cTnI), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) by ELISA. Then the mice were sacrificed and left ventricles were isolated for observation of morphology and structure of myocardium by HE staining. The expression of HIF-1α and NOD-like receptor protein 3 (NLRP3) was detected by Western blot. Cardiac function was assessed by echocardiography at 24 h of reperfusion. **Results:** Compared with sham group, the concentrations of cTnI, IL-1β and TNF-α were significantly increased, myocardial tissue structure disorder, myocardial fiber rupture, myocardial cell swelling, inflammatory cell infiltration were significantly increased, the expression of NLRP3 in myocardial tissue was significantly increased, and stroke volume (SV), ejection fraction (EF) % and fractional shortening (FS) % were significantly decreased in I/R, 2ME2, DEX and DM groups ($P<0.05$).

* 基金项目:国家自然科学基金项目(81960053)

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(收稿日期:2023-06-23 接受日期:2023-07-18)

Compared with I/R group , the expression of HIF-1α was significantly increased, the expression of NLRP3 was significantly decreased, the concentrations of cTnI, IL-1β and TNF-α were significantly decreased, myocardial tissue structure was significantly improved, inflammatory cell infiltration was significantly decreased, SV, EF and FS were significantly increased in DEX and DM groups (P<0.05). Compared with the DEX group, the expression of HIF-1α was significantly decreased, the expression of NLRP3 was significantly increased, the concentrations of cTnI, IL-1β and TNF-α were significantly increased, myocardial tissue structure disorder, myocardial fiber rupture, myocardial cell swelling , inflammatory cell infiltration were significantly increased, SV, EF and FS were significantly decreased in the DM group (P<0.05). **Conclusions:** DEX can alleviate myocardial I/R injury in diabetic mice by up-regulating HIF-1α, inhibiting the activation of NLRP3 inflammasome and reducing inflammatory response.

Key words: Dexmedetomidine; Type 2 diabetes; Myocardium; Ischemia-reperfusion injury; Hypoxia-inducible factor-1α; Nod-like receptor protein 3

Chinese Library Classification(CLC): R-33; R587.2; R541.4; R614 Document code: A

Article ID: 1673-6273(2024)02-206-05

前言

再灌注治疗是心肌梗死(myocardial infarction,MI)最重要的治疗方法[1]。然而,冠状动脉血流的恢复可能会导致心肌进一步损伤,即缺血再灌注损伤(ischemia-reperfusion injury,IRI)[2]。研究表明,再灌注后的炎症反应在心肌 IRI 的发生发展中起重要作用[3]。糖尿病是心肌梗死(MI)最常见的危险因素之一,糖尿病患者 MI 后较非糖尿病患者心肌损伤更重, 预后更差[4,5]。糖尿病心肌引起炎症反应的加重可能是导致心肌 IRI 更为严重的主要机制之一[6]。HIF-1α 上调可抑制其下游 NLRP3 炎症反应信号通路的激活,减少促炎因子的产生,抑制组织炎症,减轻心肌 IRI[7-9]。然而,多种信号通路的缺失降低了糖尿病心肌对治疗的敏感性,导致大多数心肌保护策略在糖尿病患者中治疗效果不佳[10]。DEX 是一种高选择性α2 肾上腺素能受体激动剂,具有较强的抗炎作用[11]。多项研究表明 DEX 可改善糖尿病心肌 IRI [12]。然而,DEX 减轻糖尿病心肌 IRI 的具体机制尚待阐明。本研究拟探讨 DEX 减轻糖尿病心肌 IRI 可能的分子机制。

1 材料与方法

1.1 材料

SPF 级 C57BL 雄性小鼠 60 只,8 周龄,20-25 g, 购于新疆医科大学动物实验中心。本研究经过新疆医科大学第一附属医院动物伦理委员会审查批准(IACUC-20190225-23)。所有实验小鼠均自由进食、饮水,实验前适应性喂养一周。动物饲养环境为室温 18-23℃,湿度 40 %-70 %,12 h 昼夜循环。

