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由平原进入高原低压低氧环境后大鼠肾损伤的研究

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【摘要】 **目的** 模拟由平原进入高原低压低氧环境后,大鼠肾功能、肾损伤指标及肾病理随时间的变化特点。**方法** 30 只雄性 Sprague-Dawley 大鼠随机分成 5 组,每组 6 只,对照组置于舱外常压常氧环境,实验组置于低压低氧舱内模拟海拔 5000 m 低压低氧(low-pressure and low-oxygen,LPLO)环境,分别在舱内生活 3 d、7 d、14 d、28 d。观察各组大鼠肾损伤及肾功能指标:血清肌酐(creatinine,CRE)、血清胱抑素 C(cystatin C,CysC)、血清中性粒细胞明胶酶相关脂质运载蛋白(neutrophil gelatinase-associated lipocalin,NGAL)、血清肾损伤因子 1(kidney injury molecule-1,KIM-1)及血清白细胞介素 18(interleukin-18,IL-18)水平。HE 染色及 PAS 染色观察肾病理变化并评价:肾小球平均直径、肾小管周毛细血管(peritubular capillary,PTC)数/肾小管(tubule)数、肾小管损伤评分、肾外髓质(outer medulla,OM)充血评分。**结果** 与对照组比较,实验组 NGAL、KIM-1、CysC 及 CRE 水平均显著升高(均 $P<0.05$)。肾小球平均直径:LPLO 3 天组显著缩小,LPLO 14 天组显著增大(均 $P<0.05$)。PTC/tubule 显著降低,肾小管损伤评分、OM 充血评分显著升高(均 $P<0.05$)。回归分析:PTC/tubule 与低压低氧时间呈线性负相关,CRE、CysC 及病理指标(肾小球平均直径、OM 充血评分及肾小管损伤评分)与低压低氧持续时间呈曲线相关(均 $P<0.05$)。对呈曲线相关变量使用限制性立方样条(restricted cubic splines,RCS)分析:各曲线呈“倒 L”形,拐点均在第 7 天,提示各项指标在低压低氧 7 d 内增高速率最大,7~28 d 增高速率减缓。**结论** 模拟由平原进入高原低压低氧环境后肾从结构到功能多方面均存在显著的损伤,肾对高原环境存在自适应及调整过程。

【关键词】 高原缺氧;肾损害;肾损伤标记物;肾病理改变
【中图分类号】R-33 **【文献标识码】**A **【文章编号】**1671-7856(2025)04-0079-09

Renal injury in rats induced by a low-pressure and low-oxygen environment simulating movement from the plains to the plateau

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【**Abstract**】　**Objective**　To explore time-related changes in renal function, renal injury biomarkers, and renal pathology in rats entering a low-pressure and low-oxygen (LPLO) environment simulating moving from the plains to a plateau. **Methods**　Thirty male Sprague-Dawley rats were divided randomly into five groups ($n=6$ rats per group). Rats in the Control group were placed outside the chamber under normal pressure and oxygen conditions. Rats in the experimental groups were placed in an LPLO chamber to simulate a plateau environment at 5000 m above sea level, and were maintained in the chamber for 3, 7, 14, and 28 days, respectively. Serum levels of creatinine (CRE), cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18) were measured as biomarkers of renal injury. Pathological changes in the kidney were observed by hematoxylin and eosin and periodic acid-Schiff staining, with quantitative assessment of the following parameters: average glomerular diameter, peritubular capillary (PTC) density per tubule, tubular injury score, and outer medulla (OM) congestion score. **Results**　NGAL, KIM-1, CysC, and CRE were significantly increased in the experimental compared with the Control group (all $P<0.05$). The average glomerulus diameter was significantly reduced in the LPLO 3 d group and significantly increased in the LPLO 14 d group (both $P<0.05$). The peritubular capillary (PTC)/tubule ratio was significantly decreased. The renal tubular injury and OM congestion scores were significantly increased (both $P<0.05$). Regression analysis showed that PTC/tubule was linearly negatively correlated with the LPLO duration, while CRE, CysC, and pathological indicators (mean glomerular diameter, OM congestion score, renal tubular injury score) were curvilinearly correlated with the duration of LPLO (all $P<0.05$). Variables with a curvilinear correlation were analyzed using restricted cubic splines(RCS). Each curve exhibited an inverted-L shape, with inflection points on day 7, indicating that the rate of increase of all indicators was highest within the first 7 days of LPLO, and the rate of increase then slowed from 7 days to 28 days. **Conclusions**　A simulated move from a plains to a plateau environment was associated with significant structural and functional renal damage, but the kidneys then showed a self-adaptive adjustment process towards the plateau environment.

