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慢阻肺患者运动负荷气道反应性与 T 细胞亚群的关系 *

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摘要 目的:探讨与分析慢性阻塞性肺疾病(COPD)患者运动负荷气道反应性与 T 细胞亚群的关系。**方法:**2020 年 1 月到 2022 年 4 月选择在本院诊治的慢阻肺患者 88 例作为慢阻肺组,同期选择在本院进行健康体检者 88 例作为健康组,检测两组 T 细胞亚群含量,判定两组的运动负荷气道反应性情况并进行相关性分析。**结果:**慢阻肺组的 CD8⁺T 淋巴细胞比例明显高于健康组,CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞比例明显低于健康组($P<0.05$)。慢阻肺组的运动负荷气道反应性发生率为 20.9%,明显高于健康组的 1.2%($P<0.05$)。在慢阻肺中,Spearsman 分析显示运动负荷气道反应性发生率与 CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞、CD8⁺T 淋巴细胞比例存在相关性($P<0.05$)。logistic 回归分析显示 CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞、CD8⁺T 淋巴细胞比例都为影响运动负荷气道反应性发生的重要危险因素($P<0.05$)。**结论:**慢阻肺患者多伴随有 T 细胞亚群异常,也多伴随有运动负荷气道反应性,运动负荷气道反应性与 T 细胞亚群存在相关性,也表明 T 细胞亚群紊乱是导致运动负荷气道反应性发生的重要因素。

关键词:COPD; T 细胞亚群异常; 运动负荷气道反应性; 相关性; 影响因素

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The Relationship between Exercise Load Airway Responsiveness and T Cell Subsets in Patients with Chronic Obstructive Pulmonary Disease*

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ABSTRACT Objective: To explore and analysis the relationship between exercise load airway reactivity and T cell subsets in patients with COPD. **Methods:** From January 2020 to April 2022, 88 cases of patients with COPD who were diagnosed and treated in our hospital were selected as the COPD group, and 88 cases of healthy subjects who underwent physical examination in our hospital during the same period were selected as the healthy group. The contents of T cell subsets in the two groups were detected, and the airway reactivity to exercise load was determined and the correlation analysis was carried out. **Results:** The proportion of CD8⁺T lymphocytes in the COPD group were significantly higher than that in the healthy group, and the proportions of CD3⁺T lymphocytes and CD4⁺T lymphocytes were lower than those in the healthy group ($P<0.05$). The incidence rates of exercise-stress airway reactivity in the COPD group were 20.9%, which were higher than that in the healthy group (1.2%) ($P<0.05$). In the COPD patients, Spearsman analysis showed that the incidence of airway reactivity to exercise stress were correlated with the proportions of CD3⁺T lymphocytes, CD4⁺T lymphocytes, and CD8⁺T lymphocytes ($P<0.05$). Logistic regression analysis showed that the proportions of CD3⁺T lymphocytes, CD4⁺T lymphocytes, and CD8⁺T lymphocytes were important risk factors for the occurrence of airway reactivity during exercise stress ($P<0.05$). **Conclusion:** COPD patients are often accompanied by abnormal T cell subsets, as well as exercise load airway reactivity. There are correlation between exercise load airway reactivity and T cell subsets. Disturbance of T cell subsets are the important factors leading to the occurrence of exercise-stress airway reactivity.

Key words: COPD; Abnormal T cell subsets; Exercise stress airway reactivity; Correlation; Influencing factors

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前言

慢性阻塞性肺疾病(Chronic obstructive pulmonary disease, COPD)是一种呼吸系统疾病,具有气流受限不完全可逆、持续

呼吸道等症状^[1]。由于各种因素的影响,当前慢阻肺的发病人数显著增加,具有死亡率高、致残率高、病程长等特点,给社会和经济带来沉重负担,也已经成为一种公共卫生性问题^[2]。且患者年龄均较大,大多为老年人,因基础疾病等降低机体免疫功能,

