

# 血清 TNF- $\alpha$ 和 HIF-1 $\alpha$ 水平与高血压合并中重度 OSAHS 的关系及 nCPAP 治疗对其的影响\*

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**[摘要]** 目的: 观察经鼻持续正压通气(nCPAP)对高血压合并中重度阻塞性睡眠呼吸暂停低通气综合征(OSAHS)患者血清肿瘤坏死因子 $\alpha$ (TNF- $\alpha$ )、缺氧诱导因子-1 $\alpha$ (HIF-1 $\alpha$ )水平的影响。方法: 42例高血压合并中重度 OSAHS 患者为研究组, 40例单纯高血压患者为高血压组, 同期 20例体检正常者为对照组; 于入院或者体检时采用酶联免疫吸附实验法(ELISA)检测 3组受试者血清 TNF- $\alpha$  及 HIF-1 $\alpha$  的水平; 研究组患者再均分为常规治疗组(常规药物治疗)及联合治疗组(常规药物治疗联合 nCPAP 治疗), 分别检测治疗前、治疗 1个月及 6个月时血清 TNF- $\alpha$  及 HIF-1 $\alpha$  水平, 并记录 AHI 值及血压。结果: 3组被检者血清 TNF- $\alpha$  及 HIF-1 水平研究组 > 高血压组 > 对照组, 差异有统计学意义( $P < 0.05$ ); 治疗后, 联合治疗组 AHI 值、血压及血清 TNF- $\alpha$ 、HIF-1 $\alpha$  水平均较常规治疗组降低, 差异有统计学意义( $P < 0.05$ ); 治疗后, 联合治疗组患者 AHI 值、血压及血清 TNF- $\alpha$ 、HIF-1 $\alpha$  水平均较治疗前显著降低( $P < 0.05$ ), 且治疗 6个月时的数值显著低于治疗 1个月( $P < 0.05$ ); 常规治疗组患者仅治疗 6个月时血压、血清 TNF- $\alpha$  均较治疗前显著降低, 差异有统计学意义( $P < 0.05$ ); 其余指标比较差异无统计学意义( $P > 0.05$ )。结论: 常规治疗联合 nCPAP 对高血压合并 OSAHS 患者的治疗效果可能与降低患者血液 TNF- $\alpha$  及 HIF-1 $\alpha$  水平有关。

**[关键词]** 阻塞性睡眠呼吸暂停低通气综合征; 睡眠呼吸暂停低通气指数; 高血压; 经鼻持续正压通气; 缺氧诱导因子-1 $\alpha$ ; 肿瘤坏死因子 $\alpha$

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## Correlation between Serum HIF-1 $\alpha$ /TNF- $\alpha$ Level and Hypertension Patients with Moderate to Severe OSAHS and the Effect of nCPAP Therapy

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**[Abstract]** **Objective:** To investigate the curative effects and prognosis of nasal continuous positive airway pressure (nCPAP) treatment by observing the levels of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and TNF- $\alpha$  in hypertension patients with moderate to severe obstructive sleep apnea hypopnea syndrome (OSAHS). **Method:** 42 hypertension patients with moderate to severe OSAHS were chosen as study group. 40 hypertension patients without OSAHS as hypertension group. In addition, 20 people received physical examination were chosen as blank group. The expression of TNF- $\alpha$  and HIF-1 $\alpha$  levels of all groups were detected by ELISA when admitted to hospital or during physical check. Patients in