【**Keywords**】　high-altitude hypoxia; kidney injury; renal injury markers; renal pathological changes

Conflicts of Interest: The authors declare no conflict of interest.

全球有 1.4 亿人生活在海拔超过 2400 m 的高原地区[1],每年有数十万人从平原地区迁移到高海拔地区,对于高原地区的人群,特别是由平原进入高原的人群,高海拔心脏病、脑水肿和肺水肿的发生严重影响重要脏器的功能,甚至危及生命。高海拔地区具有低大气压力及低氧的环境特点,肾在缺氧情况下易受损伤[2]。流行病学资料显示,我国西藏地区的慢性肾病(chronic kidney disease,CKD)患病率为 18.3%~30.4%[3],显著高于我国 CKD 总体的 10.8%患病率[4];另外有研究发现登山者由平原进入高原后,其肾小球滤过率(glomerular filtration rate,GFR)在短期内下降[5-6],提示低压低氧环境对肾结构和功能以及肾疾病进展具有一定的影响[7]。研究发现,在低压低氧舱模拟海拔 5000 m 的环境,大鼠出现足细胞损伤伴蛋白尿[8]。但是,截至目前,低压低氧环境下肾损伤的研究资料尚不完整,尤其缺乏随着低压低氧持续时间的延长,肾发生相应的病理生理变化的连续性信息。因此,本研究建立模拟高原低压低氧条件下肾损伤的大鼠模型,通过观察低压低氧持续时间相关的大鼠血清学及肾病理指标的变化,探讨由平原进入模拟海拔 5000 m 的低压低氧环境后对肾功能及组织结构的影响。

1　材料和方法

1.1　实验动物

SPF 级 8 周龄雄性 Sprague-Dawley 大鼠 30 只,体质量 260~280 g,购于北京维通利华实验动物技术有限公司[SCXK(京)2021-0011]。动物饲养于北京世纪坛医院临床实验动物中心[SYXK(京)2022-0049],适应性饲养 1 周后进行实验。期间自由进食饮水,饲养室温度为(22±2)℃,湿度为 50%~60%,维持 12 h 光照和 12 h 黑暗的昼夜节律。本实验设计经首都医科大学附属北京世纪坛医院实验动物伦理委员会批准[sjtkkll-lx-2023(011)],实验过程中严格遵守动物实验 3R 原则。

1.2　主要试剂与仪器

血清 NGAL 检测试剂盒(ab119602,批号:GR3362911-1);血清 KIM-1 检测试剂盒(ab119597,批号:GR3413976-2);血清 CysC 检测试剂盒(ab201281,批号:GR3416876-2);血清 CRE 检测试剂盒(ab65340,批号 GR3405925-2);血清 IL-18 检测试剂盒(ab213909,批号:GR3388522-1)均购自美国 Abcom。

低压低氧舱(DSF-Ⅱ动物实验负压舱)购自潍坊华信氧业公司;显微镜购自日本奥林巴斯 BX43;病理切片扫描仪购自 3DHISTECH-D12;石蜡切片机购自浙江省金华市科迪仪器有限公司;分光光度计购自舜宇恒平 UV-2600。

1.3　实验方法

1.3.1　动物模型构建和分组

对照组(6 只):于舱外常压常氧的环境生活 28 d;实验组(24 只):进入低压低氧舱,模拟海拔 3000 m 环境预适应 2 d,随后将低压低氧舱参数以 2 m/s 的速度缓慢上升达到海拔 5000 m 水平(大气压 50 kPa,氧浓度 10%),将实验组进一步随机平分为 4 组,分别在模拟海拔 5000 m 环境生活 3 d、7 d、14 d 及 28 d[7,9];各组生活达预定天数后取血、取肾。

1.3.2　样本收集

达到模拟高原环境生活天数后,用戊巴比妥钠麻醉大鼠,心脏取血 2~3 mL,室温静置 1 h 后,在 4 ℃环境下以 3000 r/min 离心 20 min,取上层血清置于-80 ℃冰箱中待测。统一检测 CRE、CysC、NGAL、KIM-1、IL-18。