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进而引发该疾病。其中免疫状态低下主要表现为 T 细胞亚群比例发生失调^[3,4]。部分报道显示 T 细胞亚群的调节功能紊乱可能与慢阻肺发病有关^[5]。特别是在患者气道、肺实质及外周血中存在大量 CD8⁺T 淋巴细胞,并且其增多程度与机体肺功能存在相关性^[6]。且随着炎症细胞数量的大幅度上升,将会对肺组织的结构进行破坏,并促进炎症反应,促使炎症细胞释放更多炎性介质,局部仍浸润有 T 细胞亚群紊乱等^[7]。鉴于此,此次研究探讨了慢阻肺患者运动负荷气道反应性与 T 细胞亚群的关系,旨在为今后临床慢阻肺患者的治疗提供有效的依据。现报道如下。

1 资料与方法

表 1 一般资料对比

Table 1 The comparison of the general data

Groups	n	Gender (male / female)	Age (year)	Body mass index (kg/m ²)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Fasting blood glucose (mmol/L)	Heart rate (secondary / min)
COPD group	86	46/40	56.38±3.29	23.21±1.84	123.33±8.48	78.33±4.20	5.53±0.12	85.39±3.32
Health group	86	45/41	56.64±2.23	23.76±2.09	123.32±8.11	78.54±5.00	5.55±0.17	85.87±4.14

1.2 T 细胞亚群检测

抽取所有人群的空腹采集静脉血 4 mL 左右于 EDTA 抗凝试管中,室温保存,24 h 内进行处理。测定设备包括 FAC-SCalibur 流式细胞仪、CD3/CD16+56/CD45/CD19 四色荧光抗体、CD3/CD8/CD45/CD4 抗体等,采用流式细胞仪测定 CD3⁺T、CD4⁺T、CD8⁺T 比例。

1.3 运动负荷气道反应性测定

所有患者都给予支气管激发试验,计算运动负荷气道反应发生率。保证所有人群休息 15 min 左右,使用乙酰甲胆碱作为诱发剂。采用肺功能检查仪检测患者的肺功能,当 FEV₁ % pred ≥ 70.0 % 时依次吸入生理盐水和不同浓度的乙酰甲胆碱,使用潮式呼吸,测试吸气阻力 2 min,当比气道传导率下降到原先的 35.0 % 时停止实验,吸入适量的支气管舒张剂,测定肺功能直到恢复测定之前的水平,比气道传导率下降 35.0 % 需要乙

1.1 研究对象

2020 年 1 月到 2022 年 4 月选择在本院诊治的慢阻肺患者 88 例作为慢阻肺组,同期选择在本院进行健康体检者 88 例作为健康组。本院伦理委员会批准了此次研究。

纳入标准:慢阻肺组符合慢阻肺的诊断标准;健康组体检前 3 个月未患呼吸系统疾病,体检前 1 个月未使用支气管舒张剂;所有人群知情同意本研究;年龄 30-80 岁。

排除标准:合并其他严重肺部疾病;合并有高危传染性疾病者;需要有创呼吸机辅助通气者;长期口服激素及免疫抑制剂者;妊娠期与备孕期、哺乳期妇女。

两组人群一般资料对比无差异 ($P>0.05$)。见表 1。

酰甲胆碱积累量 <8 mg/mL 判定为支气管激发实验阳性,也就是运动负荷气道高反应性。

1.4 统计学方法

研究采用 SPSS22.0 统计软件和 GraphPad Prism version7.01 进行整理和分析,计量资料采用 ($\bar{x} \pm s$) 表示,计数数据采用 n% 表示,使用 t 检验与卡方 χ^2 检验分析,所有 P 值均为双尾,相关性分析采用 Spearmen 分析,采用 Logistic 回归分析影响因素,当 $P<0.05$ 时,则表示数据差异具有统计学意义。

2 结果

2.1 T 细胞亚群比例对比

慢阻肺组的 CD8⁺T 淋巴细胞比例明显高于健康组,CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞比例明显低于健康组 ($P<0.05$)。见表 2。

表 2 T 细胞亚群比例对比(% , $\bar{x} \pm s$)

Table 2 Comparison of T cell subsets (% , mean $\pm$ standard deviation)

Groups	n	CD3 ⁺ T lymphocytes	CD4 ⁺ T lymphocytes	CD8 ⁺ T lymphocytes
COPD group	86	65.33±2.18	34.57±2.82	31.49±2.58
Health group	86	75.33±3.19	51.40±3.19	24.55±3.11

Note: compared with the health group, [#] $P<0.05$, the same below.

