

· 老年人心肾疾病专栏 ·

## 慢性阻塞性肺疾病患者血清低氧诱导因子-1 $\alpha$ 水平与早期肾损伤相关性分析

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**【摘要】目的** 探讨慢性阻塞性肺疾病(COPD)患者血清低氧诱导因子-1 $\alpha$  (HIF-1 $\alpha$ ) 的水平与早期肾损伤的相关性及其临床意义。**方法** COPD组: 收集2012年1月至7月新入住宁夏人民医院呼吸内科首次确诊为COPD稳定期、无急性重症感染、非吸氧患者58例; 对照组: 同期该院体检中心年龄、性别相匹配的健康体检者50例。COPD组再依据氧分压(PaO<sub>2</sub>)分为3个亚组: I级(60mmHg < PaO<sub>2</sub> ≤ 80mmHg, 1mmHg = 0.133kPa)、II级(40mmHg < PaO<sub>2</sub> ≤ 60mmHg)、III级(PaO<sub>2</sub> ≤ 40mmHg)。两组均采集静脉血, COPD组同时采集动脉血做血气分析, 采用ELISA方法检测血清HIF-1 $\alpha$ 、胱抑素C(CysC)、血清结缔组织转化生长因子- $\beta$ (TGF- $\beta$ )水平。采用全自动生化分析仪检测血清肌酐(SCr), 根据慢性肾脏病流行病学合作研究(CKD-EPI)公式计算估算肾小球滤过率(eGFR)。分析比较两组上述指标的变化。**结果** (1)与对照组比较, COPD组患者血清HIF-1 $\alpha$ 、CysC水平明显升高, 差异有统计学意义( $P < 0.05$ ), eGFR、SCr、TGF- $\beta$ 升高不明显, 差异无统计学意义( $P > 0.05$ )。(2)亚组分析: 与对照组及I级缺氧亚组比较, 血清HIF-1 $\alpha$ 在II、III级缺氧亚组明显升高。与对照组比较血清CysC在各级缺氧亚组均明显升高, 而eGFR则仅在III级缺氧亚组明显降低, 差异均有统计学意义( $P < 0.05$ )。血清SCr、TGF- $\beta$ 在3个不同缺氧亚组中均无明显升高, 差异无统计学意义( $P > 0.05$ )。(3)Pearson相关性分析显示, 血清HIF-1 $\alpha$ 与CysC呈正相关( $r = 0.665$ ,  $P = 0.001$ ), 血清CysC、HIF-1 $\alpha$ 与eGFR呈负相关( $r = -0.827$ ,  $r = -0.739$ ,  $P < 0.001$ )。**结论** 血清HIF-1 $\alpha$ 可能是评估慢性低氧患者早期肾损伤较好的生物标志物, 其与CysC联合检测可能有更好的临床实用价值。

**【关键词】** 慢性阻塞性肺疾病; 低氧诱导因子-1 $\alpha$ ; 胱抑素-C; 早期肾损伤; 生物标志物

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## Correlation of serum level of hypoxia-inducible factor-1 $\alpha$ with early renal injury in patients with chronic obstructive pulmonary disease