1.3.3　肾组织病理学检查及评价

将大鼠右肾称重并测量长度:肾组织石蜡切片脱蜡后进行苏木素-伊红(HE)染色、Masson 染色,显微镜下观察肾组织病理变化。在肾组织皮质及髓质交界处随机选取 10 个高倍镜视野(200 倍)对肾组织损伤的形态学变化进行分析,肾小管损伤评分依据肾小管的形态改变对损伤的严重程度进行:0 分,无明显可见异常;1 分,单个视野形态异常<10%;2 分,10%<单个视野形态异常<25%;3 分,25%<单个视野形态异常<50%;4 分,50%<单个视野形态异常<75%;5 分,单个视野形态异常>75%。肾小管损伤包括肾小管管腔狭窄,肾小管上皮细胞肿胀、萎缩,肾小管上皮细胞数量减少[10-11]。肾髓质充血程度评分在 HE 染色切片选取外髓质(outer medulla,OM)区域,观察红细胞充血(瘀滞)程度,评分为 0~5 分,独立反映每个观察区域的红细胞充血程度。0 分表示所有血管开放良好(0%充血),5 分表示所有可见血管充血(100%充血),分级:0=0%、1=20%、2=40%、3=60%、4=80%、5=100%[12]。肾小管周围毛细血管(peritubular capillary, PTC)密度评分:每张切片圈定 10 个 120 000 μm^2 区域,计算该区域内 PTC 数/肾小管数(PTC/tubule)比值[13-14]。肾小球大小测量依据董鸿瑞等[15]使用的肾小球毛细血管袢直接测量法:使用蔡司数字病理软件(ZEN 3.3)测量病理照片中的最大剖面肾小球(含血管极和(或)尿极的肾小球(含极肾小球))毛细血管袢上相互垂直的两条最长直径,求平均值。每只大鼠肾切片测量 10 个肾小球,各组间比较肾小球大小差异。以上所有评分均使用盲法。

1.4　统计学方法

采用 SPSS 22.0 软件、R 语言(version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria),以及 MSTATA 软件(https://www.mstata.com/)进行统计学分析。正态分布的计量资料以平均数±标准差($\bar{x}\pm s$)表示,多组间比较采用单因素方差分析;非正态分布的计量资料以中位数(25%、75%百分位数)表示,多组间比较采用 Kruskal-Wallis H 检验。以模拟高原环境生活时间长度(天数)为自变量,以大鼠肾功水平(CRE、CysC)、肾损伤指标(NGAL、KIM-1、IL-8)及肾病理指标(肾小球平均直径、PTC/tubule、肾髓质充血评分、肾小管损伤评分)为因变量,构建回归模型,显著性<0.05 视为模型能够拟合,以 R 平方评价模型拟合效果。对以上有统计学意义的非线性回归模型,使用 RCS 分析,以赤池信息量准则(Akaike information criterion)最低值作为优先模型选择。以第 10、50 和 90 百分位作为节点(knots),$P<0.05$ 视为自变量与因变量之间存在显著性关联,P-Nonliner<0.05 提示自变量与因变量之间存在显著的非线性关系。以 RCS 曲线斜率变化最大时间点作为拐点(inflection point),用于寻找暴露于低压低氧环境下各项指标斜率变化最大的时间拐点。$P<0.05$ 为差异具有统计学意义。

2 结果

2.1 各组间肾功能、肾损伤指标及肾组织病理学比较

2.1.1 肾功能指标

与对照组比较,血清 CRE 在 LPLO 14 天组显著升高,LPLO 28 天组最高($P<0.05$);血清 CysC 在 LPLO 3 天组显著升高,LPLO 7 天组达最高值,LPLO 28 天组较 7 天组显著下降(均 $P<0.05$)。见图 1。