2.2 运动负荷气道反应性发生率对比

慢阻肺组的运动负荷气道反应性发生率为 20.9 %,明显高

于健康组的 1.2 % ($P<0.05$)。见表 3。

表 3 运动负荷气道反应性发生率对比(n)

Table 3 Comparison of the incidence of airway reactivity between the two exercise load groups (n)

Groups	n	Exercise load of airway reactivity	The incidence rate of airway reactivity with exercise load
COPD group	86	18	20.9 % [#]
Health group	86	1	1.2 %

2.3 相关性分析

在慢阻肺中,Spearsman 分析显示运动负荷气道反应性发

生率与 CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞、CD8⁺T 淋巴细胞比例存在相关性($P<0.05$)。见表 4。

表 4 慢阻肺患者运动负荷气道反应性与 T 细胞亚群的关系(n=86)

Table 4 Relationship between exercise loading airway reactivity and T cell subsets in COPD patients (n=86)

Indexs	CD3 ⁺ T lymphocytes	CD4 ⁺ T lymphocytes	CD8 ⁺ T lymphocytes
r	0.674	0.699	0.733
P	0.000	0.000	0.000

2.4 影响因素分析

在慢阻肺中,logistic 回归分析显示 CD3⁺T 淋巴细胞、

CD4⁺T 淋巴细胞、CD8⁺T 淋巴细胞比例都为影响运动负荷气道反应性发生的重要危险因素($P<0.05$)。见表 5。

表 5 影响慢阻肺患者运动负荷气道反应性的多因素分析(n=86)

Table 5 Multivariate analysis of the airway reactivity of exercise load in COPD patients (n=86)

Indexs	β	SE	Wald	P	OR	95%CI
CD3 ⁺ T lymphocytes	-2.492	1.224	4.298	0.008	0.098	0.012-0.824
CD4 ⁺ T lymphocytes	-3.313	1.302	6.194	0.013	0.037	0.004-0.495
CD8 ⁺ T lymphocytes	5.024	1.872	7.198	0.004	7.872	2.488-11.388

3 讨论

慢阻肺已成为一种公共卫生性疾病,但具体发病机制仍未完全阐明。当前大多认为慢阻肺的发病与肺部自主神经功能失调、氧化应激等有关,且其重要病因是呼吸道慢性炎症反应^[8,9]。慢阻肺患者在气道炎症细胞增加的同时,细胞炎症反应将会异常增加,淋巴细胞将释放多种炎性介质,进一步损伤肺组织,并导致上皮坏死纤维组织的增生,可促进炎症反应,破坏肺内结构,从而影响患者的身心健康^[10]。

T 淋巴细胞是组成机体淋巴细胞的主要部分,细胞膜上的巨蛋白分子构成 T 淋巴细胞的表面标志^[11,12]。CD3⁺T 淋巴细胞下降表明外周血中成熟 T 淋巴细胞总数的减少^[13]。CD4⁺T 淋巴细胞经增生扩散进而激活其它类型的免疫细胞,从而导致机体产生免疫反应。CD4⁺T 淋巴细胞参与其它淋巴细胞发挥作用,在整个免疫反应中具有重要作用,可增强体液免疫和细胞免疫^[14,15]。CD8⁺T 淋巴细胞为一种细胞毒 T 淋巴细胞,可以对产生特殊抗原反应的目标细胞进行杀灭,起消灭受感染细胞的作用^[16]。本研究显示慢阻肺组的 CD8⁺T 淋巴细胞比例明显高于健康组,CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞比例明显低于健康组($P<0.05$),表明慢阻肺患者多伴有 T 细胞亚群异常。分析可知,一定比例的 T 细胞亚群可对机体正常免疫功能状态进行维持。机体免疫功能失衡的重要标志便是 CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞比例下降,且其下降程度与疾病严重程度、预后不良相关。CD4⁺T 是 Th 细胞,能促使 B 细胞产生抗体。而 CD4⁺T/CD8⁺T 是评价人体免疫功能的重要指标,其水平下降会相应提示机体免疫功能低下,且免疫功能与疾病严重程度呈负相关^[17,18]。特别是慢阻肺患者容易反复发病,导致营养摄入不足而消耗增加,T 淋巴细胞亚群异常,还会引发免疫功能紊乱,影响 B 淋巴细胞增殖分化抗体功能,导致免疫功能受损,从而改变 T 淋巴细胞的数量及功能,使得 CD8⁺T 淋巴细胞比例上升^[19,20]。