1.2 方法

1.2.1 2 型糖尿病小鼠模型建立 高脂(胆固醇 1 %、牛胆盐 0.2 %、蛋黄粉 10 %、猪油 10 %、普通饲料 78.8 %)喂养 6 周。于第 7 周禁食不禁水 12 h 后腹腔注射 45 mg/kg/d 链脲佐菌素(streptozotocin,STZ)溶液(STZ 溶于冰浴的 0.1 mol/L 柠檬酸钠缓冲液,避光、现用现配),1 次 / d ,连续 5 天,腹腔注射于 30 min 内完成。于第 8 周第 2 天及第 5 天检测空腹血糖,空腹血糖大于 11.1 mmol/L 的小鼠确定为模型构建成功。采用随机数字表法将糖尿病小鼠分为五组:sham 组、I/R 组、2ME2 组、DEX 组、DM 组,每组 12 只。

1.2.2 心肌缺血再灌注损伤模型的建立 所有糖尿病小鼠称重备皮,均予以 2 %七氟烷吸入麻醉后用 20G 穿刺针行气管插管,插管后连接小动物呼吸机行机械通气,潮气量 0.8-0.9 mL,呼吸频率 120 次 / 分,吸呼比 1:1。sham 组仅切开皮肤后缝合,其余四组均在胸骨左侧第三肋间隙剪开皮肤及皮下组织,钝性分离肋间肌进入胸腔,切开心包暴露心脏,结扎冠状动脉左前降支:采用 6-0 线从左心耳根下 1 ~ 2 mm 处穿入,从肺动脉锥左侧边缘穿出。缝合方向平行于左心耳下缘。当左心室前壁及心尖周围心肌运动减弱颜色变白时,提示结扎成功。缺血 60 min 后,解除结扎,再灌注 120 min。2ME2 组于再灌注开始时即刻腹腔注射 2ME2 (货号:HY-12033 MCE 公司,美国)15 mg/kg;DEX 组于再灌注开始时腹腔注射 DEX (批号:23021131 扬子江药业集团有限公司)20 μg/kg;DM 组于再灌注开始时即刻先腹腔注射 2ME2 15 mg/kg,再注射 DEX 20 μg/kg。

1.2.3 血清样本的收集 每组随机取 8 只小鼠,于再灌注 120 min 时腹腔注射 10 %水合氯醛 300 mg/kg, 抽取小鼠腹主动脉血,4℃3000 转 /min 离心 10 min,取上清液,ELISA(南京建成生物工程研究所)检测血清 cTnI、IL-1β,TNF-α 的含量,具体操作步骤见说明书。

1.2.4 心肌组织形态观察 采血结束后,随机取 4 只小鼠立即处死,取心脏,分离左心室,冲洗干净后 4%多聚甲醛固定,石蜡包埋、切片,HE 染色后在光学显微镜 400 倍视野下观察心肌组织形态结构的变化情况。

1.2.5 Western blot 检测蛋白的表达 采血结束后取剩余 4 只小鼠立即处死,取心脏,分离左心室,充分裂解研磨,超声细胞破碎机破碎,4℃离心,取上清,用 BCA 法进行蛋白定量。取所需蛋白样品,煮沸变性,取样品 10 μg 于 SDS-PAGE 凝胶中电泳,转膜,5 %脱脂奶粉封闭 2 h,TBST 漂洗。分别加入一抗:兔抗小鼠 HIF-1α 单克隆抗体(1:2000 稀释,abcam 公司,美国)和兔抗小鼠 NLRP3 单克隆抗体 (1:2000 稀释,abcam 公司,美国),4℃孵育过夜。TBST 漂洗后加入二抗: 山羊抗兔 IgG(1:2000 稀释,北京中杉金桥生物技术有限公司),室温孵育 2 h,TBST 漂洗,显影,ImageJ 分析计算蛋白条带灰度值。

1.2.6 超声心动图检查 每组剩余 4 只小鼠于再灌注 24 h 时用小动物超声心动图(visualsonics VEVO 3100 system,Canada)对心功能进行评估。通过 M- 型超声连续扫描 5 个心动周期获取心功能各项参数:SV、EF、FS。

1.3 统计学分析

采用 SPSS 26.0 进行统计学分析, 计量资料采用均数±标

准差($\bar{x}\pm s$)表示，多组间比较采用单因素方差分析，两组间比较采用两独立样本 t 检验，P<0.05 为差异有统计学意义。

2 结果

2.1 各组血清 cTnI 含量的比较

与 sham 组相比，I/R 组、2ME2 组、DEX 组、DM 组的血清 cTnI 含量明显升高(P<0.05)；与 I/R 组相比，DEX 组、DM 组血清 cTnI 含量明显下降(P<0.05)，2ME2 组血清 cTnI 含量差异无统计学意义(P>0.05)；与 DEX 组相比，DM 组血清 cTnI 含量明显增加(P<0.05)。见表 1。

