

单肺通气导致的肺炎性损伤及姜黄素的干预作用

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摘要:【目的】探讨姜黄素预先给药对兔单肺通气导致的肺炎性损伤的影响及可能机制。【方法】将 12 只健康新西兰白兔随机分为 2 组, 每组 6 只: 开胸单肺通气+对照剂组(组 1)和开胸单肺通气+姜黄素组(组 2)。两组兔经腹腔注射分别预先给予对照剂和姜黄素, 每天早晚各 1 次。连续给药 7 d 后, 两组兔均经口插入单腔气管导管行右侧单肺通气, 并左胸开一小口模拟手术操作。分别于机械通气前(T0)及实验结束前(T4)采集动脉血行血气分析, 计算氧合指数。处死动物后, 行右侧支气管肺泡灌洗测定髓过氧化物酶(MPO)含量及中性粒细胞数量; 取左侧肺组织, 观察病理学结果并行肺损伤评分; 采用 ELISA 法分别检测左右侧肺组织匀浆中白细胞介素-8(IL-8)、IL-10、IL-1 β 、肿瘤坏死因子 α (TNF- α)、巨噬细胞炎性蛋白-1(MIP-1)的含量; 采用免疫组化法检测左侧肺组织中核因子- κ B(NF- κ B), 髓样分化因子 88(MyD88)和 Toll 样受体 2(TLR2)的表达。【结果】T4 时组 2 氧合指数较组 1 显著升高($P < 0.05$)。与组 1 比较, 组 2 支气管肺泡灌洗液中 MPO 含量、中性粒细胞计数、肺损伤评分、肺组织匀浆中 IL-8、IL-1 β 、TNF- α 、MIP-1 含量均降低, IL-10 含量升高($P < 0.05$)。同组内两侧肺比较, 组 1 非通气侧肺炎性损伤更严重($P < 0.05$), 组 2 无差异($P > 0.05$)。与组 1 比较, 组 2 肺组织中 NF- κ B, MyD88 和 TLR2 的表达明显减少。【结论】姜黄素预先给药显著抑制开胸手术单肺通气时炎症因子的释放, 减轻肺炎性损伤, 其机制可能与 TLR2 通过 MyD88 信号通路调节 NF- κ B 的活性有关。

关键词:姜黄素; 机械通气, 单肺通气; 肺损伤, 呼吸窘迫综合征; 动物, 兔

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Mechanism of Lung Inflammatory Injury Induced by One-lung Ventilation and Effects of Curcumin in a Rabbit Model of Thoracic Surgery

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Abstract:【Objective】 To investigate the effect and mechanism of curcumin on lung inflammatory injury induced by one-lung ventilation (OLV) in a rabbit model of thoracic surgery. 【Methods】 Twelve New Zealand rabbits weighing 2.0~2.5 kg were randomly allocated into two groups ($n = 6$ each): OLV+placebo group (group 1) received 10% dimethyl sulfoxide (DMSO) as placebo and OLV+curcumin group (group 2) received curcumin 40 mg/kg which dissolved in 10% DMSO by intraperitoneal injection. After seven consecutive days of pretreatment, the animals were received orotracheal intubation and the model of OLV-induced lung injury in thoracic surgery was established. Then two groups were received mechanical ventilation (VT = 12 mL/kg, RR = 40 bpm, I:E = 1:2, FiO₂ = 0.6). After two lung ventilation (TLV) for 30 min, they received OLV for 3 h, and then turned to TLV for 30 min. Monitoring blood pressure, heart rate and peak inspiratory pressure of animals in two groups continuously, and collecting arterial blood samples to calculate the PaO₂/FiO₂ ratio (P/F ratio) before (T0) and after (T4) mechanical ventilation, respectively. At the end of the experiment, the animals were killed and bronchoalveolar lavage was performed in the right lung lobes for the concentration of MPO and neutrophil counts. The left lobes were collected for HE stain to observe pathological morphological changes and get lung injury score. Then the concentration of IL-8, IL-10, IL-1 β , TNF- α , and MIP-1 (macrophage inflammatory protein-1) in two lungs were quantified using enzyme-linked immunosorbent assay (ELISA). Furthermore, the levels of nuclear factor kappa B (NF- κ B), myeloid differentiation factor 88 (MyD88) and Toll-like receptor 2 (TLR2) were analyzed by immunohistochemistry. 【Results】 The P/F ratio