运动负荷气道反应性可对慢阻肺患者气流受限严重程度进行反映,运动负荷气道反应性状况与机体的细胞免疫功能存在相关性^[21]。本研究显示慢阻肺组的运动负荷气道反应性发生率为 20.9%,明显高于健康组的 1.2%($P<0.05$),表明慢阻肺患者多伴有运动负荷气道反应性。分析可知,气道高反应性往往是由于气道长期处于炎症状态,气道内平滑肌增厚,导致管壁狭窄,形成通气障碍,导致病情反复发作,构成恶性循环。慢阻肺患者体内激活的 CD8⁺T 淋巴细胞具有高度的细胞毒作用,使得肺组织破坏、弹性纤维断裂,进而使肺组织释放抗原,从而启动相应的免疫应答过程,从而影响自身的运动负荷气道反应性^[22,23]。慢阻肺患者外周血中 CD4⁺T 淋巴细胞数量会明显下降,可减弱免疫调节、免疫抑制作用,加重气道重塑、薄壁组织的破坏^[24,25]。

慢阻肺在临床上较为常见,可由个体、环境等多种病因引起。且发现 T 淋巴细胞在肺组织的局部浸润与慢阻肺发生、发展具有极大的关联性。主要在于慢阻肺患者的细胞免疫功能严重受损,减少胸腺肽分泌,进而造成 T 淋巴细胞数量、质量的下降,导致免疫功能下降。此外,因慢阻肺患者大多具有慢性吸烟史或环境危险因素接触史,造成细胞免疫功能的损伤,在此基础上反复病原菌的感染将进一步导致急性加重,最终抑制免疫系统,损伤细胞免疫。并且很多患者由于慢性缺氧,导致机体处于应激状态,可参与调节 T 淋巴细胞特异性膜受体,致使 CD4⁺T 淋巴细胞凋亡,对 T 淋巴细胞活化、分泌细胞抑制作用,从而诱发急性加重,诱发形成运动负荷气道反应性^[26,27]。本研究 Spearsman 分析显示慢阻肺患者的运动负荷气道反应性发生率与 CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞、CD8⁺T 淋巴细胞比例存在相关性($P<0.05$);logistic 回归分析显示 CD3⁺T 淋巴细胞、CD4⁺T 淋巴细胞、CD8⁺T 淋巴细胞比例都为影响运动负荷气道反应性发生的重要危险因素($P<0.05$),表明慢阻肺患者运动负荷气道反应性与 T 细胞亚群存在相关性,也表明 T 细胞亚群紊乱是导致运动负荷气道反应性发生的重要因素。慢阻肺患者

存在异常增加的细胞炎症反应,在气道炎症细胞增加的同时,激活的淋巴细胞将释放多种炎性介质,将破坏肺结构并促进炎症反应,致使肺组织损伤及上皮坏死纤维组织增生。在慢阻肺患者的气道、肺实质及外周血中主要是增多的CD8⁺T淋巴细胞,慢阻肺急性加重患者CD4⁺T淋巴细胞凋亡增加,导致CD4⁺T/CD8⁺T比值倒置,是造成CD4⁺T/CD8⁺T比例失衡的重要原因,从而使患者细胞免疫功能下降。慢阻肺患者细胞免疫处于被抑制状态,可需要抗菌药物治疗,而抗菌药物对细胞的免疫功能具有抑制作用,可使得炎症细胞因子过度分泌,同时大量增加支气管粘膜腺体的分泌,进而形成恶性循环,最终造成病情恶化^[28-30]。本研究存在一定不足,未对慢阻肺患者进行病情分组,未对患者的预后进行分析,观察患者数量比较少,将在后续研究中探讨。

总之,慢阻肺患者多伴随有T细胞亚群异常,也多伴随有运动负荷气道反应性,运动负荷气道反应性与T细胞亚群存在相关性,也表明T细胞亚群紊乱是导致运动负荷气道反应性发生的重要因素。

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