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**【Abstract】Objective** To evaluate the correlation between the serum level of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and early renal injury in the patients with chronic obstructive pulmonary disease (COPD) and investigate its clinical value. **Methods** A total of 58 patients with freshly diagnosed stable COPD in the Department of Respiratory Disease, Ningxia People's Hospital from January to July 2012 were subjected and prospectively analyzed in this study. Another 50 sex- and age-matched healthy individuals receiving physical examination during the same period served as normal controls. The COPD patients were all at stable phase, without severe acute infection, and with no need for oxygen inhalation, and were assigned into 3 subgroups according to hypoxia degrees: subgroup I (60mmHg < PaO<sub>2</sub> ≤ 80mmHg, 1mmHg = 0.133kPa), subgroup II (40mmHg < PaO<sub>2</sub> ≤ 60mmHg), and subgroup III (PaO<sub>2</sub> ≤ 40mmHg). Routine renal function and laboratory markers of kidney injury were detected by EILSA, including serum creatinine (SCr), and cystatin C (CysC), HIF-1 $\alpha$  and transforming growth factor- $\beta$  (TGF- $\beta$ ). Estimated glomerular filtration rate (eGFR) was calculated by chronic kidney disease epidemiology collaboration (CKD-EPI) formula. Statistical analysis was carried out to compare the differences of above indices between these groups. **Results** The serum levels of HIF-1 $\alpha$  and CysC were significantly higher in the COPD group than in control group ( $P < 0.05$ ), but the levels of SCr and TGF- $\beta$  and eGFR were increased though without significant difference between the 2 groups ( $P > 0.05$ ). Further comparison among subgroups showed that the level of HIF-1 $\alpha$  was significantly higher in subgroups II and III than in the control group and subgroup I ( $P < 0.05$ ). The level of CysC in subgroups I, II and III was significantly higher than that in the control group ( $P < 0.05$ ). The eGFR was significantly lower in subgroup III than in the control group ( $P < 0.05$ ). There was no significant difference in the serum levels of SCr and TGF- $\beta$  among the 3 subgroups of COPD patients compared with the control group ( $P > 0.05$ ). Pearson analysis showed that the serum level of HIF-1 $\alpha$  had positive correlation with CysC ( $r = 0.665$ ,  $P = 0.001$ ), and those of CysC and HIF-1 $\alpha$  had negative correlation with eGFR ( $r = -0.827$ ,  $r = -0.739$ ,  $P < 0.001$ ). **Conclusion** Serum HIF-1 $\alpha$  might be a good predictive biomarker for early renal injury in chronic hypoxia patients, and it might have better clinical value when combined with serum level of CysC.

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【Key words】 chronic obstructive pulmonary disease; hypoxia-inducible factor-1 $\alpha$ ; cystatin C; early renal injury; biomarkers

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慢性阻塞性肺疾病 (chronic obstructive pulmonary disease, COPD) 是中老年人群的常见病、多发病, 是以气道、肺实质、肺血管的慢性炎症和呼气功能持续进展性受限为特征的慢性缺氧性呼吸系统疾病。低氧诱导因子-1 $\alpha$  (hypoxia-inducible factor-1 $\alpha$ , HIF-1 $\alpha$ ) 是机体在低氧条件下诱导产生的一种细胞氧自稳态保护性调节因子。许多研究证实, HIF-1 $\alpha$ 在保护机体适应缺氧的同时, 也可以诱导其下游的许多细胞因子高表达, 引起肾损伤<sup>[1,2]</sup>。结缔组织转化生长因子- $\beta$  (transforming growth factor- $\beta$ , TGF- $\beta$ ) 就是近几年研究较多和肾纤维化高度相关的此类因子之一<sup>[3-5]</sup>。但些研究多是建立在缺氧动物组织模型上的, 用于人体研究通过肾穿刺活检获取组织标本缺少临床适应证, 且存在一定风险, 是不现实的。能否在血清中找到反映慢性缺氧患者早期肾损伤的生物标志物具有重要的临床意义。本研究选取COPD稳定期患者为研究对象, 以健康体检者作对照, 通过检测血清HIF-1 $\alpha$ 水平及其他肾损伤因子, 旨在探讨血清HIF-1 $\alpha$ 与早期肾损伤的相关性及其临床意义。

## 1 对象与方法

### 1.1 研究对象

收集2012年1月至7月新入住宁夏人民医院呼吸内科首次确诊为COPD稳定期的患者58例作为COPD组, 其中男33例, 女25例, 年龄62~75 (68.0 $\pm$ 3.5) 岁; 选择同期该院体检中心的健康体检者50例作为对照组, 其中男32例, 女18例, 年龄50~70 (65.0 $\pm$ 5.8) 岁。两组年龄、性别差异无统计学意义 ( $P>0.05$ )。