2.1.2 肾损伤指标

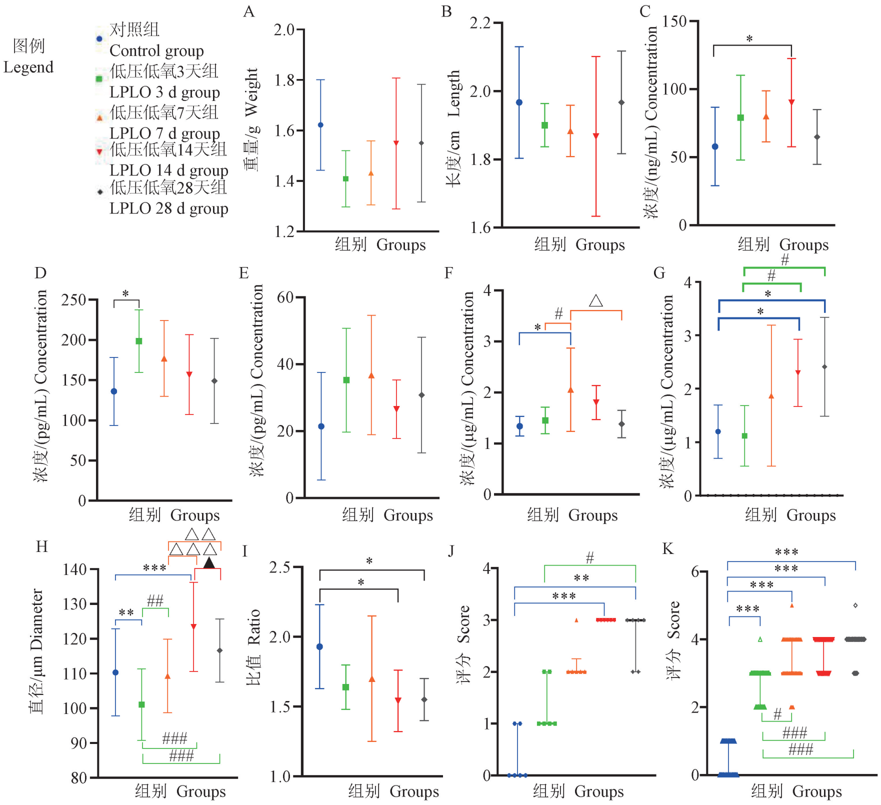
与对照组比较,血清 NGAL 在 LPLO 14 天组显著升高,血清 KIM-1 在 LPLO 3 天组显著升高(均 $P<0.05$)。血清 IL-18 各组间无显著性差异。见图 1。

2.1.3 肾病理

与对照组比较,各个实验组肾重量及长径均无显著性差异。见图 1。

与对照组比较,各实验组 PTC/tubule 比值呈下降趋势,其中 LPLO 14 天组及 28 天组 PTC/tubule 比值显著降低($P<0.05$),OM 充血评分及肾小管损伤评分呈上升趋势,其中 LPLO 14、28 天组 OM 充血评分显著升高,LPLO 3、7、14、28 天组肾小管损伤评分显著升高($P<0.001$)。见图 1。

对照组肾小球、肾小管及肾间质结构正常,



注:A:右肾重量;B:右肾长度;C:血清 NGAL 水平;D:血清 KIM-1 水平;E:血清 IL-18 水平;F:血清 CysC 水平;G:血清 CRE 水平;H:肾小球平均直径;I:PTC/tubule 比值;J:肾髓质充血评分;K:肾小管损伤评分。与对照组相比,$^{*}P<0.05$,$^{**}P<0.01$,$^{***}P<0.001$;与 LPLO 3 天组相比,$^{\#}P<0.05$,$^{\#\#}P<0.01$,$^{\#\#\#}P<0.001$;与 LPLO 7 天组相比,$^{\triangle}P<0.05$,$^{\triangle\triangle}P<0.01$,$^{\triangle\triangle\triangle}P<0.001$;与 LPLO 14 天组相比,$^{\blacktriangle}P<0.05$。

图 1 各组大鼠肾功能、肾损伤指标及肾病理评分指标比较

Note. A, Weight of right kidney. B, Length of right kidney. C, Serum NGAL. D, Serum KIM-1. E, Serum IL-18. F, Serum CysC. G, Serum CRE. H, Average diameter of glomeruli. I, Ratio of PTC/tubule. J, OM congestion score. K, Renal tubular injury score. Compared with Control group, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. Compared with LPLO 3 d group, $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#}P<0.001$. Compared with LPLO 7 d group, $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$, $^{\triangle\triangle\triangle}P<0.001$. Compared with LPLO 14 d group, $^{\blacktriangle}P<0.05$.

Figure 1 Comparison of renal function, renal injury indicators, and renal pathological scoring indicators among different groups of rats

