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慢性阻塞性肺疾病患者血清NE、α1-AT、CRP、PCT的表达及与肺功能的关系研究

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摘要 目的: 探讨慢性阻塞性肺疾病(COPD)患者血清中性粒细胞弹性蛋白酶(NE)、α1-抗胰蛋白酶(α1-AT)、C-反应蛋白(CRP)、降钙素原(PCT)的表达水平及其与肺功能的相关性。**方法:** 选取2013年3月-2015年6月河北北方学院附属第一医院呼吸内科收治的COPD患者87例作为研究对象,其中急性加重期(急性组)患者49例,稳定期(稳定组)患者38例,另选取同时期在本院进行健康体检的志愿者30例为对照组,检测并对比急性组、稳定组和对照组受试者的血清NE、α1-AT、CRP、PCT水平及肺功能指标,并分析COPD患者NE、α1-AT、CRP、PCT水平与肺功能的相关性。**结果:** 与对照组对比,急性组与稳定组患者的NE、CRP、PCT水平均明显升高,α1-AT水平明显降低(P<0.05),且急性组患者的NE、CRP、PCT水平高于稳定组,α1-AT水平低于稳定组(P<0.05);急性组与稳定组患者的第1秒用力呼气容积占预计值的百分比(FEV1%)、第1秒用力呼气容积/用力肺活量(FEV1/FVC)均低于对照组,且急性组FEV1%、FEV1/FVC低于稳定组(P<0.05);经Spearman相关性分析显示,NE、CRP、PCT与FEV1%及FEV1/FVC均呈负相关,α1-AT与FEV1%及FEV1/FVC呈正相关(P<0.05)。**结论:** COPD患者血清NE、CRP、PCT表达水平均明显升高,α1-AT表达水平明显降低,且NE、α1-AT、CRP、PCT均与肺功能存在一定相关性,加强对此类指标的监测有助于对COPD患者病情判断及治疗指导。

关键词: 慢性阻塞性肺疾病;中性粒细胞弹性蛋白酶;α1-抗胰蛋白酶;C-反应蛋白;降钙素原;肺功能

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Chronic Obstructive Pulmonary Disease: Expression of Serum Protease, Antiprotease, C-reactive Protein and Procalcitonin and Their Relationship with Pulmonary Function

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ABSTRACT Objective: To investigate the expression of neutral granulocyte elastase (NE), α1- antitrypsin (α1-AT), C-reactive protein (CRP) and procalcitonin (PCT) in patients with chronic obstructive pulmonary disease (COPD) and its correlation with pulmonary function. **Methods:** A total of 87 COPD patients, who were treated in First Affiliated Hospital of Hebei North University from March 2013 to June 2015, were chosen as subjects, among them, 49 cases were acute exacerbation (acute group), 38 cases were stable phase (stable group); another 30 volunteers, who underwent physical examination during the same period, were chosen as control group. The serum levels of NE, α1-AT, CRP, PCT and pulmonary function in the acute group, stable group and control group were detected and compared, the correlation of NE, α1-AT, CRP and PCT levels with pulmonary function in COPD patients was analyzed. **Results:** Compared with the control group, the levels of NE, CRP and PCT in the acute group and the stable group were significantly increased, and the level of α1-AT was significantly lower (P<0.05); the levels of NE, CRP and PCT in the acute group were higher than those in the stable group, and the level of α1-AT was lower than that in the stable group (P<0.05). Percentage of forced expiratory volume at first second to predicted value (FEV1%) and forced expiratory volume at first second to forced vital capacity (FEV1/FVC) in the acute and the stable group were lower than those in the control group, FEV1%, FEV1/FVC in the acute group was lower than that in the stable group (P<0.05). Spearman correlation analysis showed that NE, CRP and PCT were negatively correlated with FEV1% and FEV1/FVC, and α1-AT was positively correlated with FEV1% and FEV1/FVC (P<0.05). **Conclusion:** The levels of serum NE, CRP and PCT in the patients with

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COPD are significantly increased, the expression level of α1-AT is obviously decreased, and NE, α1-AT, CRP and PCT are related to pulmonary function. To strengthen the monitoring of such indicators is helpful for the diagnosis and treatment of COPD patients.