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the study group were equally and randomly divided into conventional study group (conventional drug therapy) and combined study group (conventional drug therapy combined with nCPAP therapy). Serum TNF-α and HIF-1α level were detected before treatment, 1 month and 6 months after treatment; blood pressure and AHI value were recorded. **Results:** HIF-1α and TNF-α level in decreasing order as, study group, simple hypertension and blank group, differences were statistically significant ( $P < 0.05$ ); after treatment, AHI value, blood pressure and serum HIF-1α and TNF-α level of combined treatment group was lowered than conventional treatment group, differences were statistically significant ( $P < 0.05$ ); after treatment, AHI value, blood pressure and serum HIF-1α and TNF-α level of combined treatment group was significantly lowered than before treatment ( $P < 0.05$ ), and the value of 6 months after treatment was significantly lower than that of one month ( $P < 0.05$ ); blood pressure and serum TNF-α of conventional treatment group 6 months after treatment were obviously lowered than before treatment, differences were statistically significant ( $P < 0.05$ ); other parameters were not statistically significant ( $P > 0.05$ ). **Conclusions:** The efficacy of conventional treatment combined nCPAP on hypertension patient with OSAHS might be related with the patients' serum HIF-1α and TNF-α. [Key words] obstructive sleep apnea hypopnea syndrome; sleep apnea hypopnea index; hypertension; nasal continuous positive airway pressure; hypoxia inducible factor 1α; tumor necrosis factor α

阻塞性睡眠呼吸暂停低通气综合征 (obstructive sleep apnea-hypopnea syndrome, OSAHS) 是指每夜 7 h 睡眠过程中呼吸暂停及低通气反复发作 30 次以上、或睡眠呼吸暂停低通气指数 (AHI)  $> 5$  的临床症候群<sup>[1]</sup>。呼吸睡眠呼吸暂停能促进炎症因子诱导炎症反应的发生<sup>[2-3]</sup>, 经鼻持续正压通气治疗 (nasal continuous positive airway pressure, nCPAP) 可通过纠正缺氧、改善睡眠结构从而降低炎症因子水平, 改善内皮功能, 有利于血压恢复正常<sup>[4-6]</sup>。本研究对高血压合并中重度 OSAHS 患者给与常规治疗和常规联合 nCPAP 治疗, 观察患者血清缺氧诱导因子-1α (hypoxia-inducible factor-1α, HIF-1α)、肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)、AHI 及血压变化情况, 报告如下。

## 1 对象和方法

### 1.1 研究对象

选择 2014 年 2 月 ~ 2016 年 2 月收治的 42 例中重度 OSAHS 合并高血压患者为研究组, 其中男 29 例、女 13 例, 平均  $(56.12 \pm 4.15)$  岁, 体质指数 (BMI) 为  $(24.73 \pm 2.99)$  kg/m<sup>2</sup>; 选取同期 40 例单纯高血压患者作为高血压病组, 其中男 30 例、女 10 例, 平均  $(55.01 \pm 5.32)$  岁, BMI  $(23.82 \pm 2.34)$  kg/m<sup>2</sup>; 选取 20 例无打鼾史正常体检者作为对照组, 其中男 16 例、女 4 例, 平均  $(56.8 \pm 5.89)$  岁, BMI  $(24.32 \pm 1.98)$  kg/m<sup>2</sup>; 3 组受试者性别、年龄及 BMI 比较, 差异无统计学意义 ( $P > 0.05$ )。OSAHS 诊断及分

度参考文献[7]: AHI 5 次/h  $\leq$   $\sim < 15$  次/h 为轻度、15 次/h  $\leq$   $\sim < 30$  次/h 为中度、AHI  $\geq 30$  次/h 为重度。所有受试者排除继发性高血压、纽约心脏病协会 (NYHA) 心衰分类 III ~ IV 级者, 排除继发感染、肿瘤、全身免疫性疾病、严重肝肾疾病及糖尿病患者, 排除接受甾体激素类药物、免疫抑制剂或其它抗炎药物治疗者。

### 1.2 观察指标

于入院或者体检时采集 3 组受试者清晨空腹静脉血, 3 000 r/min 离心分离血清, 采用酶联免疫吸附实验 (ELISA) 检测血清 TNF-α 及 HIF-1α 的水平。研究组患者随机分为常规治疗组和联合治疗组、每组 21 例, 常规治疗组接受常规药物治疗, 联合治疗组在常规药物治疗的同时接受 nCPAP 治疗。分别于治疗前、治疗 1 个月及 6 个月时采集两治疗组患者清晨空腹静脉血, 测定血清 TNF-α 及 HIF-1α 水平, 并记录 AHI 值及血压。