表 1 五组小鼠血清 cTnI 含量的比较(n=8，$\bar{x}\pm s$)

Table 1 Comparison of serum cTnI levels among five groups of mice (n=8, $\bar{x}\pm s$)

Groups	cTnI(ng/mL)
Sham Group	0.17±0.03
I/R Group	1.21±0.04[a]
2ME2 Group	1.23±0.06[a]
DEX Group	0.69±0.03[abc]
DM Group	1.00±0.02[abcd]

Note: Compared with sham group, [a]P<0.05; Compared with I/R group, [b]P<0.05; Compared with 2ME2 group, [c]P<0.05; Compared with DEX group, [d]P<0.05.

2.2 各种血清 IL-1β 和 TNF-α 含量的比较

与 sham 组相比，I/R 组、2ME2 组、DEX 组、DM 组的血清 IL-1β 和 TNF-α 含量明显升高(P<0.05)；与 I/R 组相比，DEX 组、DM 组血清 IL-1β，TNF-α 含量明显下降(P<0.05)，2ME2 组血清 IL-1β，TNF-α 含量差异无统计学意义(P>0.05)；与 DEX 组相比，DM 组血清 IL-1β，TNF-α 含量明显增加(P<0.05)。见表 2。

表 2 五组小鼠血清 IL-1β 和 TNF-α 水平的比较(n=8，$\bar{x}\pm s$)

Table 2 Comparison of serum IL-1β and TNF-α levels among five groups of mice (n=8, $\bar{x}\pm s$)

Groups	IL-1β	TNF-α
Sham Group	14.7±1.3	17.7±0.7
I/R Group	43.1±8.8[a]	69.8±5.9[a]
2ME2 Group	45.1±9.4[a]	70.8±10.0[a]
DEX Group	25.9±8.1[abc]	34.4±4.4[abc]
DM Group	34.0±6.3[abcd]	58.7±8.4[abcd]

Note: Compared with sham group, [a]P<0.05; Compared with I/R group, [b]P < 0.05; Compared with 2ME2 group, [c]P<0.05; Compared with DEX group, [d]P<0.05.

2.3 各组心肌组织形态观察

Sham 组心肌组织结构基本正常，少量心肌细胞肿胀伴慢性炎症细胞浸润；与 sham 组相比，I/R 组、2ME2 组、DEX 组、DM 组心肌组织结构紊乱，心肌纤维断裂增加，心肌细胞明显肿胀，炎性细胞浸润增加；与 I/R 组相比，DEX 组、DM 组心肌组织结构明显改善，炎性细胞浸润明显减少；与 DEX 组相比，DM 组心肌组织结构紊乱，心肌纤维断裂增加，心肌细胞明显肿胀，炎性细胞浸润增加，见图 1。

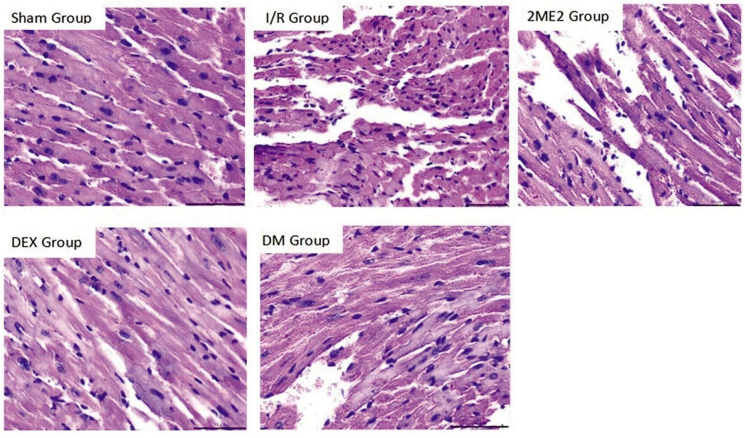

图 1 五组小鼠心肌组织 HE 染色病理学形态图(400×)

Fig. 1 Pathological morphology of myocardial tissue of five groups of mice stained with HE (400×)

