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·基础研究·

HMGB1 与 RAGE 水平在急性主动脉夹层肺损伤患者中的变化及临床意义

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摘 要 **目的：**探讨急性主动脉夹层（AAD）患者血清高迁移率族蛋白 B1（HMGB1）与晚期糖基化终产物受体（RAGE）水平与继发急性肺损伤的关系。

方法：选取 2016 年 3 月—2018 年 5 月经全主动脉 CTA 以及超声心动图等影像学检查明确诊断的 AAD 患者 56 例为研究对象。按静态吸氧状态下氧合指数（PaO_2/FiO_2）大小将患者分为肺损伤组（21 例）与非肺损伤组（35 例）。随机选取健康体检人员 30 例为对照组。AAD 患者入院后每 4 小时抽血次，对照组受试者仅抽取 1 次清晨空腹肘静脉血。采用 ELISA 法检测血清 HMGB1、RAGE 水平，同时检测 PaO_2、计算 PaO_2/FiO_2。

结果：与健康对照组比较，两组 AAD 患者入院后 24 h 的 HMGB1、RAGE 水平均明显高于健康对照组，且两者在肺损伤组均明显高于非肺损伤组（均 $P<0.05$）。两组 AAD 患者入院后 HMGB1、RAGE 水平不断上升，而 PaO_2/FiO_2 逐渐降低，并均入院后 48~60 h 达到峰值，肺损伤组的 3 项指标的变化幅度均明显大于非肺损伤组（均 $P<0.05$）；随着发病时间的推移，HMGB1、RAGE 水平达到峰值后下降，PaO_2/FiO_2 逐渐回升。AAD 患者中，HMGB1 与 RAGE 水平与 PaO_2/FiO_2 均呈明显负相关（r=-0.940、-0.794）。

结论：HMGB1/RAGE 信号通路可能在 AAD 肺损伤中发挥着重要的作用，随着 HMGB1、RAGE 水平的升高，肺损伤程度逐渐加重，监测 HMGB1、RAGE 水平可以对 AAD 并发肺损伤的风险进行评估；对 HMGB1/RAGE 信号通路深入研究可能会为 AAD 肺损伤的干预提供靶点。

关键词 动脉瘤，夹层；肺损伤；高迁移率族蛋白质类；高级糖基化终产物特异性受体
中图分类号：R654.3

Changes in HMGB1 and RAGE levels in patients with lung injury induced by acute aortic dissection and the clinical significance

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Abstract **Objective:** To investigate the association of the serum levels of high mobility group protein B1 (HMGB1) and advanced glycosylation end-product receptor (RAGE) in patients with acute lung injury secondary to acute aortic

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dissection (AAD).

Methods: From March 2016 to May 2018, 56 consecutive patients with AAD who were diagnosed by CTA of the whole aorta and echocardiography were enrolled. According to the values of oxygenation index (PaO_2/FiO_2) during oxygen inhalation in a resting state, the patients were divided into lung injury group (21 cases) and non-lung injury group (35 cases), and 30 individuals undergoing health maintenance examination were randomly selected as control group. Blood samples were drawn once per 4 h in the AAD patients after admission, and in the control group, fasting blood samples were taken only once from the elbow vein in the morning. The serum levels of HMGB1 and RAGE were measured by ELISA and PaO_2 values were detected for calculating PaO_2/FiO_2.

Results: In both groups of AAD patients, the serum levels of HMGB1 and RAGE at 24 h after admission were significantly higher than those in the healthy control group, and which were also significantly higher in lung injury group than those in non-lung injury group (all $P<0.05$). In both groups of AAD patients, the serum levels of HMGB1 and RAGE were continuously increased, while the PaO_2/FiO_2 values were gradually decreased, and all reached a peak value within 48-60 h after admission. The changing amplitudes of the 3 variables were all significantly greater in lung injury group than those in non-lung injury group (all $P<0.05$). After they reached the peak values, the HMGB1 and RAGE levels gradually decreased, while the PaO_2/FiO_2 values correspondingly increased as time elapsed. In AAD patients, both HMGB1 and RAGE levels presented a significantly negative correlation with PaO_2/FiO_2 value (r=–0.940, –0.794).