### 1.3 统计学方法

数据统计分析采用 SPSS 16.0, 计量资料采用均数  $\pm$  标准差 ( $\bar{x} \pm s$ ) 表示, 数据比较采用单因素方差分析, 两两比较采用  $t$  检验; 计数资料采用率 (%) 表示, 数据比较采用  $\chi^2$  检验,  $P < 0.05$  表明有统计学意义。

## 2 结果

### 2.1 血清 TNF-α 及 HIF-1α 水平

入院或者体检时, 研究组及高血压组患者血清

TNF-α 和 HIF-1 水平显著高于对照组,差异有统计学意义( $P < 0.05$ ),研究组又显著高于高血压组,差异有统计学意义( $P < 0.05$ )。见表 1。

表 1 入院或体检时 3 组受试者血清  
TNF-α 和 HIF-1 水平比较( $\bar{x} \pm s$ ,ng/L)

Tab.1 Comparison of serum TNF-α and  
HIF-1α levels of three groups

组别	血清	
	TNF-α	HIF-1α
对照组	9.78 ± 4.67	30.35 ± 3.21
高血压组	13.31 ± 3.05 <sup>(1)</sup>	52.08 ± 4.71 <sup>(1)</sup>
研究组	16.76 ± 4.44 <sup>(1)(2)</sup>	120.91 ± 3.69 <sup>(1)(2)</sup>

<sup>(1)</sup>与对照组比较, $P < 0.05$ ;<sup>(2)</sup>与高血压组比较, $P < 0.05$

2.2 中重度 OSAHS 合并高血压患者 AHI 值、血压及血清 TNF-α、HIF-1α 水平

治疗前,常规治疗组与联合治疗组患者 AHI 值、血压及血清 TNF-α、HIF-1α 水平比较,差异无统计学意义( $P > 0.05$ );治疗后,联合治疗组 AHI 值、血压及血清 TNF-α、HIF-1α 水平均较常规治疗组降低,差异有统计学意义( $P < 0.05$ )。治疗后,联合治疗组患者 AHI 值、血压及血清 TNF-α、HIF-1α 水平均较治疗前显著降低( $P < 0.05$ ),且治疗 6 个月时的数值显著低于治疗 1 个月( $P < 0.05$ );常规治疗组患者仅治疗 6 个月时血压、血清 TNF-α 均较治疗前显著降低,差异有统计学意义( $P < 0.05$ );其余指标比较差异无统计学意义( $P > 0.05$ )。见表 2。

表 2 两治疗组患者治疗前后 AHI 值、血压及血清 TNF-α、HIF-1α 水平比较( $\bar{x} \pm s$ )

Tab.2 Comparison of indexes before and after treatment between the two study groups

组别	时间	AHI(次/h)	收缩压(mmHg)	舒张压(mmHg)	TNF-α(ng/L)	HIF-1α(ng/L)
常规治疗组	治疗前	43.76 ± 4.23	145.18 ± 10.34	92.47 ± 7.83	16.63 ± 2.98	121.37 ± 3.87
	治疗 1 个月	42.51 ± 3.83	143.95 ± 9.81	89.73 ± 8.56	16.05 ± 3.43	120.32 ± 2.96
	治疗 6 个月	41.99 ± 6.17	133.67 ± 8.26 <sup>(2)(3)</sup>	85.82 ± 5.56 <sup>(2)(3)</sup>	14.15 ± 2.37 <sup>(2)(3)</sup>	119.42 ± 4.38
联合治疗组	治疗前	43.28 ± 4.17	146.52 ± 13.98	94.13 ± 7.14	16.87 ± 3.24	120.67 ± 4.01
	治疗 1 个月	21.31 ± 6.41 <sup>(1)(2)</sup>	137.33 ± 10.41 <sup>(1)(2)</sup>	88.06 ± 3.28 <sup>(1)(2)</sup>	15.98 ± 2.41 <sup>(1)(2)</sup>	97.42 ± 3.58 <sup>(1)(2)</sup>
	治疗 6 个月	6.13 ± 4.22 <sup>(1)(2)(3)</sup>	129.24 ± 8.45 <sup>(1)(2)(3)</sup>	81.53 ± 4.53 <sup>(1)(2)(3)</sup>	11.01 ± 2.62 <sup>(1)(2)(3)</sup>	62.57 ± 4.61 <sup>(1)(2)(3)</sup>