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in group 2 was significantly higher than that in group 1 at T4 ($P < 0.05$). Compared with group 1, the concentration of MPO and neutrophil counts in BALF, lung injury score, the contents of IL-8, IL-1 β , TNF- α , and MIP-1 in group 2 were significantly lower ($P < 0.05$), the level of IL-10 in group 2 was significantly higher ($P < 0.05$). In group 1, compared with the right (ventilated) lung, MPO concentration in BALF, neutrophil counts, lung injury score and the contents of IL-8, IL-1 β , TNF- α , and MIP-1 in the left (nonventilated) lung were significantly higher ($P < 0.05$), and the contents of IL-10 in the left lung were lower ($P < 0.05$). The expression of NF- κ B, MyD88, and TLR2 in the group 2 were much lower than those in the group 1 ($P < 0.05$). 【Conclusion】 Curcumin pretreatment attenuates inflammatory injury induced by one lung ventilation of rabbits in thoracic surgery, and the anti-inflammatory effect of curcumin is possibly related to the inhibition of TLR2, MyD88, and NF- κ B.

Key words: curcumin; mechanical ventilation, one-lung ventilation; lung injury, respiratory distress syndrome; animal, rabbit
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开胸手术时,单肺通气及手术操作可引起大量炎性因子释放,诱发肺部炎症反应,造成肺损伤,导致术后肺部并发症增加^[1-4]。姜黄素是从植物姜黄中提取的多酚色素,多项研究证实其具有抗炎、抗氧化作用^[5-7]。在多种致病因素诱发的肺损伤中,应用姜黄素后显示出较好的肺保护作用^[6-9]。据 Liu 等^[10]报道,姜黄素可通过抑制 Toll 样受体,调控核因子- κ B (NF- κ B)通路来调节炎症反应。Akira 及 Horng 等^[11-12]报道,NF- κ B 通过 Toll 样受体 2 (TLR2)、髓样分化因子 88 (MyD88)信号通路被激活后,可促使大量炎性因子产生,导致炎症反应。姜黄素能否减轻单肺通气导致的肺炎性损伤,是否通过调节该信号通路尚不清楚。为此,本研究建立兔开胸单肺通气模型,探讨姜黄素预先给药对肺炎性损伤的影响及其对 TLR2-MyD88-NF- κ B 信号通路的调节作用,初步探讨其作用机制,为其临床应用提供实验依据,并为下一步的机制研究提供新的方向。

1 材料与方 法

1.1 动物来源和分组

清洁级健康新西兰白兔 12 只,雌雄不拘,体质量 2.0 ~ 2.5 kg,由中山大学动物实验中心提供(许可证号为 SCXK(粤)20090023)。采用随机数字表法,将兔随机分为 2 组($n = 6$):开胸单肺通气+对照剂组(组 1)和开胸单肺通气+姜黄素组(组 2)。

1.2 主要试剂

姜黄素购自美国 Sigma 公司(批号 039K1615),二甲基亚砷(DMSO)购自广州东盛生

物科技有限公司,MPO 测定试剂盒(南京建成生物工程研究所,批号 20111018),IL-8、IL-10、IL-1 β 、TNF- α 、MIP-1 ELISA 试剂盒(武汉博士德生物工程有限公司,批号分别为 20110415、20110321、20110321、20110320、20110412),TLR2、MyD88 和 NF- κ B 免疫组化试剂盒(武汉博士德生物工程有限公司,批号分别为 20111125、20111129、20111115)。

1.3 主要仪器及设备

动物呼吸机(PA-500,南京普澳医疗设备有限公司),生理记录仪(MP150,Biopac 公司),离心机(型号 5424,德国 eppendorf 公司),分光光度计(型号 DUT30,BECKMAN 公司),气管导管(ID3.5mm, Mallinckrodt, Ireland)。