### 1.2 纳入及排除标准

COPD的诊断符合2011年中华医学会呼吸病学分会慢性阻塞性肺疾病学组制订的《慢性阻塞性肺疾病诊治指南》的诊断标准。所有入组者采血前都未给氧疗或其他特殊药物治疗。排除标准: (1) 排除既往患有各种原发和继发性肾病者如慢性肾小球肾炎、糖尿病性肾病、高血压性肾损害、系统性红斑狼疮性肾炎、紫癜性肾炎、骨髓瘤性肾病、乙肝相关性肾炎等; (2) 排除各种原因引起的多器官功能衰竭的患者以及年龄 $>80$ 岁的高龄老年患者; (3) 排除系COPD并发症之外各种原发、继发的心脏病患者; (4) 排除COPD以外引起急慢性缺氧及存在急性期感染的患者。

### 1.3 研究方法

依据血气分析氧分压 ( $\text{PaO}_2$ ) 检测结果, 将COPD组患者分为 I、II、III 级3个不同缺氧亚组, 其中 I 级 ( $60\text{mmHg} < \text{PaO}_2 \leq 80\text{mmHg}$ ;  $1\text{mmHg} = 0.133\text{kPa}$ )、II 级 ( $40\text{mmHg} < \text{PaO}_2 \leq 60\text{mmHg}$ )、III 级 ( $\text{PaO}_2 \leq 40\text{mmHg}$ )。收集COPD组及对照组清晨空腹静脉血, 及COPD组动脉血血气分析检测结果, 采用ELISA方法严格按照要求测定血清HIF-1 $\alpha$ 、胱抑素C (cystatin C, CysC)、TGF- $\beta$ 。试剂盒购自武汉华美CUSABIO生物工程有限公司。采用全自动生化分析仪检测血清肌酐 (serum creatinine, SCr) 数值。以慢性肾脏病流行病学合作研究 (chronic kidney disease epidemiology collaboration, CKD-EPI) 公式<sup>[6]</sup>计算估算肾小球滤过率 (estimated glomerular filtration rate, eGFR) [ $\text{ml}/(\text{min} \cdot 1.73\text{m}^2)$ ]: 女性SCr值 $\leq 62\mu\text{mol/L}$ 采用  $144 \times (\text{SCr}/62)^{-0.329} \times (0.993)^{\text{年龄}}$  公式计算, SCr $>62\mu\text{mol/L}$ 采用  $144 \times (\text{SCr}/62)^{-1.209} \times (0.993)^{\text{年龄}}$  公式计算; 男性SCr $\leq 80\mu\text{mol/L}$ 采用  $141 \times (\text{SCr}/80)^{-0.411} \times (0.993)^{\text{年龄}}$  公式计算, SCr $>80\mu\text{mol/L}$ 采用  $141 \times (\text{SCr}/80)^{-1.209} \times (0.993)^{\text{年龄}}$  公式计算。

### 1.4 统计学处理

采用SPSS19.0软件进行统计学分析。计量数据以均数 $\pm$ 标准差表示, 两组间均数比较采用独立样本t检验, 多组间均数比较应用单因素方差分析, 两指标间相关性分析采用Pearson分析。 $P<0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 两组血清HIF-1 $\alpha$ , CysC, TGF- $\beta$ , SCr及eGFR水平比较

与对照组比较, COPD组血清HIF-1 $\alpha$ 、CysC水平显著升高, 差异有统计学意义 ( $P<0.05$ ,  $P<0.01$ ), 而TGF- $\beta$ , SCr, eGFR变化不明显, 差异无统计学意义 ( $P>0.05$ ; 表1)。

### 2.2 COPD各亚组及对照组血清HIF-1 $\alpha$ , CysC, TGF- $\beta$ , SCr及eGFR水平比较

与对照组及 I 级缺氧亚组比较, COPD组患者血清HIF-1 $\alpha$ 在 II、III 级缺氧亚组水平明显升高, 与对照组比较CysC在各级缺氧亚组水平均明显升高, eGFR仅在 III 级缺氧亚组水平才明显降低, 差异均有统计学意义 ( $P<0.05$ ), 而血清SCr及TGF- $\beta$ 在各缺氧亚组中均无明显升高, 差异无统计学意义 ( $P>0.05$ ; 表2)。

