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慢性阻塞性肺疾病急性加重期患者肠道微生态环境与肺功能、血气分析的相关性

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[摘　要]　**目的：**探讨慢性阻塞性肺疾病急性加重期(acute exacerbation of chronic obstructive pulmonary disease，AECOPD)患者肠道微生态环境与肺功能、血气指标的关联性。**方法：**选取2019年1月1日至2020年12月31日于江苏大学附属宜兴医院呼吸与危重症医学科门诊及病房收治的AECOPD患者96例为研究组，另选取同期健康体检者96例为对照组。所有受检者入院后均测定肺功能，并抽取粪便样本测定肠道微生态环境相关指标、抽取血液样本测定动脉血气指标水平。统计两组肠道微生态环境相关指标水平、肺功能及血气指标水平，并统计分析肠道微生态环境相关指标与肺功能、血气指标的关联性。**结果：**研究组大肠埃希菌水平与对照组相比，差异无统计学意义(P>0.05)，研究组双歧杆菌、乳酸杆菌水平低于对照组，粪肠球菌、屎肠球菌水平高于对照组(P<0.05)。研究组第1秒用力呼气末容积(1 s forced end-expiratory volume，FEV_1)、FEV_1占预计值百分比(FEV_1 as a percentage of projected，FEV_1%pred)、FEV_1/FVC、PaO_2水平低于对照组，$PaCO_2$水平高于对照组(P<0.05)。经Pearson检验可知，双歧杆菌、乳酸杆菌水平与FEV_1、FEV_1%pred、FEV_1/FVC、PaO_2水平呈正相关、与$PaCO_2$水平呈负相关，粪肠球菌、屎肠球菌水平与FEV_1、FEV_1%pred、FEV_1/FVC、PaO_2水平呈负相关、与$PaCO_2$水平呈正相关(均P<0.05)。**结论：**AECOPD患者存在肠道微生态环境紊乱，且肠道微生态环境紊乱程度和肺功能、血气状态存在密切关联性。

[关键词]　慢性阻塞性肺疾病急性加重期；肠道微生态环境；肺功能；血气指标；关联性

Correlation of intestinal microecological environment and lung function with blood gas analysis in patients with acute exacerbation of chronic obstructive pulmonary disease

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Abstract　**Objective:** To investigate the relationship of intestinal microecological environment and lung function with blood gas index in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

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Methods: From January 1, 2019 to December 31, 2020, 96 patients with AECOPD in the outpatient and ward of the Department of Respiratory and Critical Medicine of Yixing Hospital Affiliated to Jiangsu University were selected as a study group, and 96 healthy physical examiners in the same period were selected as a control group. Pulmonary function was measured in all subjects after the admission, stool samples were taken to measure intestinal microecological environment-related indicators, and blood samples were drawn to measure arterial blood gas index levels. The levels of intestinal microecological environment-related indexes, lung function and blood gas indexes in the 2 groups were statistically analyzed, and the correlation of intestinal microecological environment-related indexes with lung function and blood gas indexes was statistically analyzed. **Results:** There was no significant difference in Escherichia coli level between the study group and the control group (P>0.05); the levels of *Bifidobacterium* and *Lactobacillus* in the study group were lower than those in the control group, and the levels of *Enterococcus faecalis* and *Enterococcus faecium* were higher than those in the control group (P<0.05). The levels of FEV_1, FEV_1%pred, FEV_1/FVC and PaO_2 in the study group were lower than those in the control group, while the $PaCO_2$ levels were higher than those in the control group (P<0.05). Pearson test showed that the levels of *Bifidobacterium* and *Lactobacillus* were positively correlated with the levels of FEV_1, FEV_1%pred, FEV_1/FVC and PaO_2, and negatively correlated with the levels of $PaCO_2$. The levels of *Enterococcus faecalis* and *Enterococcus faecium* were negatively correlated with the levels of FEV_1, FEV_1%pred, FEV_1/FVC and PaO_2, but positively correlated with the levels of $PaCO_2$ (P<0.05). **Conclusion:** AECOPD patients have intestinal microecological environment disorder, and there is a close correlation of the degree of intestinal microecological environment disorder with pulmonary function and blood gas status.