2.4 各组小鼠心肌组织 HIF-1α、NLRP3 的表达情况

与 sham 组相比，I/R 组 HIF-1α 表达量无明显差异（$P>0.05$），I/R 组、2ME2 组、DEX 组、DM 组 NLRP3 表达量显著增加（$P<0.05$）；与 I/R 组相比，DEX 组、DM 组 HIF-1α 表达量明显增加（$P<0.05$），NLRP3 表达明显降低（$P<0.05$），2ME2 组 HIF-1α、NLRP3 表达量差异均无统计学意义（$P>0.05$）；与 DEX 组相比，DM 组 HIF-1α 表达量明显降低（$P<0.05$），NLRP3 表达量明显增加（$P<0.05$）。见图 2、表 3。

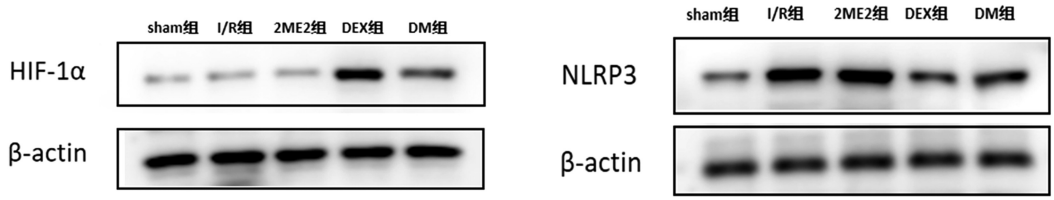

图 2 五组小鼠心肌组织 HIF-1α、NLRP3 的表达情况

Fig.2 Expression of HIF-1α and NLRP3 in myocardial tissue of the five groups of mice

表 3 五组小鼠 HIF-1α、NLRP3 表达情况的比较（n=4，$\bar{x}\pm s$）

Table 3 Comparison of HIF-1α and NLRP3 expression among five groups of mice (n=4, $\bar{x}\pm s$)

Groups	HIF-1α	NLRP3
Sham Group	0.25±0.01	0.33±0.03
I/R Group	0.29±0.01	1.02±0.01[a]
2ME2 Group	0.28±0.01	1.04±0.03[a]
DEX Group	1.46±0.08[abc]	0.53±0.02[abc]
DM Group	1.02±0.05[abcd]	0.73±0.02[abcd]

Note: Compared with sham group, [a]$P<0.05$; Compared with I/R group, [b]$P<0.05$; Compared with 2ME2 group, [c]$P<0.05$; Compared with DEX group, [d]$P<0.05$.

2.5 各组小鼠心功能的比较

与 sham 组相比，I/R 组、2ME2 组、DEX 组、DM 组 SV，EF、FS 明显降低（$P<0.05$）；与 I/R 组相比，DEX 组、DM 组 SV，EF、FS 明显升高（$P<0.05$），2ME2 组 SV，EF、FS 差异无统计学意义（$P>0.05$）；与 DEX 组相比，DM 组 SV，EF、FS 明显降低（$P<0.05$）。见表 4。

表 4 五组小鼠 SV，EF、FS 的比较（n=4，$\bar{x}\pm s$）

Table 4 Comparison of SV, EF and FS among five groups of mice (n=4, $\bar{x}\pm s$)

Groups	SV	EF(%)	FS(%)
Sham Group	46.5±2.2	74.5±6.3	44.8±1.4
I/R Group	21.3±1.7[a]	32.7±1.5[a]	25.3±2.0[a]
2ME2 Group	20.6±0.8[a]	32.5±1.6[a]	25.1±1.3[a]
DEX Group	34.8±0.7[abc]	51.3±4.1[abc]	35.8±1.8[abc]
DM Group	27.7±1.9[abcd]	42.3±1.6[abcd]	30.9±2.4[abcd]

Note: Compared with sham group, [a]$P<0.05$; Compared with I/R group, [b]$P<0.05$; Compared with 2ME2 group, [c]$P<0.05$; Compared with DEX group, [d]$P<0.05$.