Key words: Chronic obstructive pulmonary disease; Neutral granulocyte elastase;α1-antitrypsin; C-reactive protein; Procalcitonin; Pulmonary function

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前言

慢性阻塞性肺疾病(Chronic obstructive pulmonary disease, COPD)是临床常见的呼吸系统疾病,具有较高的发病率及病死率[1,2]。COPD 患者在急性发作期后,部分临床症状可出现一定的缓解,但是其肺功能仍呈现为进行性恶化,并且容易反复发作,严重影响了患者的生活质量[3-5]。目前临床上对于 COPD 的发病机制尚未明确,有研究提出蛋白酶 - 抗蛋白酶系统失衡是引发 COPD 的重要因素,其中较为重要的是 α1- 抗胰蛋白酶(α1- antitrypsin, α1-AT)与中性粒细胞弹性蛋白酶(Neutrophil elastase, NE)的失衡[6-8]。另有研究表明[9-11],COPD 的本质是肺实质、气道和肺血管的慢性炎症反应,炎症反应所释放的炎症介质使中性粒细胞的炎症反应加剧以及肺结构破坏,进而引发气流受限。降钙素原(Procalcitonin, PCT)、C 反应蛋白(C reactive protein, CRP)作为机体重要的炎性标志物,均参与了 COPD 患者急性加重期的炎症反应[12-14]。本研究对 COPD 患者血清 NE、α1-AT、CRP、PCT 表达水平及其与肺功能的相关性进行探讨,旨在对 COPD 患者病情判断及治疗指导提供方向,结果如下。

1 资料与方法

1.1 一般资料

选取 2013 年 3 月 -2015 年 6 月河北北方学院附属第一医院呼吸内科收治的 COPD 患者 87 例为研究对象。纳入标准:(1)所有入选患者均符合中华医学会呼吸病学分会慢性阻塞性肺疾病学组《慢性阻塞性肺疾病诊治指南》中的诊断标准[15];(2)患者对本研究知情同意并签署知情同意书。排除标准:(1)伴有急性或慢性感染的患者;(2)伴有其他慢性肺部疾病的患者;(3)伴有肝肾功能不全的患者;(4)伴有恶性肿瘤的患者;(5)生命体征不稳定的患者。87 例 COPD 患者中急性加重期(急性组)患者 49 例,稳定期(稳定组)患者 38 例。急性组患者中男 30 例,女 19 例,年龄 45-78 岁,平均年龄(62.31± 5.93)岁;稳定组患者中男 21 例,女 17 例,年龄 43-77 岁,平均年龄(61.42± 5.46)岁。另选取同时期在本院进行健康体检的志愿者 30 例为对照组,其中男 18 例,女 12 例,年龄 45-79 岁,平均年龄(63.94± 5.68)岁。三组的临床资料对比无显著差异(P>0.05)。本研究通过医院伦理委员会批准。

1.2 方法

抽取所有受试者的空腹静脉血 5 mL,应用离心机以 2000 r/min 的转速离心 20 min,离心半径为 10 cm,抽取上清液,置于 -70℃温度下保存,其中 NE 与 α1-AT 水平采用酶联免疫吸附法进行检测,CRP 水平采用免疫比浊法进行检测,PCT 水平采用免疫荧光双抗体夹心法进行检测,所有操作均严格按照试剂盒说明进行,试剂盒均由石家庄麦迪克试剂公司提供。肺功能指标采用肺功能仪(德国耶格公司生产,型号:HI-101Master Screen)进行检测,检测指标包括用力肺活量(Forced vital capacity, FVC)、第 1 秒用力呼气容积(Forced expiratory volume in one second, FEV1),并计算第 1 秒用力呼气容积 / 用力肺活量(FEV1/FVC)、第 1 秒用力呼气容积占预计值的百分比(FEV1%)。

