· 基础研究 ·

# 有氧运动对衰老大鼠肾脏纤维化的影响

贵永玲[1]　李晓勇[2]

[1]郑州升达经贸管理学院运动与健康研究所,郑州　451191; [2]郑州经贸学院,郑州　451191

通信作者:贵永玲,Email:guiyonglingzz@126.com

【摘要】 **目的**　观察规律有氧运动对衰老大鼠肾脏纤维化的影响并探讨其作用机制。**方法**　采用随机数字表法将 30 只雄性 SD 大鼠分为青年对照组(YC 组)、老年对照组(OC 组)及老年运动组(OE 组),每组 10 只大鼠。YC 组及 OC 组大鼠均置于鼠笼内安静饲养,OE 组大鼠则给予 8 周中等强度跑台有氧运动。于实验结束后检测各组大鼠 24 h 尿蛋白、血尿素氮(BUN)及血清肌酐(SCr)含量,采用 Masson 染色检测肾脏纤维化程度,采用 Western Blot 技术检测转化生长因子 $\beta_1$(TGF-$\beta_1$)、p38 丝裂原活化蛋白激酶(p38MAPK)、磷酸化 p38MAPK(p-p38MAPK)、E-粘钙素及 α-平滑肌肌动蛋白(α-SMA)表达水平。**结果**　与 YC 组比较,OC 组大鼠 24 h 尿蛋白、BUN 及 SCr 明显升高($P<0.05$),肾脏纤维化程度增加($P<0.05$),TGF-$\beta_1$、p-p38MAPK 和 α-SMA 蛋白表达上调($P<0.05$),E-粘钙素表达下调($P<0.05$);与 OC 组比较,OE 组大鼠 24 h 尿蛋白、BUN 及 SCr 明显降低($P<0.05$),肾脏纤维化程度减轻($P<0.05$),TGF-$\beta_1$、p-p38MAPK 和 α-SMA 蛋白表达下调($P<0.05$),E-粘钙素表达增加($P<0.05$)。**结论**　有氧运动能缓解衰老大鼠肾脏纤维化,其作用机制可能与抑制 TGF-$\beta_1$/p38MAPK 信号通路及上皮-间质转变有关。

【关键词】 有氧运动; 衰老; 肾脏纤维化; TGF-$\beta_1$/p38MAPK 信号途径; 上皮-间质转变

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**Aerobic exercise improves renal fibrosis in aged rats**

*Gui Yongling*[1], *Li Xiaoyong*[2]

[1]*Research Institute of Sports and Health, Zhengzhou Shengda University, Zhengzhou 451191, China*; [2]*Zhengzhou University of Economics and Business, Zhengzhou 451191, China*

*Corresponding author: Gui Yongling, Email: guiyonglingzz@126.com*

【**Abstract**】 **Objective**　To explore the effect of regular aerobic exercise on renal fibrosis and its mechanism. **Methods**　Thirty male Sprague-Dawley rats were randomly divided into a young control group (YC group), an old control group (OC) and an old exercise group (OE), each of 10. The YC and OC groups were kept quietly in cages, while the OE group performed moderate-intensity treadmill aerobic exercise for 8 weeks. After the experiment, renal function was evaluated by measuring 24h urine protein, blood urea nitrogen (BUN) and serum creatinine (SCr). The degree of renal fibrosis was detected by Masson staining, and the expressions of transforming growth factor $\beta_1$(TGF-$\beta_1$), p38 mitogen-activated protein kinase (p38MAPK), phosphorylated p38MAPK (p-p38MAPK), E-cadherin, and α-smooth muscle actin (α-SMA) were measured using western blotting. **Results**　Compared with the YC group, a significant increase was observed in the OC group in average 24h urine protein, BUN and SCr, but also in the degree of renal fibrosis, the protein expression of TGF-$\beta_1$, p-p38MAPK and α-SMA. There was a significant decrease in the average expression of E-cadherin. Compared with the OC group, the average 24h urine protein, BUN and SCr, the degree of renal fibrosis, the expression of TGF-$\beta_1$, p-p38MAPK and α-SMA protein had all decreased significantly in OE group, while the average expression of E-cadherin had increased significantly. **Conclusions**　Aerobic exercise relieves renal fibrosis in elderly rats, perhaps through inhibiting the TGF-$\beta_1$/p38MAPK signaling pathway and epithelial-mesenchymal transition.