1.4 动物模型的建立

两组兔于开胸手术单肺通气前 7 天开始经腹腔注射预先给药。组 1 给予对照剂(5 mL 10% DMSO),组 2 给予姜黄素 40 mg/kg(溶于 5 mL 10% DMSO 中),每天早晚各 1 次^[8]。连续给药 7 d 后,建立兔右侧单肺通气并左侧开胸手术模型^[13],即 20%乌拉坦 5 mL/kg 耳缘静脉注射,麻醉后经口插入单腔气管导管(ID:3.5 mm),接动物呼吸机双肺通气。右侧股动脉置管,采集动脉血样,进行血气分析并监测心率及平均动脉压。左颈内静脉穿刺置管连接微量注射泵,以 10 mL \cdot kg⁻¹ \cdot h⁻¹的速率持续输注乳酸林格氏液,并输注 0.05 mg/kg 顺式阿曲库铵维持肌松。双肺通气 30 min 后,置动物于右侧卧位,将导管插入右主支气管行右侧单肺通气,通过观察右侧胸廓运动、听诊右肺呼吸音及气道压力增高等变化来判断导管的位置^[14]。单肺通气期间两组兔均于左侧胸壁 5 ~ 6 肋间开一长

约3~4 cm小口至胸腔,模拟手术操作并观察左肺萎陷情况^[3]。单肺通气3 h后再恢复双肺通气(将气管导管退至气管内),缝合手术切口。单肺及双肺通气期间通气参数不变,设置为:潮气量12 mL/kg,呼吸频率40 min⁻¹,吸呼比=1:2,吸入氧浓度为0.6,氧流量为1 L/min。恢复双肺通气30 min后实验结束,放血处死动物。

1.5 指标检测和方法

于机械通气前(T₀)和实验结束时(T₄)采集动脉血,血气分析计算氧合指数(PaO₂/FiO₂, P/F ratio)。处死动物后,开胸取肺,立即结扎左主支气管,行右支气管肺泡灌洗(BALF)。利用5℃生理盐水5 mL/kg反复肺灌洗3次,回收率达80%以上。将回收得到的灌洗液用双层无菌纱布过滤,1 503 ×g离心15 min。将细胞沉渣重新悬浮于1 mL生理盐水中,涂片瑞氏染色计数中性粒细胞。上清液采用双抗体夹心ABC-ELISA法测定MPO活性。于左肺上下肺叶相应的腹侧和背侧共四个部位,分别取约1.0 cm³肺组织置入40 g/L多聚甲醛溶液中固定,常规石蜡包埋切片,HE染色光镜下参照文献^[3]进行肺损伤评分,无改变0分,轻度改变1分,中度改变2分,重度改变3分,极重度改变4分,然后累计总分。每张切片观察10个高倍视野,取10次评分均值,以每组标本的均值作为该组的肺损伤评分。分别取左、右下肺叶约1.0 cm³肺组织按1:9质量体积比加入PBS缓冲液(pH=7.4)制备成10%组织匀浆,4℃745×g离心10 min,上清液采用ELISA法测定IL-8、IL-10、IL-1β、TNF-α、MIP-1的含量。分别取两组动物左肺叶约0.5 cm³肺组织制成石蜡切片,严格按照说明书步骤采用免疫组化法分别检测肺组织中NF-κB、MyD88和TLR2的表达。每只动物肺组织取两张切片,每张切片随机观察3个高倍视野(×400)。采用Image-Pro Plus图像分析系统分析各指标的免疫组化图片,测定各随机视野下阳性染色肺组织的平均光密度值(mean optical density, MOD)。最后分别计算各组各指标MOD平均值并以此作为反映该指标蛋白表达含量的依据^[15]。

1.6 统计学分析

采用SPSS17.0软件包进行分析,正态分布的计量资料以均数±标准差($\bar{x} \pm s$)表示。组间各指

标比较采用两独立样本 t 检验,组内左右肺各指标比较采用配对 t 检验测定差异显著性, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组兔动脉氧分压和氧合指数的比较

T₀(机械通气前)及T₄(实验结束前)时两组MAP、PaCO₂及HCO₃⁻无差异($P > 0.05$)。同组内比较,T₄时两组PaO₂均较T₀时升高,氧合指数与T₀时相比均明显降低($P < 0.05$)。组间比较,T₀时两组PaO₂及氧合指数比较无差异($P > 0.05$),T₄时组2 PaO₂及氧合指数显著高于组1($P < 0.05$,图1)。