表1 COPD组和对照组血清HIF-1 $\alpha$ , CysC, TGF- $\beta$ , SCr, eGFR比较

Table 1 Comparison of the serum HIF-1 $\alpha$ , CysC, TGF- $\beta$ , SCr and eGFR between COPD group and control group ( $\bar{x} \pm s$ )

| Group   | n  | HIF-1 $\alpha$ ( $\mu$ g/L) | CysC( $\mu$ g/L)    | TGF- $\beta$ ( $\mu$ g/L) | SCr( $\mu$ mol/L) | eGFR[ml/(min $\cdot$ 1.73m <sup>2</sup> )] |
|---------|----|-----------------------------|---------------------|---------------------------|-------------------|--------------------------------------------|
| Control | 50 | 260.15 $\pm$ 76.55          | 108.41 $\pm$ 35.35  | 25.01 $\pm$ 11.00         | 73.23 $\pm$ 13.87 | 90.31 $\pm$ 21.45                          |
| COPD    | 58 | 332.15 $\pm$ 92.74**        | 126.68 $\pm$ 34.60* | 29.21 $\pm$ 4.56          | 78.26 $\pm$ 29.21 | 87.12 $\pm$ 14.91                          |

COPD: chronic obstructive pulmonary disease; HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; CysC: cystatin C; TGF- $\beta$ : transforming growth factor- $\beta$ ; SCr: serum creatinine; eGFR: estimated glomerular filtration rate. Compared with control group, \* $P < 0.05$ , \*\* $P < 0.01$

表2 COPD各缺氧亚组及对对照组血清HIF-1 $\alpha$ , CysC, TGF- $\beta$ , SCr, eGFR比较

Table 2 Comparison of the serum HIF-1 $\alpha$ , CysC, TGF- $\beta$ , SCr and eGFR between three subgroups and control group ( $\bar{x} \pm s$ )

| Group        | n  | HIF-1 $\alpha$ ( $\mu$ g/L) | CysC( $\mu$ g/L)    | TGF- $\beta$ ( $\mu$ g/L) | SCr( $\mu$ mol/L) | eGFR[ml/(min $\cdot$ 1.73m <sup>2</sup> )] |
|--------------|----|-----------------------------|---------------------|---------------------------|-------------------|--------------------------------------------|
| Control      | 50 | 260.15 $\pm$ 76.55          | 108.41 $\pm$ 35.35  | 25.01 $\pm$ 11.00         | 76.23 $\pm$ 13.87 | 93.31 $\pm$ 21.45                          |
| Subgroup I   | 18 | 321.64 $\pm$ 84.54          | 124.46 $\pm$ 30.25* | 24.37 $\pm$ 4.69          | 78.71 $\pm$ 20.06 | 90.00 $\pm$ 22.96                          |
| Subgroup II  | 23 | 352.33 $\pm$ 61.61*#        | 135.77 $\pm$ 38.32* | 20.71 $\pm$ 11.14         | 85.00 $\pm$ 17.51 | 87.79 $\pm$ 12.29                          |
| Subgroup III | 17 | 367.19 $\pm$ 59.81*#        | 163.93 $\pm$ 58.53* | 23.63 $\pm$ 7.45          | 95.53 $\pm$ 15.84 | 73.50 $\pm$ 19.91*                         |

Subgroup I: 60mmHg  $<$  PaO<sub>2</sub>  $\leq$  80mmHg; Subgroup II: 40mmHg  $<$  PaO<sub>2</sub>  $\leq$  60mmHg; Subgroup III: PaO<sub>2</sub>  $\leq$  40mmHg; COPD: chronic obstructive pulmonary disease; HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; CysC: cystatin C; TGF- $\beta$ : transforming growth factor- $\beta$ ; SCr: serum creatinine; eGFR: estimated glomerular filtration rate. 1mmHg=0.133kPa. Compared with control group, \* $P < 0.05$ ; compared with control subgroup I, # $P < 0.05$