【**Key words**】 Aerobic exercise; Ageing; Renal fibrosis; TGF-$\beta_1$/p38MAPK signaling; Epithelial-mesenchymal transition

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衰老是所有生物生命进程中不可避免的生理现象,在该过程中身体各器官功能逐渐减弱;肾脏作为活跃的代谢器官及主要的排泄器官,是机体快速衰老器官之一,常伴有间质纤维化,主要表现为细胞外基质

(extracellular matrix, ECM)过度沉积[1]。相关研究发现,上皮-间质转变(epithelial-mesenchymal transition, EMT)是多种组织发生纤维化的重要原因之一[2];肾脏 EMT 主要发生于肾小管上皮细胞,并诱导上皮表面标志物改变,包括 E-粘钙素和 α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)等[3]。有学者发现,转化生长因子 $\beta_1$(transforming growth factor $\beta_1$, TGF-$\beta_1$)是 ECM 合成的关键调控因子,此外 TGF-$\beta_1$ 在调控肾小管 EMT 中同样具有重要作用,最终引发肾脏纤维化[3]。TGF-$\beta_1$ 下游信号经由 Smads 家族介导,此为 TGF-$\beta_1$ 经典途径[4];近年来相关研究证实[5],肾脏纤维化过程中同样存在 TGF-$\beta_1$ 非 Smads 依赖途径,即 TGF-$\beta_1$ 与相应受体结合后激活 p38 丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK),继而通过炎症反应以及自噬途径介导肾脏纤维化;通过调控 TGF-$\beta_1$/p38MAPK 信号通路活性能减轻肾脏 ECM 沉积,因此是防治肾脏纤维化的重要生物学靶点。

大量文献表明,有氧运动是一种重要的非药物康复手段,能延缓机体骨骼肌及脑组织衰老[6-7],改善心肺功能[8]。相关临床研究证实[9],有氧运动对慢性肾病患者具有多维度健康效益,包括降低心血管危险因素、改善身体机能、提高运动能力及生活质量等,但关于有氧运动是否能延缓自然衰老引起的肾脏纤维化目前鲜见报道。基于此,本研究拟观察规律有氧运动对衰老大鼠肾脏纤维化的影响,并探讨 TGF-$\beta_1$/p38MAPK 信号通路及 EMT 在其间的作用机制,为开发防治肾脏纤维化的运动康复处方提供实验依据。

## 材料与方法

一、动物与分组

采用随机数字表法将 30 只雄性 Sprague-Dawley (SD)大鼠分为青年对照组(young control group,简称 YC 组,6 月龄)、老年对照组(old control group,简称 OC 组,22 月龄)及老年运动组(old exercise group,简称 OE 组,22 月龄),各组均有 10 只大鼠,其中 YC 组及 OC 组大鼠均置于鼠笼内安静饲养,OE 组大鼠则进行 8 周中等强度跑台有氧运动。

二、有氧运动方案

大鼠先进行 3 d 跑台适应性训练,设置跑台速度为 5~10 m/min,坡度 0°,每天持续训练 15~20 min;随后开始正式训练,设置跑台速度为 15 m/min,坡度 5°(运动强度相当于 65%最大摄氧量水平[10]),每天持续训练 60 min,每周训练 5 d,共训练 8 周。

三、标本取材

末次训练后 48 h 期间所有大鼠夜间禁食,于代谢笼内留取 24 h 尿液。大鼠经称量体重后用 20%乌拉坦腹腔麻醉并固定,开胸后左心室采血 3 ml,肝素抗凝,经 4 ℃、3 000 rpm 离心取血清;游离左侧肾脏组织并将其分为 2 份,一份用于组织病理学观察,另一份用于目标蛋白定量检测。

