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胸腺五肽联合辛伐他汀治疗 COPD 合并肺动脉高压的疗效及对患者血清 PAF-AH、esRAGE、CA125 水平的影响 *

窦志芳[1] 陈乾华[1] 付 伟[1] 郑 野[1] 王 敏[2]

（1 中国医科大学航空总医院 呼吸科 北京 100012；2 甘肃省中医药大学附属医院 呼吸科 甘肃 兰州 730000）

摘要 目的：探讨胸腺五肽联合辛伐他汀治疗慢性阻塞性肺疾病(COPD)合并肺动脉高压的疗效及对患者血清血小板活化因子乙酰水解酶(PAF-AH)、内源性分泌型晚期糖基化终末产物受体(esRAGE)、糖类抗原 125(CA125)水平的影响。**方法：**选择 2016 年 1 月至 2017 年 12 月我院接诊的 65 例 COPD 合并肺动脉高压患者，通过随机数表法分为观察组 35 例和对照组 30 例。对照组在常规治疗基础上给予辛伐他汀治疗，观察组在对照组基础上给予胸腺五肽治疗，两组均连续治疗 4 周。治疗后，比较两组血清 PAF-AH、esRAGE、CA125 水平、免疫功能、肺功能、血气分析指标的变化及不良反应的发生情况。**结果：**治疗后，观察组血清 PAF-AH、esRAGE 水平明显高于对照组，而血清 CA125 水平明显低于对照组[(187.20± 15.10)ng/mL vs. (135.13± 11.42)ng/mL，(0.32± 0.08)ng/L vs. (0.26± 0.05)ng/L，(21.06± 3.27)U/mL vs. (30.49± 4.23)U/mL](*P<0.05*)；观察组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 明显高于对照组[(69.56± 7.89)% vs. (57.56± 6.05)%，(43.30± 5.11)% vs. (37.86± 4.53)%，(2.14± 0.30) vs. (1.82± 0.26)](*P<0.05*)；观察组血清第一秒用力呼气容积(FEV1)、FEV1/ 用力肺活量(FVC)明显高于对照组，肺动脉收缩压(PASP)明显比对照组低[(2.17± 0.34)L vs (1.84± 0.29)L，(67.34± 8.28)% vs. (60.37± 6.05)%，(36.23± 3.15)mmHg vs. (42.85± 3.88)mmHg](*P<0.05*)；观察组动脉血压分压(PaO_2)明显高于对照组，二氧化碳分压($PaCO_2$)明显低于对照组[(89.45± 7.40)mmHg vs. (80.23± 6.82)mmHg，(33.83± 3.11)mmHg vs. (40.02± 3.86)mmHg](*P<0.05*)。两组不良反应的总发生率比较差异无统计学意义(*P>0.05*)。**结论：**胸腺五肽联合辛伐他汀治疗 COPD 合并肺动脉高压患者效果显著优于单用辛伐他汀治疗，可更有效改善患者肺功能和肺动脉高压状态，其内在机制可能和调节血清 PAF-AH、esRAGE、CA125 水平及缓解气道炎症反应相关。

关键词：慢性阻塞性肺疾病；肺动脉高压；胸腺五肽；辛伐他汀；血清因子

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Curative Efficacy of Thymic Five Peptide Combined with Simvastatin in the Treatment of COPD Combined with Pulmonary Hypertension and Its Effects on the Serum PAF-AH, esRAGE and CA125 Levels*

DOU Zhi-fang[1], CHEN Qian-hua[1], FU Wei[1], ZHENG Ye[1], WANG Min[2]

(1 Department of respiration, General Hospital of China Aviation, China Medical University, Beijing, 100012, China;

2 Department of respiration, Affiliated Hospital of Gansu traditional Chinese Medicine University, Lanzhou, Gansu, 730000, China)