1.3 观察指标

检测并对比 COPD 急性组、稳定组和对照组的血清 NE、α1-AT、CRP、PCT 水平及肺功能指标,并分析 COPD 患者血清 NE、α1-AT、CRP、PCT 水平与肺功能的相关性。

1.4 统计学方法

采用 SPSS19.0 统计学软件对数据进行统计学处理,计量资料均以($\bar{x}$± s)的形式表示,组间对比经 t 检验分析,多组间对比经方差分析,计数资料以(%)的形式表示,经 x^2 检验分析,NE、α1-AT、CRP、PCT 水平与肺功能的相关性采用 Spearman 相关性分析,以 P<0.05 为差异有统计学意义。

2 结果

2.1 三组受试者血清 NE、α1-AT、CRP、PCT 水平对比

与对照组对比,COPD 急性组与稳定组患者的 NE、CRP、PCT 水平均明显升高,α1-AT 水平明显降低(P<0.05),且急性组患者的 NE、CRP、PCT 水平高于稳定组,α1-AT 水平低于稳定组(P<0.05)。见表 1。

表 1 三组受试者血清 NE、α1-AT、CRP、PCT 水平对比($\bar{x}$± s)

Table 1 Comparison of serum NE, α1-AT, CRP and PCT levels among three groups($\bar{x}$± s)

Groups	n	NE(μg/L)	α1-AT(mg/L)	CRP(mg/L)	PCT(ng/mL)
Acute group	49	100.93± 20.72*#	8687.74± 2156.73*#	33.49± 4.27*#	5.19± 1.32*#
Stable group	38	78.65± 12.57*	12443.69± 4512.67*	17.29± 2.43*	1.63± 0.45*
Control group	30	58.81± 10.16	19733.57± 5142.38	6.02± 1.37	0.57± 0.14
F	-	9.156	12.187	10.174	7.312
P	-	0.036	0.012	0.021	0.039

Note: compared with control group, *P<0.05; compared with stable group, #P<0.05.

2.2 三组受试者肺功能指标对比

COPD 急性组与稳定组患者的 FEV1%、FEV1/FVC 均低于对照组，且 COPD 急性组 FEV1%、FEV1/FVC 低于稳定组（P<0.05）。见表 2。

表 2 三组受试者肺功能指标对比（$\bar{x}\pm s$）

Table 2 Comparison of pulmonary function indexes among three groups ($\bar{x}\pm s$)

Groups	n	FEV1%	FEV1/FVC(%)
Acute group	49	48.09± 10.12*#	51.38± 7.14*#
Stable group	38	65.67± 12.57*	65.17± 8.54*
Control group	30	97.28± 9.73	89.64± 12.73
F	-	10.539	13.827
P	-	0.018	0.006

Note: compared with control group, *P<0.05; compared with stable group, #P<0.05.

2.3 COPD 患者血清 NE、α1-AT、CRP、PCT 水平与肺功能的相关性分析

经 Spearman 相关性分析显示，COPD 患者血清 NE、CRP、PCT 水平与 FEV1%及 FEV1/FVC 均呈负相关，α1-AT 水平与 FEV1%及 FEV1/FVC 呈正相关（P<0.05），见表 3。

表 3 COPD 患者血清 NE、α1-AT、CRP、PCT 水平与肺功能的相关性分析

Table 3 Correlation analysis of serum NE, α1-AT, CRP, PCT levels and pulmonary function in patients with COPD

Indexes	FEV1%		FEV1/FVC	
	r	P	r	P
NE	-0.714	0.014	-0.638	0.026
α1-AT	0.512	0.003	0.631	0.005
CRP	-0.476	0.032	-0.571	0.028
PCT	-0.331	0.039	-0.375	0.035