Conclusion: The HMGB1/RAGE signaling pathway may play an important role in the occurrence of lung injury in AAD, and lung injury may be worsened with the increase of HMGB1 and RAGE levels. Monitoring of the HMGB1 and RAGE levels can help to evaluate the risk of lung injury after AAD. Further investigations of the HMGB1/RAGE signaling pathway may provide interventional targets for lung injury after AAD.

Key words Aneurysm, Dissecting; Lung Injury; High Mobility Group Proteins; Advanced Glycosylation End Product-Specific Receptor

CLC number: R654.3

急性肺损伤（acute lung injury，ALI）是急性主动脉夹层（acute aortic dissection，AAD）常见并发症之一，以弥散性肺泡上皮细胞损伤和毛细血管渗透性增加为特征，其发生率高达50%以上[1-2]。并发ALI的AAD患者，带管时间及在ICU停留时间显著延长，病死率显著增加[3]。因此，研究AAD所致ALI的发病机制对于改善患者临床预后具有十分重要的指导意义，但其分子机制尚未明确，多认为与过度的炎症级联反应有关[3]。高迁移率族蛋白B1（high-mobility group box 1，HMGB1）属于HMGB家族成员，定位于人类染色体13q12，由215个氨基酸残基组成[4]。HMGB1作为一种核内非组蛋白，具有极强的促炎作用，在炎症级联反应的启动和维持中扮演关键角色[5]。当机体处于稳态、无外界刺激时主要存在于细胞核中，应激状态下，HMGB1通过非经典或被动释放等方式分泌至细胞外，并通过与特异性受体–晚期糖基化终产物受体（receptor of advanced glycosylation end-products，RAGE）相结合，激活丝裂原活化蛋白激酶途径，活化激活核因子κB（nuclear factor κB，NF-κB），诱导IL-1β、IL-6、TNF-α等炎症因子大量分泌，进而产生炎症级联效应[6]。本研究拟通过监测HMGB1/RAGE在急性主动脉夹层肺损伤患者中的表达，分析其表达与氧合指数[动脉氧气压力（PaO_2）/吸入氧气分率（FiO_2）]的相关性，并探讨其临床意义。

1 资料与方法

1.1 对象与分组

选取2016年3月—2018年5月我院经全主动脉CTA或DSA造影确诊的急性主动脉夹层患者为研究对象。纳入标准：(1) 发病24 h内入院治疗；(2) 经保守治疗4 d以上。排除标准：(1) 合并恶性肿瘤或

全身炎症性、免疫性疾病；⑵ 合并急性肺炎和慢性阻塞性肺疾病等呼吸系统疾病者。符合入排标准的患者56例。其中，男39例，女17例，男女比例2.3∶1；年龄34~81岁，平均（63.2 ± 11.7）岁。按静态吸氧状态下PaO_2/FiO_2分为肺损伤组21例（PaO_2/FiO_2≤300 mmHg，1 mmHg=0.133 kPa）及非肺损伤组35例（PaO_2/FiO_2>300 mmHg）。随机选取健康体检人员30例作为对照组。健康对照组仅抽取1次清晨空腹肘静脉血，分组以住院保守治疗期间PaO_2/FiO_2最小值为准。

1.2 研究方法

患者入院后即入住监护室，均予以吸氧、心电监护、镇痛、降压、通便等对症处理，必要时给予呼吸机辅助治疗。所有患者于入院后每4 h抽动脉血气测PaO_2，计算PaO_2/FiO_2值。并在对应时间点抽肘静脉血，血标本经3 000 *r*/min离心10 min后，留取上清液保存在−80 ℃的冰箱中待测。统一采用酶联免疫吸附法（ELISA）检测HMGB1与RAGE水平，试剂盒由上海恒远生物有限公司提供，严格按照说明书操作。对照组仅抽取1次清晨空腹肘静脉血。