四、肾功能检测

采用 AX-4280 型尿样分析仪(日本产)以双缩脲法检测各组大鼠尿液样本 24 h 尿蛋白含量,采用 Bachman AU680 型生化分析仪(美国产)检测血液样本中尿素氮(blood urea nitrogen, BUN)及肌酐(serum creatinine, SCr)含量。上述检测过程均严格按照试剂盒(武汉博士德生物工程有限公司)说明书进行操作,每个样本重复检测 3 次取平均值。

五、组织病理学观察

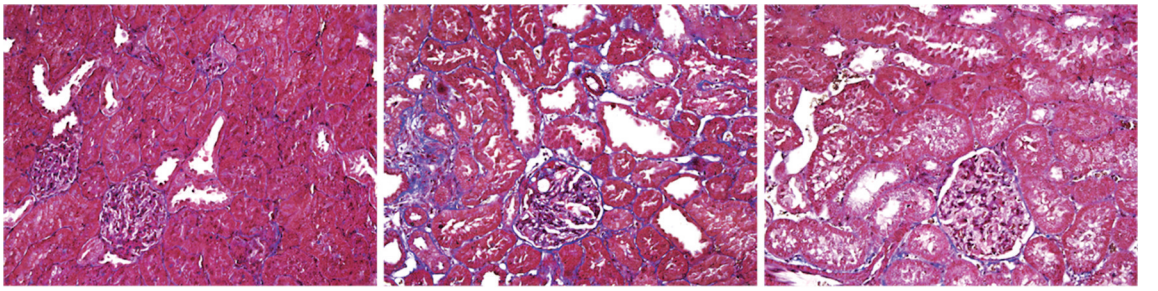
将各组大鼠肾组织用中性甲醛溶液固定 24 h,脱水后石蜡包埋,制作 4 μm 厚切片。利用梯度乙醇对组织切片进行脱水,苏木精酸染色 5 min,Masson 酸溶液孵育 3 min,随后在蒸馏水中漂洗 1 min,丽春红染色 5 min,再置于磷钼酸溶液中分化 2 min,经蒸馏水漂洗 1 min 后立即用苯胺蓝溶液染色 5 min,中性树胶固定封片(所有步骤均在室温下操作)。于 IX71 型倒置显微镜(奥林巴斯,日本)下选取 10 个视野,观察各组大鼠肾脏病理组织学特征,采用 Image Pro Plus 6.0 版图像分析软件(美国)测量切片中结缔组织面积与所测视野面积的比值(即纤维化指数)。

六、目标蛋白定量检测

采用 Western blot 法检测各组大鼠肾脏组织中 TGF-$\beta_1$、p38MAPK、磷酸化 p38MAPK(p-p38MAPK)、E-粘钙素及 α-SMA 蛋白表达量,具体操作如下:取适量肾脏组织匀浆后提取总蛋白,用考马斯亮蓝法测定总蛋白浓度。取 100 μg 蛋白样品在垂直电泳仪上经十二烷基硫酸钠-聚丙烯酰胺(sodium dodecyl sulfate polyacrylamide gel electrophoresis, SDS-PAGE)凝胶分离,随后转移至聚偏二氟乙烯(polyvinylidene fluoride, PVDF)膜上。兔抗鼠一抗 4 ℃静置孵育过夜,二抗 37 ℃孵育 1.5 h,经充分洗涤后,配置电化学发光液(electrochemiluminescence, ECL)进行发光成像,扫描各条带灰度值。将各组蛋白与 β-actin 的灰度比值作为目标蛋白相对表达量,将各组目标蛋白相对表达量与 YC 组的比值作为相对表达率。

七、统计学分析

本研究所得计量资料以($\bar{x}\pm s$)表示,采用 SPSS 20.0 版统计学软件包进行数据分析,各参数组间比较采用单因素方差分析,多重比较采用最小显著差异法(least-significant difference, LSD),$P<0.05$ 表示差异具有统计学意义。