ABSTRACT Objective: To study the curative efficacy of thymic five peptide combined with simvastatin in the treatment of chronic obstructive pulmonary disease (COPD) combined with pulmonary hypertension and its effects on the serum platelet-activating factor acetylhydrolase (PAF-AH), endogenous secretory receptor for advanced glycation end products (esRAGE) and carbohydrate antigen (CA125) levels. **Methods:** 65 patients of COPD combined with pulmonary hypertension who received therapy from January 2016 to December 2017 in our hospital, they were divided into observation group (35 cases) and control group (30 cases) by random number table method, the control group was treated with simvastatin on the basis of routine treatment, while the observation group was treated with thymopentin, they were treated for 4 weeks. The changes of serum PAF-AH, esRAGE, CA125, immune function, lung function, blood gas analysis index and adverse reactions were compared between the two groups. **Results:** After treatment, the serum PAF-AH and esRAGE levels in the observation group were significantly higher than those in the control group, and serum CA125 levels was significantly lower than those in the control group[(187.20± 15.10)ng/mL vs. (135.13± 11.42)ng/mL, (0.32± 0.08)ng/L vs. (0.26± 0.05) ng/L, (21.06± 3.27)U/mL vs. (30.49± 4.23)U/mL](*P<0.05*); the $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels in the observation group were significantly higher than those in the control group[(69.56± 7.89)% vs. (57.56± 6.05)%, (43.30± 5.11)% vs. (37.86± 4.53)%, (2.14± 0.30) vs. (1.82± 0.26)](*P<0.05*); the first second forced expiratory volume (FEV1) and FEV1/forced vital capacity (FVC) in the observation group were significantly higher than those in the control group, and the pulmonary systolic pressure (PASP) was significantly lower than those in the control group[(2.17± 0.34)L vs. (1.84± 0.29)L, (67.34± 8.28)% vs. (60.37± 6.05)%, (36.23± 3.15)mmHg vs.

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作者简介：窦志芳(1975-)，女，硕士，副主任医师，研究方向：慢阻肺，呼吸危重症方向，电话：15810388892，E-mail：yinghuajin06@aliyun.com

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(42.85± 3.88)mmHg](*P<0.05*); the partial pressure of arterial blood pressure (PaO_2) in the observation group was significantly higher than those in the control group, and the partial pressure of carbon dioxide ($PaCO_2$) was significantly lower than those in the control group[(89.45± 7.40)mmHg vs. (80.23± 6.82)mmHg, (33.83± 3.11)mmHg vs. (40.02± 3.86)mmHg](*P<0.05*); there was no significant difference in the incidence of adverse reactions between the two groups (*P>0.05*). **Conclusion:** Thymic five peptide combined with simvastatin in the treatment of COPD patients with pulmonary hypertension is significantly better than simvastatin alone., it's helpful to improve pulmonary function and pulmonary hypertension. Its internal mechanism may be related to the regulation of serum PAF-AH, esRAGE, CA125 lelves and alleviating airway inflammation.

Key words: Chronic obstructive pulmonary disease; Pulmonary hypertension; Thymic five peptide; simvastatin; Serum factor

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前言

慢性阻塞性肺疾病(COPD)是临床上较为常见的呼吸系统疾病,以不完全可逆的气流受限为主要特征,若患者气流严重受限,则极易并发症肺动脉高压,加重病情,若得不到及时控制,可发展成为肺源性心脏病,严重者甚至出现心力衰竭、死亡[1,2]。该病的发生和发展涉及到多环节,但主要和肺部对有害气体的异常炎症反应、血管内皮紊乱等密切相关[3,4]。血清血小板活化因子乙酰水解酶(PAF-AH)、内源性分泌型晚期糖基化终末产物受体(esRAGE)、糖类抗原 125(CA125)在其中发挥了重要作用[5,6]。