2.2 两组兔BALF中MPO含量及中性粒细胞数量的比较

与组1比较,组2BALF中MPO含量和中性粒细胞计数显著降低($P < 0.05$,表1)。

2.3 两组兔肺组织光镜下形态学的比较

光镜下组1肺组织:肺泡腔内渗出及出血多,肺泡间隔明显增厚,炎性细胞浸润显著增多;组2肺组织:肺泡腔内渗出物少,未见出血,炎性细胞浸润少,肺泡间隔增厚不明显。与组1相比,组2肺损伤评分明显降低($P < 0.05$)(图2,表1)。

2.4 两组兔肺组织匀浆中炎症因子的比较

与组1比较,组2左、右侧肺组织匀浆中IL-8、IL-1β、TNF-α和MIP-1浓度均降低,IL-10浓度升高($P < 0.05$);组内两侧肺组织之间比较,组1左侧(非通气侧)肺组织中IL-8、IL-1β、TNF-α和MIP-1浓度均高于右侧(通气侧),IL-10浓度低于右侧($P < 0.05$);组2左侧肺IL-1β和MIP-1浓度高于右侧,IL-10浓度低于右侧($P < 0.05$),余无差异($P > 0.05$,表2)。

2.5 两组兔肺组织中NF-κB、MyD88和TLR2的表达

免疫组化显示NF-κB、MyD88和TLR2在两组动物肺泡上皮细胞的胞浆和胞核中均出现棕黄色颗粒的阳性染色,表明单肺通气可导致兔肺组织细胞表达NF-κB、MyD88和TLR2蛋白。而与组1相比,组2肺组织中NF-κB、MyD88和TLR2三种蛋白含量的MOD值均明显降低,表明经姜黄素干预后三种蛋白的表达均明显减少($P < 0.05$,图3、4)。

表 1 两组 BALF 中 MPO 含量、中性粒细胞计数和肺损伤评分的比较

Table 1 Comparison of levels of MPO, numbers of neutrophils in BALF and injury scores between the two groups (n = 6, $\bar{x} \pm s$)

Index	Group 1	Group 2	F	P
MPO/U/L	15.9 ± 0.9	7.4 ± 0.7 ¹⁾	0.861	0.000
Neutrocytes/(×10 ⁹ /L)	10.3 ± 1.0	6.1 ± 1.1 ¹⁾	0.151	0.000
Lung leisure/scores	7.4 ± 0.9	4.7 ± 0.4 ¹⁾	7.789	0.000

Compared to group 1, 1)P < 0.05

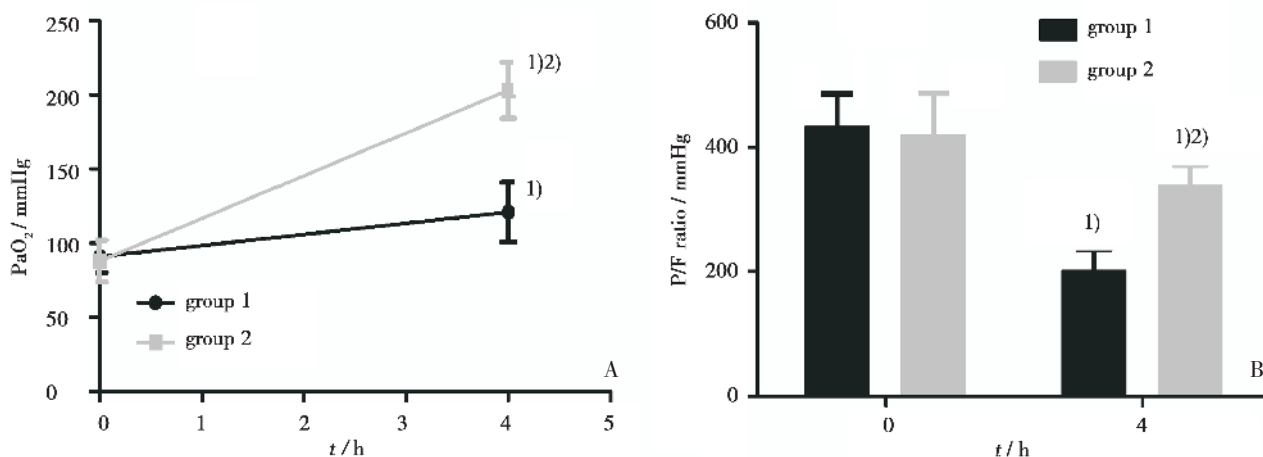


图 1 两组兔动脉氧分压和氧合指数的比较

Fig.1 Comparison of (A) PaO₂ and (B) P/F ratio at two representative time points between the two groups ($\bar{x} \pm s$, n = 6)

Compared to T₀ within the same group, 1)P < 0.05; Compared to group 1 at the same time point, 2)P < 0.05. Group 1: OLV+placebo; Group 2: OLV + curcumin. PaO₂ = arterial partial pressure of oxygen; P/F = PaO₂/FiO₂; FiO₂ = fraction of inspired oxygen.