Keywords acute exacerbation of chronic obstructive pulmonary disease; intestinal microecological environment; lung function; blood gas index; correlation

慢性阻塞性肺疾病(chronic obstructive pulmonary disease，COPD)为临床多发肺部疾病，近年来，受不良生活习惯养成、人口老龄化形势加剧等诸多因素影响，疾病发病率持续增高，已成为严重威胁人们生活质量及身心健康的疾病类型[1-2]。同时，相关统计资料[3-4]显示：COPD全因病死率在美国为第4位，而在中国高居第3位，且是中国农村首要致死病因。此外，肠道微生态菌群为维持机体内环境稳定状态的重要因素，若肠道菌群发生紊乱，则会导致肠源性内毒素异常分泌、肠道菌群移位及其他炎症递质释放，进而引起慢性炎症，造成炎症因子血清表达过度，间接或直接促进COPD发病和进展[5-6]。肺功能和血气状态是体现COPD患者机体功能状态及病情的重要指标[7]。基于此，本研究拟选取江苏大学附属宜兴医院急性加重期慢性阻塞性肺疾病(acute exacerbation of chronic obstructive pulmonary disease，AECOPD)患者，通过设置对照组进行对症研究，旨在明确肠道微生态环境与肺功能、血气指标的关联性。

1 对象与方法

1.1 对象

选取2019年1月1日至2020年12月31日于江苏大学附属宜兴医院呼吸与危重症医学科门诊及病房收治的AECOPD患者96例为研究组，另选取同期健康体检者96例为对照组。纳入标准：1)研究组符合《慢性阻塞性肺疾病基层诊疗指南(实践版·2018)》[8]中AECOPD诊断标准；2)对照组肺功能检查及肺部影像学检查正常；3)年龄>45岁；4)具有良好依从性，可配合完成调查研究。排除标准：1)合并良恶性肿瘤者；2)合并其他肺部疾病者；3)合并血液系统、代谢系统病变者；4)合并肝、胆、肾疾病者；5)合并胃肠道疾病者；6)纳入研究前1个月内采取免疫抑制剂、抗菌药物等治疗者；7)存在言语沟通障碍、认知功能障碍及神经系统病变者。研究组男69例，女27例，年龄46~79(62.44±13.22)岁；体重指数(body mass index，BMI)16.5~27.7(22.08±4.14) kg/m^2；抽烟41例，饮酒69例。对照组男64例，女22例，年龄47~78(60.95±11.89)岁；

BMI 17.1~28.2 (21.97±3.88) kg/m^2；抽烟37例，饮酒70例。两组性别、年龄、BMI、抽烟及饮酒情况等基线资料均衡可比(P>0.05)。本研究经江苏大学附属宜兴医院医学伦理委员会审核批准，受检者均签署知情同意书。

1.2 方法

1.2.1 肠道微生态环境相关指标检测

所有受检者晨起时取新鲜粪便，12 h内将标本转移至−80 ℃实验室冰箱内储存，取部分标本送检，于0.5 h内进行称量、稀释及接种，分别接种于普通血平板、厌氧菌血平板、真菌等培养基内，于37 ℃培养箱中实施厌氧与需氧培养，25 ℃培养箱中培养真菌；需氧菌培养48 h，厌氧菌培养72 h，真菌培养2周，查看培养结果；取2个平板的菌群平均值乘以稀释倍数为细菌总数；通过16 SrRNA/DNA荧光定量PCR技术检测菌落数目。

1.2.2 肺功能检测

设备选取日本捷斯特肺功能仪(CHESTAC-8800)进行检测，包括第1秒用力呼气末容积(1 s forced end-expiratory volume，FEV_1)、FEV_1占预计值百分比(FEV_1 as a percentage of projected，FEV_1%pred)、FEV_1/FVC，指导受检者深吸气后快速呼气实施测量，所有指标均测量3次，以最高值为准；研究组在舒张后接受肺功能检测。

1.2.3 血气指标检测

设备选取美国MDEICA公司Easy Blood Gas全自动血气分析仪测定，包括动脉血二氧化碳分压(partial pressure of carbon dioxide，$PaCO_2$)、动脉血氧分压(partial pressure of oxygen，PaO_2)，取受检者桡动脉血实施检测。