### 2.3 COPD组HIF-1 $\alpha$ 与CysC的相关性及HIF-1 $\alpha$ , CysC, TGF- $\beta$ 与eGFR的相关性

血清HIF-1 $\alpha$ 与CysC呈正相关( $r = 0.665, P = 0.001$ ); 血清HIF-1 $\alpha$ , CysC与eGFR呈负相关( $r = -0.739, r = -0.827, P < 0.001$ ); 血清TGF- $\beta$ 与eGFR无明显相关( $P > 0.05$ ; 表3, 图1, 图2, 图3)。

表3 COPD组HIF-1 $\alpha$ 与CysC相关性、HIF-1 $\alpha$ , CysC, TGF- $\beta$ 与eGFR的相关性

Table 3 The correlation of HIF-1 $\alpha$  with CysC, and of HIF-1 $\alpha$ , CysC and TGF- $\beta$  with eGFR in COPD group

| Item           | eGFR   |       | CysC  |       |
|----------------|--------|-------|-------|-------|
|                | $r$    | $P$   | $r$   | $P$   |
| HIF-1 $\alpha$ | -0.739 | 0.000 | 0.665 | 0.001 |
| CysC           | -0.827 | 0.000 | —     | —     |
| TGF- $\beta$   | -0.263 | 0.801 | —     | —     |

COPD: chronic obstructive pulmonary disease; HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; CysC: cystatin C; TGF- $\beta$ : transforming growth factor- $\beta$ ; eGFR: estimated glomerular filtration rate

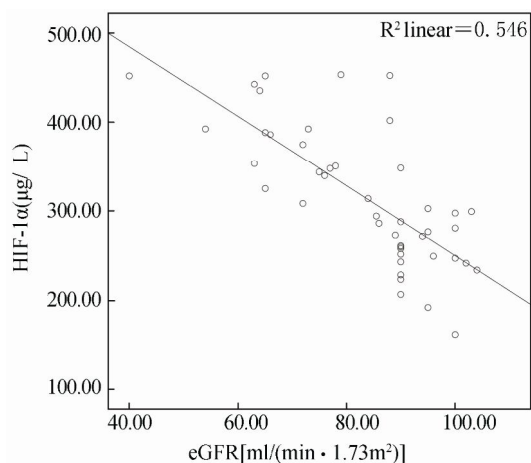


图1 HIF-1 $\alpha$ 与eGFR相关性散点图

Figure 1 The correlation between HIF-1 $\alpha$  and eGFR  
HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; eGFR: estimated glomerular filtration rate

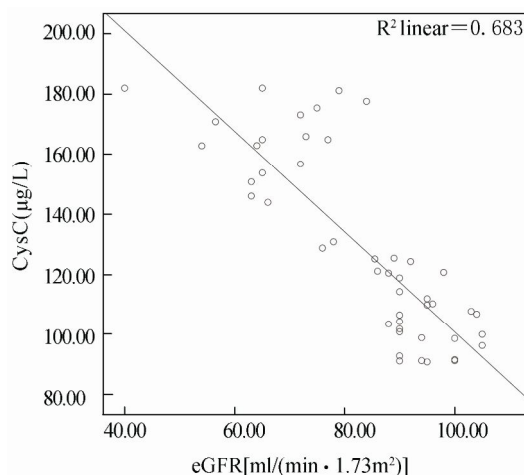


图2 CysC与eGFR相关性散点图

Figure 2 The correlation between CysC and eGFR  
CysC: cystatin C; eGFR: estimated glomerular filtration rate

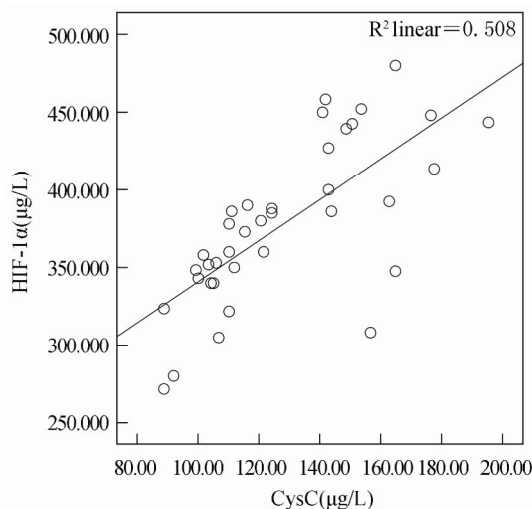


图3 HIF-1 $\alpha$ 与CysC相关性散点图

Figure 3 The correlation between HIF-1 $\alpha$  and CysC  
HIF-1 $\alpha$ : hypoxia-inducible factor-1 $\alpha$ ; CysC: cystatin C