目前,COPD 合并肺动脉高压无特效疗法,以对症治疗、增加活动耐量、预防疾病进展等为主。辛伐他汀作为作为临床上常用的降脂药物,除调节血脂作用外,还具有抗氧化、抗炎、改善内皮功能、阻止动脉管壁重构等作用[7,8]。胸腺五肽作为一种人工合成的五肽活性片段,具有免疫调节作用,近年来有学者发现其可通过调节 COPD 患者的低免疫状态,提高机体抗病能力,达到改善预后的目的,对 COPD 患者具有辅助治疗效果[9,10]。但目前关于其用于 COPD 合并肺动脉高压患者的相关报道较少。因此,本研究主要探讨了胸腺五肽联合辛伐他汀联合用于治疗 COPD 合并肺动脉高压的优势, 并观察其对患者血清 PAF-AH、esRAGE、CA125 水平的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 1 月至 2017 年 12 月我院接诊的 65 例 COPD 合并肺动脉高压患者进行研究。纳入标准[11]:① 符合《慢性阻塞性肺疾病诊治指南》、《肺动脉高压筛查诊断与治疗专家共识》中相关诊断标准;② 美国纽约心脏病学会(NYHA)分级 I~II 级;③ 签署本研究知情同意书。排除标准[12]:① 严重肺部感染;② 合并肺动脉栓塞、支气管哮喘、过敏性鼻炎等;③ 合并严重肝肾功能障碍、心脏疾病等;④ 近 3 个月内服用过内皮素受体拮抗剂、他汀类药物等;⑤ 对研究药物具有禁忌症。通过随机数表法将患者分为观察组 35 例和对照组 30 例,两组一般资料比较差异无统计统计学意义(*P>0.05*),具体见表 1。

1.2 治疗方法

所有患者均给予常规处理,包括机械通气或吸氧、化痰、平喘、抗炎、解除气道痉挛、强心、利尿等,给予糖皮质激素扩张支气管,给予头孢类药物抗菌。对照组在此基础上给予辛伐他汀(规格 20 mg, 厂家: 杭州默沙东制药有限公司, 国药准字 J20130068)治疗,40 mg/ 次,睡前服用 1 次;观察组在对照组基础上给予胸腺五肽注射液(规格 1 ml:10 mg,厂家:北京世桥生物制药有限公司,H20061226)10 mg 肌肉注射,每周 2 次。均连续治疗 4 周。

1.3 观察指标

1.3.1 血清 PAF-AH、esRAGE、CA125 水平 采集治疗前、后空腹静脉血 5 mL,置于加入抗凝管的 EDTA 试管中,离心机分离血清(3000 r/min,10 min),置于低温箱中储存待检,各指标均使用酶联免疫吸附法进行,试剂盒购于美国 R&D 公司。

1.3.2 **免疫功能** 使用美国 Culter 公司生产的流式细胞仪 EPICS-XL 型, 检测指标包括 T 淋巴细胞亚群 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$。

1.3.3 **肺功能** 使用德国耶格 Master Screen diff 肺功能仪检测第一秒用力呼气容积(FEV1)、FEV1/ 用力肺活量(FVC),使用荷兰飞利浦飞凡多普勒超声仪 M2540A 检测肺动脉收缩压(PASP)。

1.3.4 **血气分析** 使用丹麦雷度血气分析仪 ABL90 检测,指标包括动脉血压分压(PaO_2)、二氧化碳分压($PaCO_2$)。

1.3.5 **不良反应的发生情况**。

1.4 统计学分析

以 spss18.0 软件包处理实验数据,计量资料用均数± 标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验,计数资料组间比较采用 x^2 检验,以 *P<0.05* 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后清 PAF-AH、esRAGE、CA125 水平的比较

两组治疗前血清 PAF-AH、esRAGE、CA125 水平比较差异无统计学意义 (*P>0.05*), 和治疗前相比, 两组治疗后血清 PAF-AH、esRAGE 均明显升高, 而血清 CA125 水平明显降低(*P<0.05*), 且观察组血清 PAF-AH、esRAGE 水平明显高于对照组,血清 CA125 水平明显低于对照组(*P<0.05*),见表 2。

2.2 两组治疗前后免疫功能的比较

两组治疗前 T 淋巴细胞亚群比较差异无统计学意义 (*P>0.05*),和治疗前相比,两组治疗后 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均明显高于治疗前(*P<0.05*),且观察组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 明显高于对照组(*P<0.05*),见表 3。

2.3 两组治疗前后肺功能的比较

两组治疗前 FEV1、FEV1/FVC、PASP 比较差异无统计学

表 1 两组一般资料的比较[$\bar{x}\pm s$, n(%)]

Table 1 Comparison of the general data between two groups [$\bar{x}\pm s$, n(%)]