<sup>(1)</sup>与常规治疗组同时点比较, $P < 0.05$ ;<sup>(2)</sup>与同组治疗前比较, $P < 0.05$ ;<sup>(3)</sup>与同组治疗 1 个月比较, $P < 0.05$

3 讨论

OSAHS 是心脑血管疾病一个常见的危险因素,近期的文献报道指出它的发生率越来越高<sup>[8-10]</sup>。心脑血管疾病主要危险因素有高血压、糖尿病、高脂血症、吸烟和酗酒及慢性压力等。OSAHS 相关疾病的发病机制有交感神经系统的激活、肾素-血管紧张素-醛固酮系统的激活、内皮功能障碍、系统性和血管炎症、氧化应激、代谢异常、自主心血管系统的改变、动脉硬化以及心脏功能和结构的改变等<sup>[11-13]</sup>。炎症因子参与了高血压合并 OSAHS 患者的发生发展过程,nCPAP 是治疗 OSAHS 的有效措施之一<sup>[14-15]</sup>,它通过纠正缺氧、改善睡眠结构、降低炎症因子水平,改善内皮功能等,可以降低猝死、卒中等临床恶性事件的发生,可能也有助于高血压合并 OSAHS 患者血压的控制<sup>[16]</sup>。HIF-1 是近年发现的一种新型转录因子,在氧平衡调节中起关键作用,包含有 HIF-1α 和

HIF-1β 两个亚基的异源二聚体,而 HIF-1 的生理活性主要取决于其 α 亚基的表达和活性。OSAHS 在呼吸暂停时能够增加活性蛋白-1(activator protein-1,AP-1)和 HIF-1 的转录活性,因此推测在 OSAHS 合并高血压患者中 HIF-1α 水平会较正常人偏高<sup>[17]</sup>。OSAHS 患者经 nCPAP 治疗能降低血浆中 TNF-α 的水平<sup>[18]</sup>,因此本研究以 TNF-α 为参考,检测高血压合并中重度 OSAHS 患者血清 HIF-1α 的水平变化。

本研究结果所示,高血压合并中重度 OSAHS 患者 HIF-1α 水平明显高于单纯高血压病患者及正常对照者,经 nCPAP 治疗 6 个月后高血压合并中重度 OSAHS 患者血清 HIF-1α 水平较治疗前明显下降。有研究表明 nCPAP 治疗对血压影响较小<sup>[19]</sup>,也有部分研究表明对舒张压改善较显著<sup>[20]</sup>。Sapiña 等<sup>[21]</sup>对阻塞性睡眠呼吸暂停合并有顽固性高血压患者给予 CPAP 治疗进行的多中心、前瞻性、观察性的队列研究,结果提示有助于改善顽固性高血压患者的血压。本研究结果显示,

nCPAP 治疗有助于高血压合并中重度 OSAHS 患者血压的控制,包括舒张压。

综上所述,HIF-1 $\alpha$  可能参与了 OSAHS 合并高血压的发生发展过程,通过 nCPAP 的治疗能够降低 HIF-1 $\alpha$  的水平,有助于患者血压的控制。