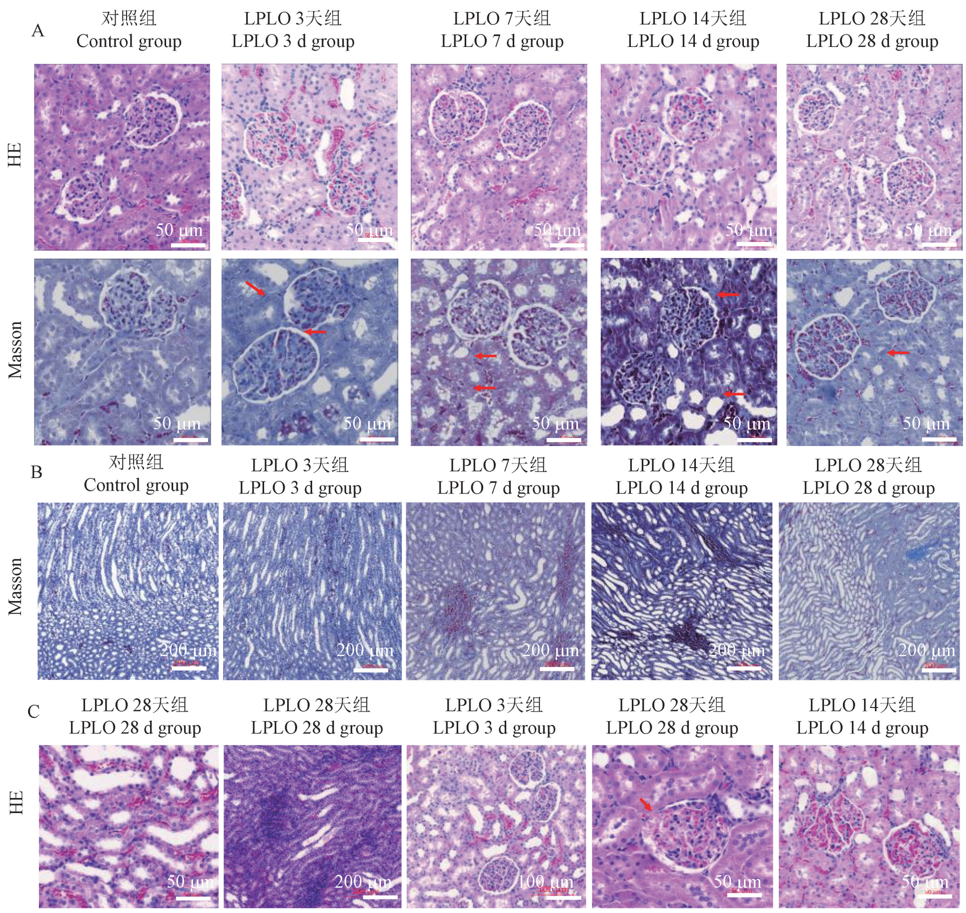
毛细血管清晰,肾髓质无明显充血。随着实验时间的延长,实验组肾小球直径呈“缩小-增大-缩小”的变化趋势:LPLO 3 天组为各组中最低,LPLO 14 天组达最高值,LPLO 28 天组较 14 天组显著缩小($P<0.05$,图 1);部分肾小球出现毛细血管袢充血、毛细血管袢破裂。肾小管出现管腔狭窄、管腔扩张、肾小管上皮细胞肿胀、萎缩及脱落,部分肾小管上皮细胞可见空泡样变性,部分小管管腔内可见红细胞管型;肾小管周围毛细血管呈现不同程度的数量变化及管腔扩张;肾外髓质出现显著的充血,红细胞瘀滞;肾间质淋巴细胞浸润增加。见图 2。

2.2　低压低氧持续时间与肾功能、肾损伤指标及肾组织病理评分的关系

回归分析结果显示,PTC/tubule 与低压低氧时间呈线性负相关,CRE、CysC 及肾组织病理改变(肾小球平均直径、OM 充血评分及肾小管损伤评分)与低压低氧持续时间呈曲线相关(均 $P<0.05$);血清 NGAL、KIM-1 及 IL-18 水平与低压低氧时间无关。见表 2,图 3。

2.3　相关变量 RCS 分析

如图 4 所示,CRE、CysC 水平及肾病理指标(肾小球平均直径、OM 充血评分及肾小管损伤评分)的变化与低压缺氧持续时间呈非线性关系,各项指标随着低压低氧时间延长,其恶化风险逐渐增高。绘制 RCS 图分析高原停留时间与 CRE、CysC、肾小球平均直径、OM 充血评分及肾小管损伤评分的关联性,各曲线呈“倒 L”形,拐点均在第 7 天,提示各项指标在低压低氧 7 d 内增高速率最大,7~28 d 增高速率减缓。