1.3 观察指标

1)统计两组肠道微生态环境相关指标水平；2)统计分析两组肺功能及血气指标水平；3)统计分析肠道微生态环境相关指标与肺功能、血气指标的关联性。

1.4 统计学处理

采用SPSS 22.0统计学软件处理数据，计量资料采取Bartlett方差齐性检验与Kolmogorov-Smirnov正态性检验，均确认具备方差齐性且近似服从正态布，以均数±标准差($\bar{x}\pm s$)表示，组间比较行独立样本t检验，组内比较行配对t检验，计数资料用例(%)表示，当例数<40或理论频数$T\leqslant1$时采用确切概率法，当例数≥40且T>5或1<T<5时用χ^2检验，肠道微生态环境相关指标与肺功能、血气指标的关联性采用Pearson相关性分析。P<0.05为差异有统计学意义。

2 结果

2.1 两组肠道微生态环境相关指标水平比较

研究组大肠埃希菌水平与对照组相比，差异无统计学意义(P>0.05)，研究组双歧杆菌、乳酸杆菌水平低于对照组，粪肠球菌、屎肠球菌水平均高于对照组(均P<0.05，表1)。

2.2 两组肺功能及血气指标水平比较

研究组FEV_1、FEV_1%pred、FEV_1/FVC、PaO_2水平均低于对照组，$PaCO_2$水平均高于对照组(均P<0.05，表2)。

2.3 肠道微生态环境相关指标与肺功能、血气指标的关联性分析

经Pearson检验可知，双歧杆菌、乳酸杆菌水平与FEV_1、FEV_1%pred、FEV_1/FVC、PaO_2水平均呈正相关、与$PaCO_2$水平呈负相关，粪肠球菌、屎肠球菌水平与FEV_1、FEV_1%pred、FEV_1/FVC、PaO_2水平均呈负相关、与$PaCO_2$水平呈正相关(均P<0.05，表3)。

表1 两组肠道微生态环境相关指标水平比较(n=96)

Table 1 Comparison of the levels of intestinal microecological environment-related indicators between the 2 groups (n=96)

组别	大肠埃希菌/(lgCFU·g^{-1})	双歧杆菌/(lgCFU·g^{-1})	乳酸杆菌/(lgCFU·g^{-1})	粪肠球菌/(lgCFU·g^{-1})	屎肠球菌/(lgCFU·g^{-1})
研究组	6.83 ± 1.28	6.20 ± 1.04	5.59 ± 1.11	8.98 ± 2.13	8.90 ± 1.89
对照组	6.51 ± 1.61	7.31 ± 1.56	7.51 ± 2.02	5.23 ± 1.29	5.60 ± 2.21
t	1.524	5.801	8.162	14.755	11.119
P	0.129	<0.001	<0.001	<0.001	<0.001

表2 两组肺功能及血气指标水平比较(n=96)

Table 2 Comparison of pulmonary function and blood gas index levels between the 2 groups (n=96)

组别	肺功能指标			血气指标	
	FEV_1/FVC/%	FEV_1%pred/%	FEV_1/L	PaO_2/mmHg	$PaCO_2$/mmHg
研究组	51.40 ± 4.96	73.53 ± 5.25	1.69 ± 0.60	73.71 ± 6.99	49.14 ± 3.97
对照组	82.61 ± 5.09	92.13 ± 6.77	2.61 ± 0.53	98.35 ± 1.25	32.18 ± 4.50
t	43.027	21.272	11.260	33.999	27.691
P	<0.001	<0.001	<0.001	<0.001	<0.001

1 mmHg=0.133 kPa.