## 4 参考文献

- [1] LIEBERMAN J A. Obstructive sleep apnea (OSA) and excessive sleepiness associated with OSA: recognition in the primary care setting[J]. Postgrad Med, 2009, 121(4): 33-41.
- [2] BIELICKI P, MACLEOD A K, DOUGLAS N J, et al. Cytokine gene polymorphisms in obstructive sleep apnoea/hypopnoea syndrome[J]. Sleep Med, 2015, 16(6):792-795.
- [3] HUI P, JIA S, MA W, et al. The clinical significance and changes of serum tumor necrosis factor and plasma endothelium in patients with OSAHS associated Type 2 diabetes mellites[J]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2016,30(3):217-225.
- [4] YOKOE T, MINOGUCHI M K, MATSUO H. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased nasal continuous positive airway pressure [J]. Circulation, 2003, 107(8):1129-1134.
- [5] GARCIA-RIO F I, PINO J M, ALONSO A, et al. White coat hypertension in patients with obstructive sleep apnea-hypopnea syndrome [J]. Chest, 2004, 125(3): 817-822.
- [6] PEPPARD P E, YOUNG T, PALTA M, et al. Prospective study of the association between sleep disordered breathing and hypertension[J]. N Engl J Med, 2000, 324(19):1378-1384.
- [7] AMERICAN ACADEMY OF SLEEP MEDICINE TASK FORCE. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research [J]. Sleep, 1999, 22(5):667-689.
- [8] KING S, CUELLAR N. Obstructive sleep apnea as an independent stroke risk factor: A review of the evidence, stroke prevention guidelines, and implications for neuroscience nursing practice[J]. J Neurosci Nurs, 2016,48(3):133-142.
- [9] PARATI G, OCHOA J E, BILO G, et al. Obstructive sleep apnea syndrome as a cause of resistant hypertension [J]. Hypertens Res, 2014,37(7): 601-613.
- [10] ZHANG P, GUO W J. The research progress of OSAHS and cardiovascular disease[J]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2016,30(6):442-445.
- [11] JIN Z N, WEI Y X. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system[J]. J Geriatr Cardiol, 2016, 13(4):333-343.
- [12] JENNUM P, RIHA R L. Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing[J]. Eur Respir J, 2009, 33(4):907-914.
- [13] VECCHIERINI M F. Obstructive sleep apnea-hypopnea syndrome: evolution of an old concept[J]. Neurochirurgie, 2006,52(5): 432-442.
- [14] BARBÉ F, DURÁN-CANTOLLA J, SÁNCHEZ-DE-LA-TORRE M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial[J]. JAMA, 2012, 307(20): 2161-2168.
- [15] GUEST J F, HELTER M T, MORGA A, et al. Cost-effectiveness of using continuous positive airway pressure in the treatment of severe obstructive sleep apnoea/hypopnoea syndrome in the UK[J]. Thorax, 2008, 63(10): 860-865.
- [16] MARCELLA R, ATUL R, KENNETH N. Obstructive sleep apnea and its effects on cardiovascular diseases: a narrative review[J]. Anatol J Cardiol, 2016,15(11): 944-950.
- [17] MO X, LIU J, XIE Y, et al. Analysis of clinical characteristics and risk factors of obstructive sleep apnea hypopnea syndrome with hypertension[J]. Zhong hua Yi Xue Za Zhi, 2016, 96(8):605-609.
- [18] MINOGUCHI K, TAZAKI T, YOKOE T, et al. Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome [J]. Chest, 2004, 126(5):1473-1479.
- [19] WANG X, QIU J, WANG Y, et al. Beneficial response of blood pressure to short-term continuous positive airway pressure in Chinese patients with obstructive sleep apnea-hypopnea syndrome [J]. Blood Press Monit, 2018, 23(4):175-184.
- [20] CAMPOS-RODRIGUEZ F, GONZALEZ-MARTINEZ M, SANCHEZ-ARMENGOL A, et al. Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea[J]. Eur Respir J, 2017, 50(2):257-264.
- [21] SAPIÑA-BELTRÁN E, TORRES G, MARTÍNEZ-ALONSO M, et al. Rationale and methodology of the SARAH trial: long-term cardiovascular outcomes in patients with resistant hypertension and obstructive sleep apnea[J]. Arch Bronconeumol, 2018,22(10):1016-1019.

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