注:A:各组大鼠肾皮质病理,其中红色箭头标识为呈蓝色的胶原纤维;B:各组大鼠肾髓质病理;C:实验组大鼠肾损伤病理。

图 2　模拟高原环境与大鼠肾病理变化

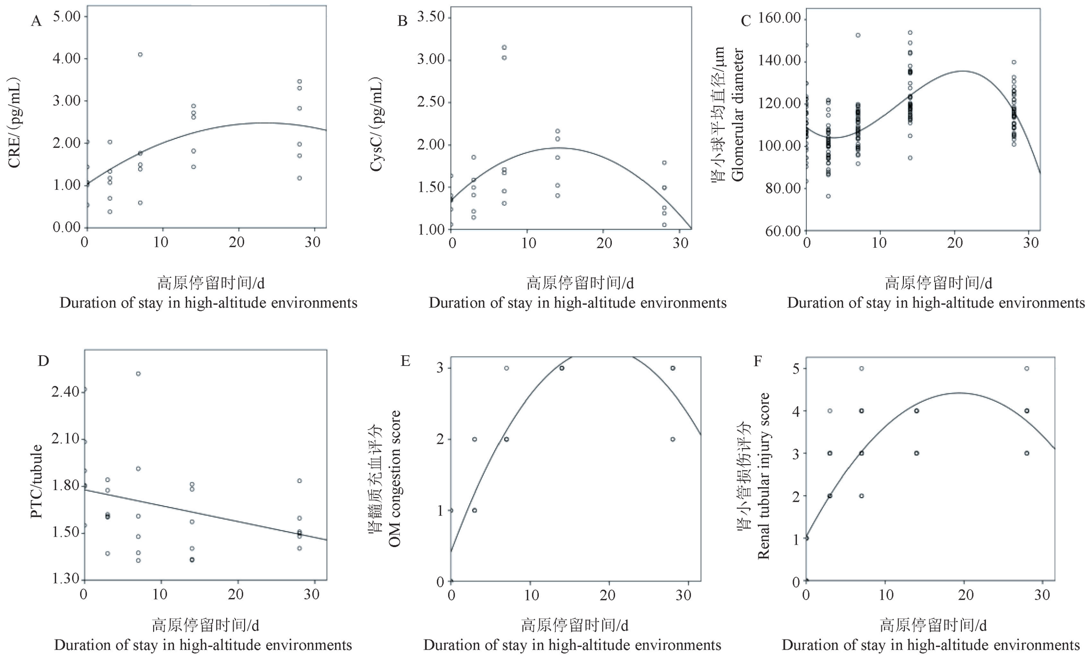
Note. A, Pathology of renal cortex in each group of rats, the red arrows indicate blue collagen fibers. B, Pathology of renal medulla in each group of rats. C, Pathology of renal injury in experimental group rats.

Figure 2　Simulating high-altitude environment and pathological changes in rat kidneys

表 2 低压低氧持续时间与肾功能、肾损伤指标及肾组织病理评分关系的回归分析

Table 2 Regression analysis of the relationship between the duration of low-pressure hypoxia and renal function, renal injury indicators, and renal histopathological scores

观察指标 Observation target	模型类型 Model type	R^2	F	P	常数 Constant	β1/β2/β3
CRE/(pg/mL)	二次曲线 Quadratic curve	0.322	5.950	0.008	1.040	0.123/−0.003
CysC/(pg/mL)	二次曲线 Quadratic curve	0.238	3.904	0.033	1.327	0.075/−0.003
NGAL/(pg/mL)	二次曲线 Quadratic curve	0.161	2.495	0.102	–	–
KIM-1/(pg/mL)	二次曲线 Quadratic curve	0.042	0.570	0.572	–	–
IL-18/(pg/mL)	二次曲线 Quadratic curve	0.017	0.206	0.815	–	–
右肾重量/g Weight of right kidney	二次曲线 Quadratic curve	0.031	0.431	0.654	–	–
右肾长度/cm Length of right kidney	二次曲线 Quadratic curve	0.081	1.191	0.319	–	–
肾小球平均直径/μm Average diameter of glomeruli	三次曲线 Cubic curve	0.298	24.876	<0.001	109.074	−2.902/0.454/−0.012
PTC/tubule	线性 Liner	0.122	3.861	0.050	1.778	−0.010
肾髓质充血评分 OM congestion score	二次曲线 Quadratic curve	0.848	75.450	<0.001	0.414	0.299/−0.008
肾小管损伤评分 Renal tubular injury score	二次曲线 Quadratic curve	0.707	213.811	<0.001	1.042	0.348/−0.009