YC组　　OC组　　OE组

**图 1**　各组大鼠肾脏组织病理学观察(肾脏 Masson 染色,×400)

## 结　　果

一、各组大鼠肾功能变化分析

与 YC 组比较,OC 组大鼠 24 h 尿蛋白、BUN 及 SCr 均明显升高($P<0.05$);与 OC 组比较,OE 组大鼠 24 h 尿蛋白、BUN 及 SCr 均显著下降($P<0.05$),具体数据见表 1。

**表 1**　各组大鼠肾功能变化分析

| 组别 | 只数 | 24 h 尿蛋白 (mg/24 h) | BUN (mmol/L) | SCr (μmol/L) |
|---|---|---|---|---|
| YC 组 | 10 | 92.3±7.5 | 6.1±1.2 | 30.1±4.7 |
| OC 组 | 10 | 129.6±11.2[a] | 13.9±2.3[a] | 65.5±8.9[a] |
| OE 组 | 10 | 98.0±8.9[b] | 8.7±1.6[b] | 41.4±5.8[b] |

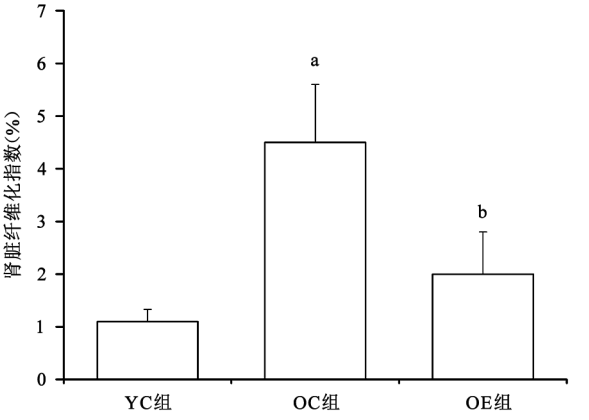
注:与 YC 组比较,[a]$P<0.05$;与 OC 组比较,[b]$P<0.05$

二、各组大鼠肾脏病理学观察及纤维化指数比较

各组大鼠肾脏 Masson 染色情况详见图 1,其中蓝色区域代表胶原纤维;通过镜下观察发现,YC 组大鼠肾小球及肾小管形态、结构正常,几乎无胶原纤维;OC 组肾小球萎缩,细胞溶解程度增加,肾小管上皮细胞连接间隙缩小,肾小管壁增厚,胶原纤维大量沉积;OE 组肾小球萎缩、肾小管壁增厚以及间质纤维化程度均较 OC 组明显减轻。各组大鼠肾脏纤维化指数见图 2 所示,与 YC 组比较,OC 组大鼠肾脏纤维化指数明显增加($P<0.05$);与 OC 组比较,OE 组大鼠肾脏纤维化指数明显降低($P<0.05$)。

三、各组大鼠目标蛋白表达量比较

与 YC 组比较,OC 组大鼠 TGF-$\beta_1$、p-p38MAPK 及 α-SMA 蛋白表达明显上调($P<0.05$),E-粘钙素表达明显下调($P<0.05$);与 OC 组比较,OE 组大鼠 TGF-$\beta_1$、p-p38MAPK 及 α-SMA 蛋白表达均明显下降($P<0.05$),E-粘钙素表达明显增加($P<0.05$);各组大鼠 p38MAPK 蛋白表达量组间差异均无统计学意义($P>0.05$),具体数据见表 2。




注:与 YC 组比较,[a]$P<0.05$;与 OC 组比较,[b]$P<0.05$

**图 2**　各组大鼠肾脏纤维化指数比较

## 讨　　论

本研究结果发现,自然衰老大鼠肾脏组织中存在轻微病理结构改变及胶原沉积,上皮细胞表面标志物 E-粘钙素表达下调,成肌纤维细胞表面标志物 α-SMA 表达上调,TGF-$\beta_1$/p38MAPK 信号通路持续激活;而规律有氧运动可抑制老年大鼠 TGF-$\beta_1$/p38MAPK 信号通路,上调 E-粘钙素并下调 α-SMA 表达量,从而改善胶原沉积所致的肾脏纤维化。