1.3 统计学处理

采用SPSS 18.0软件进行数据分析。计数资料以例数（百分比）[*n*（%）]表示，计量资料以均数 ± 标准差（$\bar{x} \pm s$）表示。组间比较采用*t*检验、方差分析、χ^2检验，相关性采用直线相关分析法，以α=0.05为检验水准，*P*<0.05为差异有统计学意义。

2 结　果

2.1 基本情况对比

两组患者在性别、年龄、吸烟史、糖尿病史、高血压史、冠心病史、肌酐、脑纳肽（BNP）、射血分数（EF）值差异均无统计学意义（均*P*>0.05）（表1）。

2.2 HMGB1 与 RAGE 水平在 AAD 患者中的变化

两组AAD患者入院后24 h的HMGB1、RAGE水平水平均高于健康对照组（均*P*<0.05），且肺损伤组两者水平明显高于非肺损伤组（均*P*<0.05）（表2）。

表 1　肺损伤组与非肺损伤组患者基本资料比较

Table 1　Comparison of the general data between lung injury group and non-lung injury group

资料	肺损伤组（*n*=21）	非肺损伤组（*n*=35）	χ^2/t	*P*
男性 [*n*（%）]	17（80.9）	22（62.8）	2.033	0.154
年龄≥ 60 岁 [*n*（%）]	19（90.4）	27（77.1）	0.737	0.390
吸烟史 [*n*（%）]	14（66.7）	27（77.1）	0.735	0.391
糖尿病史 [*n*（%）]	7（33.3）	11（31.4）	0.022	0.883
高血压史 [*n*（%）]	19（90.5）	32（91.4）	0.015	0.904
冠心病史 [*n*（%）]	7（33.3）	12（34.2）	0.005	0.942
肌酐（μmol/L，$\bar{x} \pm s$）	82.9 ± 23.5	90.6 ± 20.4	−1.295	0.201
BNP（pg/mL，$\bar{x} \pm s$）	102.0 ± 43.7	100.7 ± 30.2	0.135	0.893
EF 值（$\bar{x} \pm s$）	68.1 ± 6.5	65.9 ± 7.81	1.09	0.280

表 2 AAD 患者入院 24 h 与健康对照组 HMGB1、RAGE 水平比较（μg/L，$\bar{x} \pm s$）

Table 2 Comparison of HMGB1 and RAGE levels between AAD patients and heathy controls (μg/L, $\bar{x} \pm s$)

组别	*n*	HMGB1	RAGE
肺损伤组	21	88.4 ± 11.3[1), 2)]	98.7 ± 15.1[1), 2)]
非肺损伤组	35	52.1 ± 14.8	71.9 ± 12.6
健康对照组	30	13.3 ± 5.9	21.3 ± 11.7
F/*t*		32.70	33.14
P		0.000	0.000

注：1）与健康对照组比较，*P*<0.05；2）与非肺损伤组比较，*P*<0.05

Note: 1) *P*<0.05 *vs.* heathy control group; 2) *P*<0.05 *vs.* non-lung injury group

2.3 AAD 患者 HMGB1、RAGE 与 PaO_2/FiO_2 的变化关系

发病后两组患者HMGB1、RAGE水平不断上升，PaO_2/FiO_2逐渐降低，并在入院后48~60 h达到峰值，肺损伤组的3项指标的变化幅度均明显大于非肺损伤组（均*P*<0.05）；HMGB1、RAGE水平达峰值后下降，PaO_2/FiO_2逐渐回升（图1），HMGB1、RAGE与PaO_2/FiO_2值均呈负线性相关（*r*=−0.940、−0.794）（图2）。