3 讨论

本研究采用高脂饮食联合连续 5 天小剂量腹腔注射 STZ 建立了 2 型糖尿病小鼠模型，进一步采用结扎糖尿病小鼠冠状动脉左前降支缺血 60 min，再灌注 120 min 建立了心肌缺血再灌注损伤模型。本研究结果显示，与 sham 组相比，I/R 组、2ME2 组、DEX 组、DM 组的血清 cTnI 含量明显升高，IL-1β，TNF-α 的含量明显升高，心肌组织结构紊乱，心肌纤维断裂增多，心肌细胞明显肿胀，呈空泡状，大量炎性细胞浸润，局部组织有坏死，SV，EF、FS 明显降低，提示心肌损伤且伴有炎症反应，心功能下降，I/R 组、2ME2 组、DEX 组和 DM 组心肌缺血再灌注损伤模型均制备成功。

NLRP3 炎性小体参与心肌 IRI，NLRP3 炎性小体的形成和激活促进心肌缺血再灌注后心肌进一步损伤 [13]。NLRP3 是 NLRP3 炎性小体的重要组成部分，NLRP3 表达增加会导致 NLPP3 炎性小体的激活和 IL-1β 的过量产生[14]。一项体外细胞实验表明，NLRP3 是 DEX 介导的抑制 NLRP3 炎性小体激活的分子靶点，DEX 可以通过作用于 NLRP3 来抑制 NLRP3 炎性体的激活，从而减轻炎症反应改善心肌 IRI [15]。NLRP3 是 HIF-1a 的下游炎症调控因子[9,16,17]。IL-1β 是炎症反应的关键细胞因子，也是心肌缺血损伤的关键机制，其产生增加可损害缺血心肌的收缩功能[18,19]。TNF-α 目前已成为心肌功能障碍的重

要因素,与动脉粥样硬化的发生发展以及急性缺血性事件的风险密切相关[20,21]。NLRP3 可以促进 IL-1β 的释放,进一步促进 IL-6、TNF-α 等炎性介质的释放,形成失控的炎症级联 " 瀑布效应 "[22],因此,IL-1β 和 TNF-α 的血清浓度与心肌组织的炎症程度及损伤程度密切相关。

HIF-1α 在心肌 I/R 损伤中发挥关键作用,HIF-1α 的表达上调是在心肌缺血分子水平上最早的适应性反应之一,可通过抗炎、抗氧化应激等机制对心肌细胞产生保护作用[23,24]。然而,在糖尿病状态下,心肌 HIF-1α 信号通路受损,由其介导的对抗心肌缺血再灌注损伤的作用弱化。在本研究中,与 sham 组相比,I/R 组 HIF-1α 表达量无明显差异,NLRP3 表达量显著增加,血清 cTnI、IL-1β、TNF-α 含量明显升高,心肌结构紊乱,纤维断裂增加,细胞肿胀明显,炎症细胞浸润增多,SV、EF、FS 明显降低,提示糖尿病心肌发生 IRI 时,HIF-1α 不能上调,NLRP3 被激活,炎症反应加重,导致糖尿病心肌对缺血缺氧的正常保护反应缺失,引起更为严重的心肌损伤,这与本课题组前期研究结果以及多项国内外研究结果一致[25,26]。尽管由于多种信号通路的缺失导致大多数干预措施对糖尿病状态下的 IRI 失去保护作用,但 DEX 似乎可以逆转糖尿病心肌受损的信号通路,减轻心肌 IRI[27]。

在本研究中,与 I/R 组相比,DEX 组、DM 组 HIF-1α 表达量明显增加,NLRP3 表达明显降低,血清 cTnI、IL-1β、TNF-α 浓度明显下降,心肌组织结构明显改善,心肌纤维断裂、细胞肿胀明显减轻,炎症细胞浸润减少,SV、EF、FS 明显升高;与 DEX 组相比,DM 组 HIF-1α 表达量明显降低,NLRP3 表达明显升高,血清 cTnI、IL-1β、TNF-α 浓度明显增加,心肌结构紊乱,心肌纤维断裂增加,细胞肿胀明显,炎症细胞浸润增多,SV、EF、FS 明显降低,提示 DEX 可以逆转糖尿病心肌 HIF-1α 的表达,抑制 NLRP3 的激活,减少炎症因子的释放,减轻心肌损伤,改善心功能。

综上所述,HIF-1α 可能参与了 DEX 对糖尿病心肌 IRI 的保护机制,DEX 可能通过上调 HIF-1α,抑制 NLRP3 炎性体的激活,减轻炎症反应,改善糖尿病小鼠心肌缺血再灌注损伤,本研究为 DEX 应用于糖尿病心肌 IRI 提供了新的理论依据。

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