3 讨论

采用潮气量(VT)12 mL/kg 单肺通气 3 h 即可

造成兔及猪较典型的肺炎性损伤表现^[4,13],因而本研究采用经口气管插管并最大程度模拟临床开胸手术及机械通气的过程,设置了 VT 12 mL/kg 单肺通气 3 h。本研究参照文献^[8,13]中姜黄素给药方法、

表 2 两组肺组织匀浆中炎症因子浓度的比较

Table 2 Comparison of levels of IL-8, IL-10, IL-1β, TNF-α, and MIP-1 in lung homogenate between the two groups (n = 6, $\bar{x} \pm s$)

Index	Group 1		Group 2	
	left lung	right lung	left lung	right lung
IL-8/(ng/L)	145 ± 8	112 ± 10 ¹⁾	92 ± 6 ²⁾	75 ± 4 ²⁾
IL-10/(ng/mL)	101 ± 11	139 ± 8 ¹⁾	189 ± 16 ²⁾	274 ± 20 ¹⁾²⁾
IL-1β/(pg/mL)	884 ± 68	597 ± 14 ¹⁾	457 ± 21 ²⁾	334 ± 21 ¹⁾²⁾
TNF-α (ng/L)	194 ± 21	160 ± 8 ¹⁾	135 ± 7 ²⁾	123 ± 13 ²⁾
MIP-1/(ng/L)	311±36	242 ± 9 ¹⁾	180 ± 14 ²⁾	153 ± 6 ¹⁾²⁾

Group 1 : OLV+placebo; Group 2 : OLV+curcumin. Compared to left lung, 1)P < 0.05; Compared to group 1, 2)P < 0.05

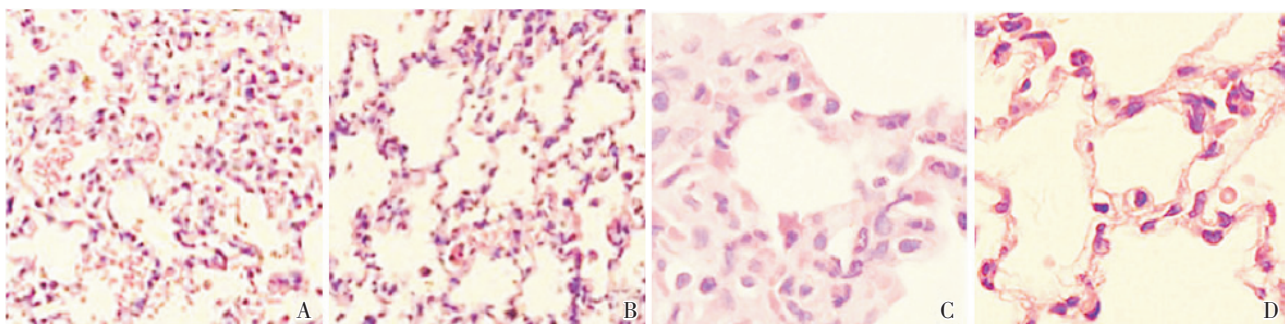


图 2 两组兔肺组织 HE 染色病理学比较

Fig.2 Pathematology comparison of lung tissue between the two groups

Group 1 : OLV+placebo; Group 2 : OLV+curcumin. A: lung tissue of group 1, $\times 100$; B: lung tissue of group 2, $\times 100$; C: lung tissue of group 1, $\times 400$; D: lung tissue of group 2, $\times 400$