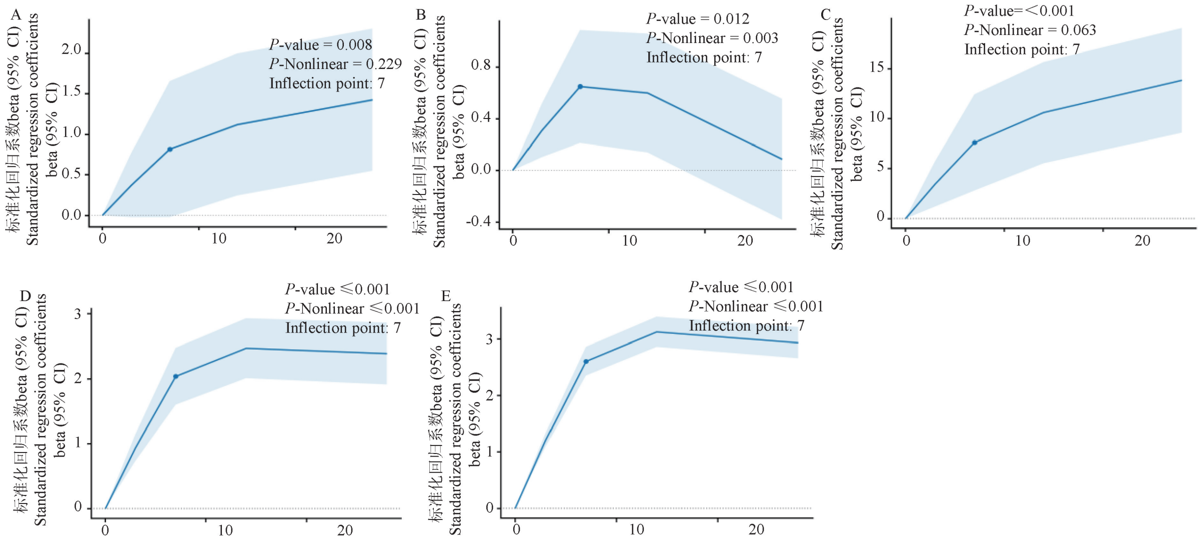


注:A:模拟高原环境停留时间与血清 CRE;B:模拟高原环境停留时间与血清 CysC;C:模拟高原环境停留时间与肾小球平均直径;D:模拟高原环境停留时间与 PTC/tubule;E:模拟高原环境停留时间与肾髓质充血评分;F:模拟高原环境停留时间与肾小管损伤评分。

图 3 模拟高原环境停留时间与大鼠肾功能及病理评分的相关性分析

Note. A, CRE levels with duration of stay in high-altitude environments. B, CysC levels with duration of stay in high-altitude environments. C, Glomerular diameter with duration of stay in high-altitude environments. D, PTC/tubule with duration of stay in high-altitude environments. E, OM congestion score with duration of stay in high-altitude environments. F, Renal tubular injury score with duration of stay in high-altitude environments.

Figure 3 Correlation analysis between simulated high-altitude environment residence time and rat kidney function and pathological score



注：A：模拟高原环境停留时间与血清 CRE；B：模拟高原环境停留时间与血清 CysC；C：模拟高原环境停留时间与肾小球平均直径；D：模拟高原环境停留时间与肾髓质充血评分；E：模拟高原环境停留时间与肾小管损伤评分。

图 4　模拟高原环境停留时间与大鼠肾功能及肾病理指标变化的限制性立方样条分析

Note. A, CRE levels with duration of stay in high-altitude environments. B, CysC levels with duration of stay in high-altitude environments. C, Glomerular diameter with duration of stay in high-altitude environments. D, OM congestion score with duration of stay in high-altitude environments. E, Renal tubular injury score with duration of stay in high-altitude environments.

Figure 4　Restricted cubic spline analysis of the relationship between simulated high-altitude environment residence time and changes in renal function and renal pathological indicators in rats

3　讨论

本研究使用低压低氧舱模拟由平原进入高原环境，建立低压低氧环境下大鼠肾损伤模型，应用血清学指标结合肾病理评分，分析发现大鼠在进入高原低压低氧环境后肾损伤标记物升高，肾小球平均直径呈现动态变化，肾小管损伤显著，PTC 稀疏，外髓质充血。