**表 2**　各组大鼠目标蛋白表达量比较

| 组别 | 只数 | TGF-$\beta_1$ | p38MAPK | p-p38MAPK | E-粘钙素 | α-SMA |
|---|---|---|---|---|---|---|
| YC 组 | 10 | 1.00±0.21 | 1.00±0.17 | 1.01±0.15 | 1.00±0.19 | 0.99±0.20 |
| OC 组 | 10 | 3.15±0.87[a] | 1.06±0.20 | 2.70±0.69[a] | 0.68±0.10[a] | 3.35±1.17[a] |
| OE 组 | 10 | 1.89±0.70[b] | 0.97±0.23 | 1.37±0.51[b] | 0.89±0.18[b] | 1.90±0.86[b] |

注:与 YC 组比较,[a]$P<0.05$;与 OC 组比较,[b]$P<0.05$

随着当前人口逐渐老龄化,由衰老及老年病引起的健康问题日益突出。相关流行病学调查结果表明[11],因肾脏功能衰退诱发的相关疾病严重威胁中老年人群生命健康安全。大量研究证实[1],衰老肾脏组织表现出明显的纤维化特征;Sangaralingham 等[12]对不同鼠龄大鼠肾组织进行天狼星红染色后证实,随着鼠龄增长,其皮质区及髓质区胶原纤维沉积明显增多;Ning 等[13]通过 Masson 染色及 PAS 染色发现,与青年组大鼠比较,老年组大鼠肾小球基底膜增厚,同时伴有间质纤维化。本研究通过 Masson 染色也发现类似结果,如 OC 组大鼠出现肾小球萎缩、细胞溶解增加、胶原纤维明显沉积等现象,提示衰老大鼠发生肾脏纤维化,与前人研究结果基本一致。

有氧运动是延缓衰老的有效手段之一,能抑制机体骨骼肌及脑组织功能退化[6-7]。目前已有大量动物实验证实,有氧运动对由多种疾病引起的肾脏纤维化具有改善作用[14-15];如 Peng 等[15]发现,慢性肾病大鼠经游泳运动后其基质金属蛋白酶-2 表达下调,ECM 沉积减少,对肾脏纤维化具有改善作用。本研究对老年大鼠进行 6 周中等强度跑台有氧运动,结果显示 OE 组大鼠肾脏细胞溶解水平降低,胶原纤维沉积明显不及 OC 组,提示有氧运动能延缓老年大鼠肾脏纤维化,与 Souza 等[14]对慢性肾病大鼠进行抗阻训练的研究结果基本一致。

TGF-$\beta_1$ 是一种多能细胞因子,也是最重要的促纤维化因子,可通过 Smad 依赖性途径(经典途径)促进多种调节胶原代谢基因(如结缔组织生长因子、基质金属蛋白酶以及组织金属蛋白酶抑制物等)表达以诱导组织纤维化[4]。近年来研究证实,TGF-$\beta_1$ 还可由 p38MAPK 信号通路(非 Smad 依赖性途径)介导组织炎症并降低 ECM 自噬活性,而炎症反应及自噬活性下调是肾脏纤维化的重要病理生理机制[5];此外 p38MAPK 还能激活促炎因子如核因子-κB、白细胞介素 6、肿瘤坏死因子 α 等表达,后者又进一步上调 TGF-$\beta_1$ 活性,从而形成恶性循环并加重肾脏损害[16]。在多个肾脏纤维化动物模型中均发现 TGF-$\beta_1$/p38MAPK 信号通路持续激活[17-18],本研究(通过观察衰老肾脏纤维化大鼠模型)亦获得类似结果。另外本研究还发现,与 OC 组比较,OE 组大鼠 TGF-$\beta_1$ 及 p-p38MAPK 表达均明显下调,提示有氧运动能显著抑制 TGF-$\beta_1$/p38MAPK 信号通路活性,进而减轻肾脏炎症反应并提高 ECM 自噬活性,这可能是规律有氧运动对衰老大鼠肾脏纤维化发挥保护效应的重要分子生物学机制。有研究指出[1,19],衰老过程中伴随的自由基增多是 TGF-$\beta_1$ 表达上调的触发因素,而有氧运动则通过提高抗氧化能力促进机体氧化还原恢复平衡状态,进而下调 TGF-$\beta_1$ 水平。