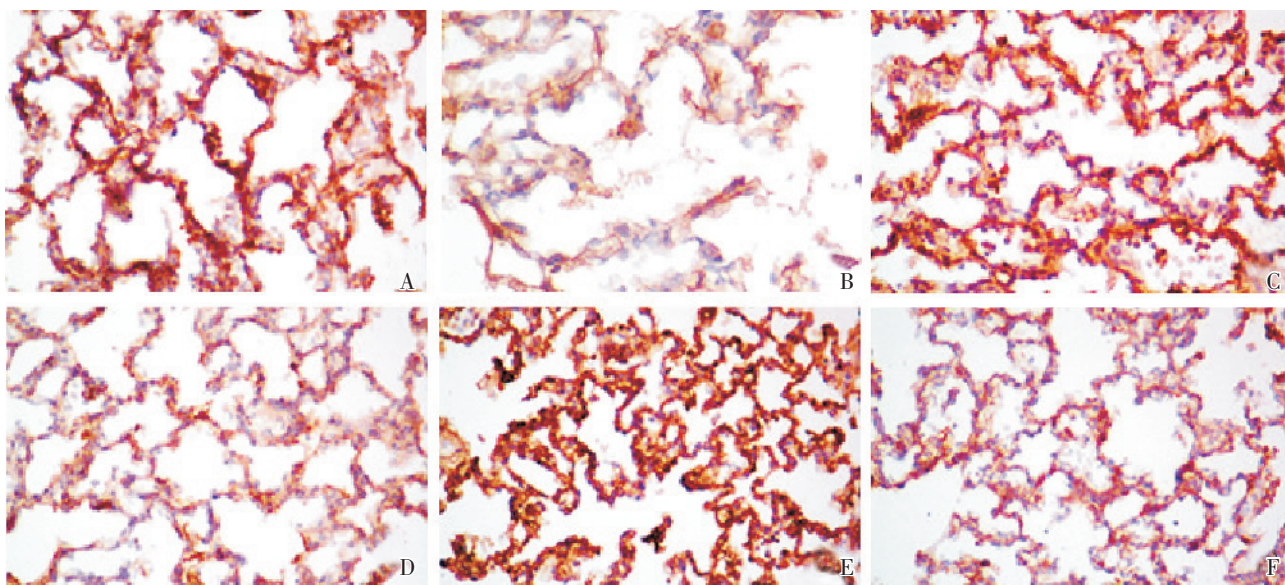


图 3 两组兔肺组织 NF- κ B、MyD88 和 TLR2 免疫组化染色

Fig.3 Immunohistochemistry staining of NF- κ B, MyD88, and TLR2 of the two groups

Group 1 : OLV+placebo; Group 2 : OLV+curcumin; $\times 400$. A: group 1 with high MOD value for NF- κ B level; B: group 2 with lower MOD value for NF- κ B level; C: group 1 with high MOD value for MyD88 level; D: group 2 with lower MOD value for MyD88 level; E: group 1 with high MOD value for TLR2 level; F: group 2 with lower MOD value for TLR2 level.

剂量及给药时间, 连续给药 7 d 旨在达到理想的治疗剂量及浓度。

开胸手术单肺通气期间, 通气侧肺受机械通气刺激, 而非通气侧肺受肺萎陷及手术牵拉、挤压等操作刺激, 均可诱发大量炎性因子的释放^[2-3]。TNF- α 、IL-1 β 可引起多种炎性介质发生失控性释放, 是形成炎性瀑布效应的始动因素。IL-8 具有明显的趋化及活化中性粒细胞的作用。MIP 是趋化

因子, 趋化单核细胞和中性粒细胞^[5]。IL-10 则抑制许多炎性细胞因子的分泌, 是抗炎因子。MPO 的活性直接反映中性粒细胞的功能和活性状态。肺炎性损伤是在炎性因子及趋化因子相互作用下, 血液中的中性粒细胞黏附、激活、迁移, 进入肺泡并释放大量氧自由基及蛋白水解酶, 破坏肺泡-毛细血管屏障功能, 造成肺泡膜通透性增强, 肺泡和间质水肿, 进而造成 PaO₂ 及氧合指数降低等

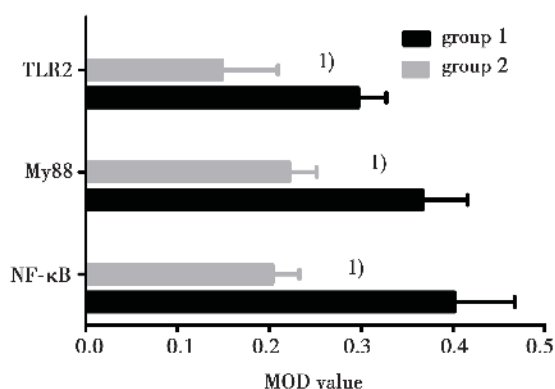


图4 两组兔肺组织NF-κB、MyD88和TLR2的MOD值比较

Fig.4 Comparison of the MOD values of NF-κB, MyD88 and TLR2 between the two groups