## 3 讨论

慢性缺氧所致的肾脏损害和慢性肾脏病在我国

患病人数正逐年升高<sup>[7]</sup>。由于其起病隐匿,不能被及时发现而易造成误诊、漏诊,一旦进入终末期肾病往往预后较差,给家庭、社会造成沉重的负担。故探讨及评估慢性缺氧引起的早期肾损伤意义重大。HIF-1 $\alpha$ 是机体在低氧状态下做出适应性反应的独特的细胞氧自稳态调节因子。尽管许多文献报道HIF-1 $\alpha$ 具有促进肾损伤修复的保护作用<sup>[8-11]</sup>,但也有研究证实,慢性缺氧会损伤肾小管上皮细胞的吸收和排泄功能,促进细胞因子和炎性介质的释放,诱导肾小球内皮细胞凋亡<sup>[1,2]</sup>。许多研究也证实,HIF-1 $\alpha$ 尚可以诱导TGF- $\beta$ 等细胞因子的高表达,肾小管上皮细胞的转分化,启动间充质成纤维细胞,导致肾组织纤维化,肾功能损伤进行性加重<sup>[3-5]</sup>。但在临床诊疗实践中通过肾穿刺活检获取组织标本往往是不现实的,而获取血清则有方便易得、易于操作等优势。慢性缺氧患者HIF-1 $\alpha$ 在血清中的表达水平及其和早期肾损伤的相关性尚未见报道。临床常用的SCr及eGFR等指标虽能对肾功能变化做出较为准确的监测,但常常因其较为滞后且受影响因素较多而受限。近些年,血清CysC对高血压、糖尿病早期肾损伤的评估作用已受到广大学者的认可<sup>[12,13]</sup>,但CysC对慢性缺氧早期肾损伤的评估作用有待于进一步观察。本研究在检测血清HIF-1 $\alpha$ 表达水平的同时也检测了CysC, eGFR及SCr等指标的水平。结果发现, COPD组血清HIF-1 $\alpha$ 和CysC较对照组明显升高,差异有统计学意义 ( $P < 0.05$ ),且二者呈正相关,而eGFR及SCr等指标升高不明显,差异无统计学意义 ( $P > 0.05$ )。表明HIF-1 $\alpha$ 和CysC评估慢性缺氧性肾损伤较eGFR和SCr早且敏感。进一步对各缺氧亚组比较发现,血清HIF-1 $\alpha$ 在缺氧较重的Ⅱ、Ⅲ级亚组明显升高, CysC在各级缺氧亚组均升高,而eGFR在缺氧最重的Ⅲ级亚组才明显降低,差异均有统计学意义 ( $P < 0.05$ )。HIF-1 $\alpha$ , CysC和eGFR呈负相关,说明肾损伤和缺氧的程度相关,血清HIF-1 $\alpha$ 虽可能对缺氧性肾损伤的敏感性不及CysC但较eGFR和SCr高,即缺氧越重,肾损伤越重,和组织观察结果一致。尽管TGF- $\beta$ 被认为是慢性缺氧重要的致肾纤维化因子<sup>[3-5]</sup>,但在本研究观察结果和相关性分析中均未发现有统计学意义。表明TGF- $\beta$ 在血清中的表达并不敏感,不是反映早期肾损伤的生物标志物。也可能和样本量较小,存在一定的检验误差有关,有待在今后的观察中进一步扩大样本量。

综上所述,血清HIF-1 $\alpha$ 可能也是评估慢性缺氧患者早期肾损伤较好的生物标志物之一,其与CysC联合检测可能具有更好的临床实用价值。

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## · 消 息 ·

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