3 讨论

COPD 是以气流受限为特征的肺气肿或慢性支气管炎，慢性炎症的修复与损伤在 COPD 的发生与发展中发挥着重要的作用[16,17]。NE 在炎症反应过程中具有双重作用，一方面可影响中性粒细胞的迁移、黏附以及降解多种前炎症细胞因子，对炎症反应的发生具有一定程度的抑制作用；另一方面可促进上皮细胞对多种促炎细胞因子的释放，加剧炎症反应强度[18,19]。α1-AT 是由肝细胞产生的抗蛋白酶，对 NE 具有较强的抑制作用，其作用主要是对蛋白酶的活性进行抑制，进而避免肺部组织受到蛋白溶酶的损坏[20]。本研究结果显示，COPD 患者的 NE 水平高于对照组，且 COPD 急性组 NE 水平高于稳定组，对照组与 COPD 稳定组 α1-AT 的水平高于 COPD 急性组，提示在 COPD 急性加重期 NE 呈现为较高的表达水平，而 α1-AT 表达水平较低，分析其原因主要是因为 COPD 患者在急性加重期炎症反应加剧，受到炎症因子的作用，导致中性粒细胞大量释放 NE，进而 NE 水平急剧上升，COPD 稳定期患者部分 NE 被抗蛋白酶拮抗，其水平低于急性加重期，但仍高于正常人群。在 COPD 急性加重期 α1-AT 水平降低，导致蛋白酶 - 抗蛋白酶系统失衡，下呼吸道 NE 水平相对增多，使得肺组织不断受到损坏，进而引发肺气肿等临床症状[21,22]。CRP 是机体受到组织损伤或炎症反应刺激所产生的急性时相反应蛋白，其表达水平不受免疫抑制剂、激素等药物的影响，是反映机体炎症反应的敏感指标之一[23-25]。PCT 是降钙素前体，在预测与评估严重炎症性疾病中具有重要作用 [26,27]。本研究结果显示，CRP 与 PCT 在 COPD 急性组中的表达水平明显高于稳定组与对照组，且在稳定组中的表达水平明显高于对照组，说明 CRP 与 PCT 在 COPD 患者中的表达水平高于正常人群，且在急性加重期其水平出现异常升高。分析其原因主要是因为 COPD 患者在急性加重期炎症反应及肺组织损伤加剧，进而导致血清中 CRP 及 PCT 的水平异常升高。

肺功能检查是评估气流受限较好的客观指标，对诊断与评估 COPD 严重程度、病情进展、治疗及预后均具有重要的意义[28-30]。本研究结果显示，COPD 急性组与稳定组患者的 FEV1%、FEV1/FVC 均低于对照组，且 COPD 急性组 FEV1%、FEV1/FVC 低于稳定组，说明 COPD 患者的肺功能在急性加重期急剧下降，进而使患者的病情加重，分析其原因为 COPD 患者在急性加重期气道受限程度较稳定期及正常人群更严重，使得机体缺氧、肺泡通气不足、CO_2 潴留越严重，致使患者病情加重，肺功能降低。在 COPD 患者血清 NE、α1-AT、CRP、PCT 水平与肺功能的相关性分析中显示，NE、CRP、PCT 水平与 FEV1%及 FEV1/FVC 均呈负相关，α1-AT 与 FEV1%及 FEV1/FVC 呈正相关，说明 NE、CRP、PCT 在 COPD 在急性发病过程中发挥着重要作用，NE、CRP、PCT 水平的升高可严重损坏机体肺功能，α1-AT 则对肺组织具有保护作用。

综上所述，COPD 患者血清中 NE、CRP、PCT 表达水平均明显升高，α1-AT 表达水平明显降低，且与肺功能也存在一定相关性，临床上可根据此类指标的水平变化以判断 COPD 患者病情，同时对治疗也可以提供依据。

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