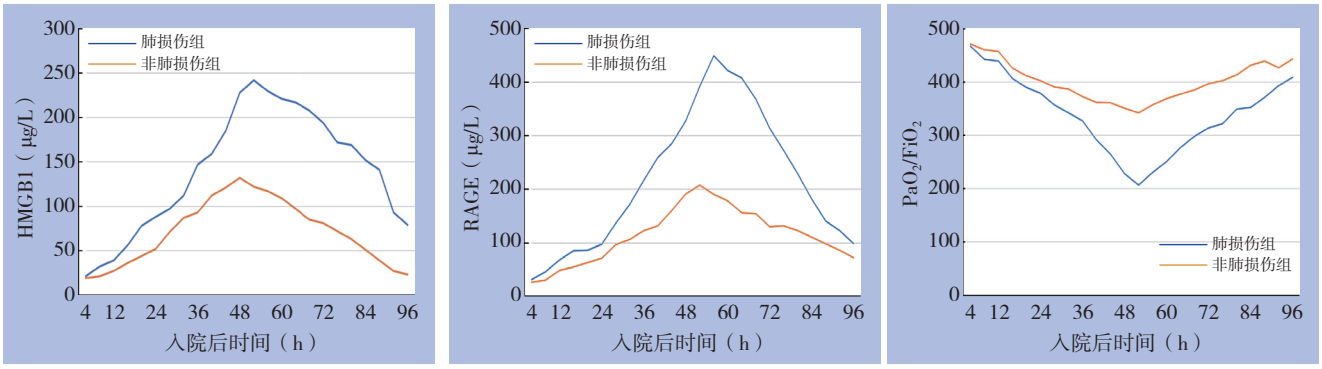

图 1 HMGB1、RAGE、PaO_2/FiO_2 变化趋势图

Figure 1 The changing trend of HMGB1, RAGE and PaO_2/FiO_2

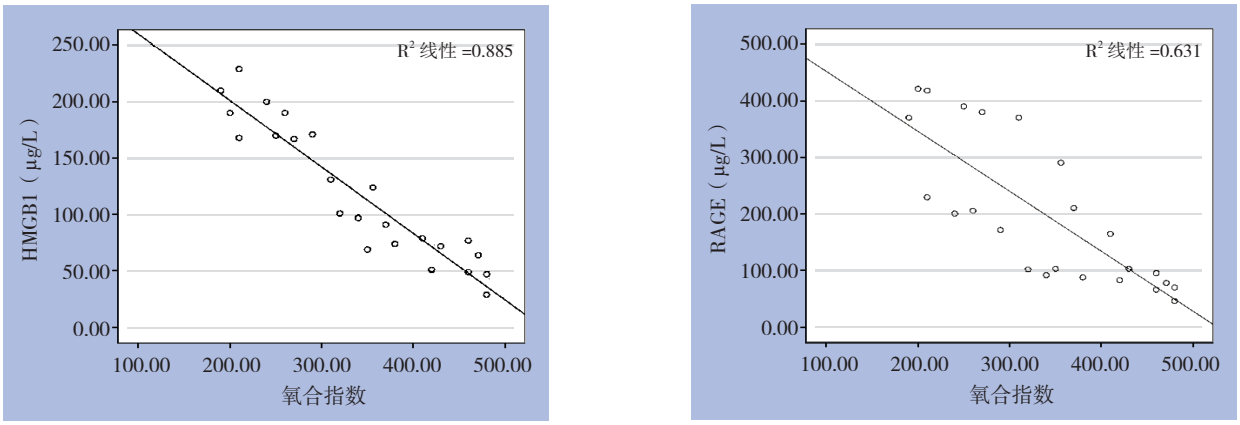

图 2 HMGB1、RAGE 与 PaO_2/FiO_2 相关性散点图

Figure 2 The correlation scatter map of HMGB1, RAGE and PaO_2/FiO_2

3 讨 论

AAD发生时主动脉内膜撕脱，血液流入假腔与主动脉中层细胞外基质接触导致炎症细胞激活，释放大量炎症介质及促炎因子，如IL-6、TNF-α等，进而介导“瀑布样”炎症级联反应[7]。应激状态下HMGB1通过非经典或被动释放等方式进入血液，激活受体RAGE。当HMGB1与RAGE结合时，下游主要有2条信号转导通路被激活：第1条通路是激活鸟苷三磷酸酶（Rac）和CDC42途径，产生包括细胞骨架的重塑、细胞运动、细胞迁移等相应的生物学效应；第2条通路是激活丝裂原活化蛋白激酶途径，NF-κB在这个过程中被活化，产生了大量的细胞因子和趋化因子以促使免疫细胞的成熟。HMGB1是通过与RAGE结合使得下游的p38MAPK磷酸化和NF-κB的活化而发挥作用。p38MAPK是MAPKs的家族成员，作为炎性激活机制里的中心信号通路分子，在细胞核内因磷酸化而被激活，进而诱导炎性细胞因子的转录与表达[8-11]。