Groups	Sex(F/M)	Age(years)	COPD course of disease(years)	Severity of pulmonary hypertension		
				Mild	Moderate	Severe
Observation group (n=35)	20/15	61.85± 7.40	3.61± 0.38	10(28.57)	21(60.00)	4(11.43)
Control group (n=30)	17/13	62.03± 7.26	3.67± 0.35	8(26.67)	18(60.00)	4(13.33)

表 2 两组治疗前后血清 PAF-AH、esRAGE、CA125 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum PAF-AH, esRAGE and CA125 between two groups before and after treatment($\bar{x}\pm s$)

Groups		PAF-AH(ng/mL)	esRAGE(ng/L)	CA125(U/mL)
Observation group(n=35)	Before treatment	93.45± 8.21	0.17± 0.04	45.34± 5.69
	After treatment	187.20± 15.10*#	0.32± 0.08*#	21.06± 3.27*#
Control group(n=30)	Before treatment	92.97± 8.35	0.18± 0.04	45.71± 5.52
	After treatment	135.13± 11.42*	0.26± 0.05*	30.49± 4.23*

Vs the before treatment, *$P<0.05$; vs the control group, #$P<0.05$.

表 3 两组治疗前后免疫功能的比较($\bar{x}\pm s$)

Table 3 Comparison of the immunologic function between two groups before and after treatment($\bar{x}\pm s$)

Groups		$CD3^+$(%)	$CD4^+$(%)	$CD4^+/CD8^+$
Observation group(n=35)	Before treatment	47.25± 5.04	32.49± 3.50	1.49± 0.24
	After treatment	69.56± 7.89*#	43.30± 5.11*#	2.14± 0.30*#
Control group(n=30)	Before treatment	47.49± 4.87	32.18± 3.76	1.53± 0.22
	After treatment	57.56± 6.05*	37.86± 4.53*	1.82± 0.26*

Vs the before treatment, *$P<0.05$; vs the control group, #$P<0.05$.

意义 ($P>0.05$)，和治疗前相比，两组治疗后血清 FEV1、FEV1/FVC 均明显升高，PASP 明显降低($P<0.05$)，且观察组血清 FEV1、FEV1/FVC 明显高于对照组，PASP 明显比对照组低($P<0.05$)，见表 4。

表 4 两组治疗前后肺功能的比较($\bar{x}\pm s$)

Table 4 Comparison of the pulmonary function between two groups before and after treatment($\bar{x}\pm s$)

Groups		FEV1(L)	FEV1/FVC(%)	PASP(mmHg)
Observation group(n=35)	Before treatment	1.37± 0.28	48.52± 3.79	53.48± 4.82
	After treatment	2.17± 0.34*#	67.34± 8.28*#	36.23± 3.15*#
Control group(n=30)	Before treatment	1.41± 0.26	48.83± 3.71	53.72± 4.60
	After treatment	1.84± 0.29*	60.37± 6.05*	42.85± 3.88*

Vs the before treatment, *$P<0.05$; vs the control group, #$P<0.05$.

2.4 两组治疗前后血气分析指标的比较

两组治疗前 PaO_2、$PaCO_2$ 比较差异无统计学意义($P>0.05$)，两组治疗后 PaO_2、$PaCO_2$ 较治疗前均得到明显改善($P<0.05$)，观察组 PaO_2 明显高于对照组，$PaCO_2$ 明显低于对照组 ($P<0.05$)，见表 5。

2.5 两组不良反应发生情况的比较

治疗期间，观察组出现 2 例胃肠道反应、1 例头痛，对照组出现 1 例胃肠道反应、1 例头痛，两组不良反应总发生率分别为 8.57%(3/35)和 6.67%(2/30)，组间比较差异无统计学意义($P>0.05$)。

3 讨论

肺动脉高压是 COPD 患者最常见的并发症，主要发生原因和 COPD 患者气道、肺血管、肺实质发生的慢性炎症反应所致的气道壁损伤、修复和结构重塑等相关，该过程可增加肺血管压力和阻力，诱发肺动脉高压[13,14]。PAF 是种生物活性较强的磷脂类炎性因子，参与多种慢性炎症疾病，而 PAF-AH 是种对 PAF 具有抑制作用的因子，有研究显示 PAF 在炎症反应中的生成增加，此时令局部的 PAF-AH 增加则显得极为重要，增加 PAF-AH 的表达可缓解 PAF 和氧化磷脂之间的炎性效应[15,16]。