Group 1: OLV+placebo; Group 2: OLV+curcumin. Compared to group 1, 1) $P < 0.05$ ($\bar{x} \pm s$, $n = 6$)

氧合功能障碍,其损伤程度亦可通过病理学评分反映^[3,16]。本研究中,组1 T4时 PaO₂和氧合指数降低,BALF中MPO含量、中性粒细胞计数增高,双侧肺组织中致炎因子含量增加、抗炎因子含量减少及肺损伤评分增高,出现了典型的肺炎性损伤表现;组2经姜黄素处理干预后,MPO含量及中性粒细胞数量、致炎因子及肺损伤评分显著降低,抗炎因子含量、PaO₂及氧合指数提高,表明姜黄素通过抑制致炎因子和提高抗炎因子的释放,减轻开胸手术单肺通气导致的肺炎性损伤。

核因子-κB(NF-κB)在肺部炎症的细胞信号转导调控中起核心作用,通常与抑制性蛋白IκB结合成为无活性状态存在于细胞质中,当受机械损伤、感染等多种病理因素刺激时,NF-κB被激活而与IκB解离,进入细胞核内并活化TNF-α、IL-1、IL-6、IL-8、IL-10等多种炎性细胞因子,造成炎性损伤^[17]。You等^[18]利用兔单肺通气致急性肺损伤模型,证实单肺通气通过活化NF-κB引起促炎性因子大量释放,造成肺损伤;应用NF-κB特异性阻断剂干预后能有效减轻OLV所致肺损伤。Liu等^[10]研究证实姜黄素可通过抑制细胞表面TLR4介导的MyD88蛋白依赖的信号通路抑制NF-κB,进而抑制炎性因子的释放。TLR2作为TLR家族中重要的一员,配体较TLR4更为广泛,可识别脂蛋

白、脂多肽、脂壁酸等,且同TLR4一样只在髓源性细胞(如单核巨噬细胞)上表达。已有研究证实NF-κB可通过TLR2/TIR/MyD88/Mal信号通路被激活,促使发生炎性损伤^[11-12]。在Concanavalin A导致的小鼠肝损伤^[19]、心肌缺血再灌注所致损伤^[20]中,TLR2信号通路均被证实发挥重要作用。在本研究中,免疫组化显示NF-κB、MyD88和TLR2在两组动物肺组织中均出现棕黄色颗粒的阳性染色,提示单肺通气致肺炎性损伤可能与TLR2-MyD88-NF-κB通路活化有关。与组1相比,组2三个蛋白表达显著减少,提示姜黄素能减轻单肺通气致肺损伤可能与抑制该通路的活化,减少炎性因子的释放存在密切联系。本研究尚不能确定姜黄素减轻单肺通气致肺炎性损伤的机制与TLR2-MyD88-NF-κB通路之间的确切关系,但为进一步探讨单肺通气致肺损伤及姜黄素干预作用的相关机制具有一定提示作用,为今后的深入研究提供了新的思路。

通过对两侧肺炎性损伤程度的比较,本研究还发现,组1非通气侧肺较通气侧肺炎性损伤更严重,说明肺萎陷及手术操作刺激较机械通气更易造成肺发生炎性反应,与Kozian等^[3]研究结果一致。组2经姜黄素干预处理后,两侧肺损伤同时减轻,基本一致,表明姜黄素能对单肺通气导致的肺炎性损伤具有明显的保护作用。

综上所述,姜黄素预先给药显著抑制开胸手术单肺通气时炎性因子的释放,减轻肺炎性损伤,其机制可能与调节TLR2-MyD88-NF-κB通路的活性有关。

参考文献:

- [1] Schilling T, Kozian A, Huth C, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery[J]. *Anesth Analg*, 2005, 101(4): 957-965.
- [2] Zingg U, Forberger J, Frey DM, et al. Inflammatory response in ventilated left and collapsed right lungs, serum and pleural fluid, in transthoracic esophagectomy for cancer[J]. *Eur Cytokine Netw*, 2010, 21(1): 50-57.
- [3] Kozian A, Schilling T, Rocken C, et al. Increased alveolar damage after mechanical ventilation in a porcine