高原环境的特点是低大气压力导致的氧气稀薄，低压低氧环境下，肾通过利尿效应提高红细胞比容，代偿组织缺氧[7]，利尿效应增加导致肾灌注下降、GFR 降低。PICHLER 等[5]发现，登山者在进入海拔 4500 m 后出现 GFR 下降，BESTLE 等[16]发现成年男性在海拔 4500 m 生活 3 d 后 GFR 开始出现显著下降。动物实验证实肾小球体积与 GFR 及肾灌注和超滤呈正相关[17]，本研究中实验组肾小球平均直径在 LPLO 3 天组最短，提示在进入低压低氧环境早期阶段，肾小球灌注减少，肾小球体积缩小。但是，我们发现自 LPLO 7 天组起，肾小球平均直径开始增大，LPLO 14 天组达最高值，而 LPLO 28 天组较 14 天组显著缩小并接近对照组水平，肾小球体积的变化特点提示由平原进入高原后，肾小球先出现缺血缩小，随后代偿性增大，最后恢复至接近平原水平，肾小球在进入高原环境后具有自适应调节能力。WANG 等[18]报道世居高原的藏族患者肾活检中普遍存在肾小球肥大，肾小球直径增大与血红蛋白水平呈强相关，而与血肌酐水平无关，该研究认为高原红细胞增多症是导致世居高原的藏族患者肾小球肥大的重要原因。与世居高原人群不同，由平原进入高原环境的过程，大气压力及氧含量剧烈变化，肾功能及结构改变更为复杂，还需进一步研究探索进入低压低氧环境后肾小球血流变化的机制。

肾小管主动重吸收过程极为耗能，消耗了供给肾氧气的 80%[19-20]。高海拔环境下，肺通气量增加以提高组织供氧，导致呼吸性碱中毒[21]，肾为代偿碱中毒排出过量的碳酸氢盐，同时重吸收氢离子[22]，此过程增加肾组织耗能，加重肾缺氧；此外，肾小管系统的血供来源于 PTC，PTC 具有血管再生能力差和易受损等特点[23]，因此，肾小管系统对缺氧极为敏感。PTC 为二级毛细血管，起

自肾小球出球小动脉,由单层肾小管周围毛细血管内皮细胞(renal peritubular capillary endothelial cells,RPECs)和基膜构成,PTC 血流减少及缺氧引起的 RPECs 损伤均可导致 PTC 损伤,造成 PTC 稀疏,进而加重肾小管缺氧,导致肾小管受损[23]及肾功能受损[14]。本研究中实验组 PTC/tubule 比例出现显著下降,提示低压低氧环境可导致 PTC 稀疏。血清 NGAL 和 KIM-1 是肾小管早期损伤的标记物[24],研究显示血清 NGAL 及 KIM-1 升高与缺氧所致肾损伤显著相关[25-28]。MELLOR 等[29]发现,受试者由海平面上升至海拔 1085 m 后,血清 NGAL 即呈现升高趋势,在高原徒步旅行后,血清 NGAL 显著升高。本研究观察到实验组肾小管出现显著损伤,结合既往研究,提示进入低压低氧环境后可能通过影响 PTC 导致肾小管受损。

除肾小球和肾小管的病理变化外,本研究进一步发现,实验组肾外髓质出现显著充血,OM 充血评分升高。OM 充血是红细胞在外髓质的瘀滞(red blood cell trapping)[13],缺血性 AKI 中常见 OM 充血,瘀滞在髓质的红细胞胞内成分快速外渗并被肾小管所吸收,产生肾小管毒性作用,是缺血性 AKI 的主要致病因素之一[13]。

组织损伤最终导致功能受损,血清 CRE 和 CysC 的升高可用于诊断 AKI[30],CysC 是检测新生儿缺氧相关 AKI 敏感且可靠的标记物[31],并且可以预测手术导致的 AKI[32]。实验组 CRE 及 CysC 升高提示在低压低氧环境下可导致肾功能受损。

为进一步研究低压低氧环境停留时间与肾损伤的关系,本研究使用相关性分析发现,PTC/tubule 与低压低氧舱停留时间呈线性负相关,其余均为二次曲线或三次曲线相关,提示伴随低压低氧环境停留时间的延长,肾损伤的变化速率和严重程度是非匀速发展的。RCS 分析发现呈曲线相关的各项指标其 RCS 曲线拐点均出现在 7 d,7 d 之后曲线斜率较 7 d 之前下降,提示由平原进入高原环境 7 d 内,肾受损速度较快,7 d 后受损速度减缓,因此,推测机体对进入低压低氧环境后出现的肾损伤存在代偿调节机制以逐渐适应高原缺氧环境。

综上所述,本研究构建了模拟由平原进入高原低压低氧环境后肾功能及组织病理随时间变化的动物模型,发现进入低压低氧环境后肾功能受损,肾病理损伤伴随高原停留时间逐渐加重,肾对低压低氧环境存在自适应及调整过程。本研究为高原肾病发病机制的研究提供了重要的实验室数据,提示对于由平原地区进入高原地区的人群应重视肾结构和功能的潜在变化。

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