表 5 两组治疗前后血气分析结果的比较($\bar{x}\pm s$,mmHg)

Table 5 Comparison of the blood gas analysis between two groups before and after treatment($\bar{x}\pm s$, mmHg)

Groups		PaO_2	$PaCO_2$
Observation group(n=35)	Before treatment	58.16± 5.91	60.34± 5.75
	After treatment	89.45± 7.40*	33.83± 3.11*#
Control group(n=40)	Before treatment	57.94± 6.14	60.67± 5.29
	After treatment	80.23± 6.82*	40.02± 3.86*

Vs the before treatment, *$P<0.05$; vs the control group, #$P<0.05$.

Savas Oz B 等[17]实验也证实 COPD 患者 PAF-AF 表达明显降低,且和 PASP 呈负相关,参与肺动脉高压的发生。esRAGE 是血管结构、功能中的一种重要潜在保护因子,其可对晚期糖基化终末期产物(AGES)和其受体(RAGE)产生竞争性作用,组织两者相互结合,令其无法激活细胞信号传导通路,阻碍炎症反应的发生 [18,19]。有报道指出 COPD 合并肺动脉高压患者血清 esRAGE 的表达明显比未合并肺动脉高压的患者高,且和肺动脉高压严重程度之间具有明显相关性 [20,21]。CA125 作为膜结合型粘蛋白,多在呼吸道、胃肠道、泌尿生殖系统表达,既往多用于诊断卵巢癌以及其余恶性肿瘤中,近年来有学者提出 COPD 患者由于长时间的慢性炎症刺激和起到粘液的高浓度分泌,可刺激气道上皮细胞增生,启动 CA125 粘膜屏障功能,令其表达增加。而在肺动脉高压形成过程中,肺循环阻力、机械应力的增加等,会进一步增加间皮细胞活性,致使 CA125 的进一步释放[22,23]。

COPD 合并肺动脉高压的治疗目前尚无满意的治疗方案,主要目的仍是缓解气道炎症、降低血管阻力等,他汀类药物在临床上具有有效的抗炎效果。辛伐他汀是他汀类代表药物,不仅具有有效的降血脂效果,且在改善肺血管重构、降低肺动脉高压中也具有抑制作用优势,但单独用药疗效仍有可提升的空间[24,25]。胸腺五肽中的人工合成的五肽活性片段是胸腺生成素的有效成分,可较好的模拟胸腺生成素的生理作用,主要药理作用是促 T 淋巴细胞亚群发育、成熟、活化,令 $CD4^+/CD8^+$ 正常,发挥细胞免疫保护作用[26,27]。研究表明胸腺五肽不仅明显调节 COPD 患者免疫紊乱状态,且对肺功能的改善具有促进作用[28,29]。

本研究结果显示联合胸腺五肽的患者血清 PAF-AH、esRAGE、CA125 的改善程度明显更具有优势,分析是由于胸腺五肽作为免疫调节剂,不仅对人体巨噬细胞吞噬功能具有增强作用,且可增加红细胞免疫功能,令自然杀伤细胞活性增加,刺激外周血单核细胞干扰素的生产,发挥抗炎效应。Zhu YG 等[30]报道也显示胸腺五肽可有效增加血清中超氧化物歧化酶活性,提高机体抗氧化应激能力和抗炎能力,缓解机体炎症反应。本研究中,胸腺五肽联合辛伐他汀时发挥相互协调作用,共同缓解气道炎症反应,降低间皮细胞活性,且患者的免疫功能、肺功能、血气分析指标等改善情况也明显优于单独使用辛伐他汀的患者,显示出在有效调节免疫功能、缓解气道炎症反应后,可进一步降低血管阻力,改善肺动脉高压状态,促进肺功能的恢复。

综上所述,胸腺五肽联合辛伐他汀治疗 COPD 合并肺动脉高压患者效果显著优于单用辛伐他汀治疗,可更有效改善患者肺功能和肺动脉高压状态,其内在机制可能和调节血清 PAF-AH、esRAGE、CA125 水平及缓解气道炎症反应相关。

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