既往大量研究表明HMGB1/RAGE信号通路活化与肺损伤密切相关：在肺缺血/再灌注小鼠模型中发现，RAGE敲除、外源性给予sRAGE、抗HMGB1抗体均能减轻肺部损伤；进一步机制研究表明，由巨噬细胞分泌的HMGB1通过结合肺组织细胞表面的RAGE，IL-17分泌，进而介导了肺损伤[12]。Li等[13]研究发现，在盲肠结扎穿孔法建立的脓毒症小鼠模型中，其肺组织HMGB1、RAGE表达较对照组显著增高（$P<0.05$），且其表达水平与炎症反应程度及肺组织损伤程度呈正相关。Entezari等[14]研究显示，抑制HMGB1/RAGE信号通路活化，可显著抑制炎症级联反应，并可明显减轻高氧诱导的ALI。上述研究提示，HMGB1/RAGE信号通路活化是炎症级联反应的中心环节，也是介导多种诱因所致肺损伤的关键因素[15-17]。本课题组在既往研究中亦表明CRP和IL-6、TNF-α的表达与AAD所致ALI的密切相关[18]。

本研究中，发病后24 h肺损伤组及非肺损伤

组HMGB1、RAGE表达水平均高于健康对照组，差异有统计学意义（$P<0.05$）。该结果表明无论是否合并肺损伤，主动脉夹层患者HMGB1、RAGE表达水平均高于健康人群。说明主动脉夹层患者细胞核中的HMGB1被激活释放到细胞外，诱导了局部组织和全身性炎症反应，细胞破损或坏死可导致HMGB1 的释放增加，HMGB1可刺激巨噬细胞、中性粒细胞及单核细胞，使IL-1β、IL-6、TNF-α等炎症因子大量分泌[19-23]。HMGB1诱导炎症反应主要通过结合RAGE实现[24]。RAGE是广泛存在于不同细胞表面的免疫球蛋白超家族跨膜蛋白，在正常组织细胞中的表达水平很低，其配体聚集时可诱导其表达增加[25-26]。HMGB1与RAGE受体结合后，激活JAK/STAT信号转导通路，活化NF-κB，促进炎症因子表达，反馈调节HMGB1[27]。

本研究中发现主动脉夹层发病后两组患者HMGB1、RAGE水平不断上升，PaO_2/FiO_2逐渐降低，随着发病时间的推移HMGB1、RAGE水平达到峰值后下降，PaO_2/FiO_2逐渐回升，两者关系密切，呈负线性相关。且在排除了患者年龄及基础疾病等基本情况的干扰下（$P>0.05$）。肺损伤组HMGB1、RAGE因子表达水平明显高于非肺损伤组，差异有统计学意义（$P<0.05$）。研究提示：HMGB1/RAGE信号通路活化可能是主动脉夹层患者肺损伤低氧血症的关键因素，HMGB1/RAGE因子表达水平越高，炎症反应程度越重，肺损伤程度越重；随着HMGB1/RAGE因子表达水平降低，炎症反症程度的减轻，肺损伤程度亦逐渐减轻，两者密切相关。

综上所述，急性主动脉夹层肺损伤患者HMGB1、RAGE因子水平明显高于非肺损伤患者，提示HMGB1/RAGE信号通路可能在其中发挥着重要的作用；随着HMGB1、RAGE因子水平的升高，肺损伤程度逐渐加重，监测HMGB1/RAGE信号通路中因子的表达可以对急性主动脉夹层并发肺损伤的风险进行评估，在临床上起着很好的示警作用；对HMGB1/RAGE信号通路深入研究可能会为患者干预提供潜在的治疗靶点。

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