- mode of thoracic surgery [J]. *J Cardiothoracic and vascular Anesth*, 2010, 24(4): 617-623.
- [4] Theroux MC, Fisher AO, Horner LM, et al. Protective ventilation to reduce inflammatory injury from one lung ventilation in a piglet model [J]. *Pediatric Anesthesia*, 2010, 20(4): 356-364.
- [5] Abe Y, Hashimoto S, Horie T. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages [J]. *Pharmacol Res*, 1999, 39(1): 41-47.
- [6] Ram A, Das M, Ghosh B. Curcumin attenuates allergen-induced airway hyperresponsiveness in sensitized guinea pigs[J]. *Biol Pharm Bull*, 2003, 26(7): 1021-1024.
- [7] Sun J, Guo W, Ben Y, et al. Preventive effects of curcumin and dexamethasone on lung transplantation-associated lung injury in rats[J]. *Crit Care Med*, 2008, 36(4): 1205-1213.
- [8] Guzel A, Kanter M, Aksu B, et al. Preventive effects of curcumin on different aspiration material induced lung injury in rats. *Pediatr Surg Int*, 2009, 25(1): 83-92.
- [9] Sun J, Yang D, Li S, et al. Effects of curcumin or dexamethasone on lung ischaemia-reperfusion injury in rats[J]. *Eur Respir J*, 2009, 33(2): 398-404.
- [10] Liu K, Shen L, Wang J, et al. The preventative role of curcumin on the lung inflammatory response induced by cardiopulmonary bypass in rats[J]. *J Surg Res*, 2012, 174(1): 73-82.
- [11] Akira S, Takeda K, Kaisho T. Toll-like receptors; critical proteins linking innate and acquired immunity [J]. *Nat Immunol*, 2001, 2(8): 675-680.
- [12] Horng T, Barton GM, Flavell RA, et al. The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors [J]. *Nature*, 2002, 420(6913): 329-333.
- [13] 李慧婷, 林文前, 谭红鹰, 等. 姜黄素减轻兔单肺通气导致的肺损伤[J]. *中山大学学报: 医学科学版*, 2011, 32(6): 735-740.
- Li HT, Lin WQ, Tan HY, et al. Curcumin attenuates lung oxidative injury induced by one lung ventilation in rabbits[J]. *J SUN Yat-sen Univ: Med Sci*, 2011, 32(6): 735-740.
- [14] Schreiber T, Niemann C, Schmidt B, et al. A novel model of selective lung ventilation to investigate the long-term effects of ventilation-induced lung injury[J]. *Shock*, 2006, 26(1): 50-54.
- [15] Kim BO, Liu Y, Ruan Y. Neuropathologies in transgenic mice expressing human immunodeficiency virus type 1 Tat protein under the regulation of the astrocyte-specific glial fibrillary acidic protein promoter and doxycycline [J]. *Am J Pathol*, 2003, 162(5): 1693-707.
- [16] Matute-Bello G, Downey G, Moore BB, et al. An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals[J]. *Am J Respir Cell Mol Biol*, 2011, 44(5): 725-738.
- [17] Reuter S, Charlet J, Juncker T, et al. Effect of curcumin on nuclear factor kappaB signaling pathways in human chronic myelogenous K562 leukemia cells [J]. *Ann N Y Acad Sci*, 2009, 1171(22): 436-447.
- [18] You Z, Feng D, Xu H, et al. Nuclear factor-kappa B mediates one-lung ventilation-induced acute lung injury in rabbits[J]. *J Invest Surg*, 2012, 25(2): 78-85.
- [19] Tu CT, Han B, Yao QY, et al. Curcumin attenuates Concanavalin A-induced liver injury in mice by inhibition of Toll-like receptor (TLR) 2, TLR4 and TLR9 expression[J]. *Int Immunopharmacol*, 2012, 12(1): 151-157.
- [20] Kim YS, Kwon JS, Cho YK, et al. Curcumin reduces the cardiac ischemia-reperfusion injury: involvement of the toll-like receptor 2 in cardiomyocytes [J]. *J Nutr Biochem*, 2012, 23(11): 1514-1523.

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