有研究发现[20],上皮-间质转变(EMT)是介导 ECM 成分过度沉积及肾纤维化的中心环节,因肾脏纤维化进程中有超过 1/3 的间质成肌纤维细胞来源于局部肾小管上皮发生的 EMT。该过程中上皮细胞在丢失细胞间紧密连接及失去极性的同时,上皮细胞基因表达亦重新编程(reprogramming),包括上皮细胞表面标志物 E-粘钙素下调以及成肌纤维细胞表面标志物 α-SMA 上调,即上皮细胞向具有更强 ECM 分泌能力的成肌纤维细胞转化[20]。在自然衰老诱导的肾脏纤维化[21]和输尿管闭塞性肾脏纤维化[22]大鼠模型中均获得类似结果。本研究结果显示,与 OC 组比较,OE 组大鼠 E-粘钙素表达上调,而 α-SMA 表达显著下降,提示有氧运动可抑制老年大鼠肾脏 EMT,进而减少胶原纤维沉积并改善肾脏纤维化,与对慢性肾病大鼠进行中等强度游泳训练的研究结果基本一致[15]。有研究证实[3],EMT 同样受 TGF-$\beta_1$ 调控,结合本研究结果推测有氧运动抑制 EMT 的机制与下调 TGF-$\beta_1$ 含量有关。

综上所述,本研究结果表明,规律有氧运动可延缓衰老大鼠肾脏纤维化,其作用机制可能与抑制 TGF-$\beta_1$/p38MAPK 信号通路以及 EMT 有关;当前关于 TGF-$\beta_1$ 的直接作用尚未明确,后续研究将使用 TGF-$\beta_1$ 抑制剂以观察 TGF-$\beta_1$ 信号途径在有氧运动改善肾脏纤维化过程中的直接作用。

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· 外刊撷英 ·

# Role of rehabilitation department for adult individuals with COVID-19: the experience of the SanRaffaele hospital of Milan

**ABSTRACT** The rapid evolution of the health emergency linked to the spread of severe acute respiratory syndrome coronavirus 2 requires specifications for the rehabilitative management of patients with coronavirus disease 2019 (COVID-19). The symptomatic evolution of patients with COVID-19 is characterized by 2 phases: an acute phase in which respiratory symptoms prevail and a postacute phase in which patients can show symptoms related to prolonged immobilization, to previous and current respiratory dysfunctions, and to cognitive and emotional disorders. Thus, there is the need for specialized rehabilitative care for these patients. This communication reports the experience of the San Raffaele Hospital of Milan and recommends the setup of specialized clinical pathways for the rehabilitation of patients with COVID-19. In this hospital, between February 1 and March 2, 2020, about 50 patients were admitted every day with COVID-19 symptoms. In those days, about 400 acute care beds were created (intensive care/infectious diseases). In the following 30 days, from March 2 to mid-April, despite the presence of 60 daily arrivals to the emergency department, the organization of patient flow between different wards was modified, and several different units were created based on a more accurate integration of patients' needs. According to this new organization, patients were admitted first to acute care COVID-19 units and then to COVID-19 rehabilitation units, post-COVID-19 rehabilitation units, and/or quarantine/observation units. After hospital discharge, telemedicine was used to follow-up with patients at home. Such clinical pathways should each involve dedicated multidisciplinary teams composed of pulmonologists, physiatrists, neurologists, cardiologists, physiotherapists, neuropsychologists, occupational therapists, speech therapists, and nutritionists.

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