表3 肠道微生态环境相关指标与肺功能、血气指标的关联性分析(n=96)

Table 3 Correlation analysis between the intestinal microecological environment-related indicators with the levels of lung function and blood gas indicators (n=96)

肠道菌群类型	FEV_1		FEV_1%pred		FEV_1/FVC		PaO_2		$PaCO_2$	
	r	P	r	P	r	P	r	P	r	P
双歧杆菌	0.604	<0.001	0.561	<0.001	0.592	<0.001	0.589	<0.001	−0.496	<0.001
乳酸杆菌	0.581	<0.001	0.498	<0.001	0.559	<0.001	0.610	<0.001	−0.563	<0.001
粪肠球菌	−0.622	<0.001	−0.509	<0.001	−0.511	<0.001	−0.600	<0.001	0.592	<0.001
屎肠球菌	−0.571	<0.001	−0.608	<0.001	−0.533	<0.001	−0.589	<0.001	0.583	<0.001

3 讨论

肠道内正常菌群及其所生活的环境共同构成一同构成肠道微生态系统，在机体免疫系统的调节中具有重要作用[9]。同时，肠道细菌菌群包括3个类型，即致病性细菌、机会性细菌和共生性细菌，其中多数属共生性细菌，如肠道乳酸杆菌、双歧杆菌等，具有调节及促进免疫、保护肠黏膜与生物屏障功能[10-11]。机体肠道中某些肠道菌群在正常生理状态下可激活人体免疫系统，以此强化抗感染能力，临床多认为，正常原籍菌能参与免疫反应(如双歧杆菌、乳酸杆菌等)，细菌与其裂解产物可通过促进分泌淋巴细胞因子和激活淋巴细胞，强化免疫系统，提升抗感染能力[12-14]。王英英等[15]研究发现：若机体内肠道菌群发生紊乱、免疫功能减退，则肠道菌群结构遭受损害，菌群比例异常，双歧杆菌、乳酸杆菌及其他肠道优势菌群含量减少，而粪肠球菌、屎肠球菌、大肠埃希菌与其他条件致病菌繁殖过度，进而引发炎性反应等诸多不良事件。

气道炎症为COPD发病与进展的重要因素，多种炎症因子和细胞均参与了COPD全身炎症反应的发病和进展，中性粒细胞和肺泡巨噬细胞等炎症细胞通过释放肿瘤坏死因子-α(TNF-α)、白细胞介素-6(IL-6)、IL-8等，对气道与肺实质产生不同程度损伤，致使气道狭窄、气道结构重塑，最终引发不完全可逆性气流受限[16-17]。邓素敏等[18]的研究结果表明：COPD患者双歧杆菌、乳酸杆菌含量低于对照组，粪肠球菌与屎肠球菌含量则高于对照组，且病情严重的患者上述指标水平降低或增高幅度更加显著，对肠道菌群水平和肺功能指标水平、血清炎症因子含量相关性进行统计分析得知，双歧杆菌、乳酸杆菌含量和内毒素、降钙素原、TNF-α、IL-6、IL-8水平呈负相关、与肺功能指标呈正相关，而粪肠球菌、屎肠球菌水平则与内毒素、降钙素原、TNF-α、IL-6及IL-8水平呈正相关，与肺功能指标呈负相关，故可知COPD患者肠道菌群异常和肺功能、炎症反应存在密切关联性。张军营[19]的研究结果显示：COPD患者乳酸杆菌、双歧杆菌含量和FEV_1、FEV_1%pred、FEV_1/FVC、IL-6、超敏C反应蛋白存在显著关联性。本研究结果也显示：研究组双歧杆菌、乳酸杆菌、FEV_1、FEV_1%pred、FEV_1/FVC、PaO_2水平低于对照组，粪肠球菌、屎肠球菌、$PaCO_2$水平高于对照

组，两者具有密切关联性(P<0.05)，与上述学者研究结果一致，而研究组大肠杆菌略高于对照组，但组间差异无统计学意义的原因可能与所选研究对象的病情、自身状况等有关，其在疾病中的具体表达仍需进一步探究。

此外，随COPD病程延长及病情进展，长期肺功能减弱，可造成CO_2潴留及低氧血症，气道高反应性可进一步降低PaO_2水平，加剧CO_2潴留[20]。同时，若COPD病情加剧，则用力呼气时间延长，吸入氧难以有效进入肺泡，致使患者PaO_2水平异常降低，且肺弥散功能明显减弱，最终因缺氧程度加剧而引发呼吸衰竭，增加病死风险[21-22]。刘林林等[23]的研究还证实：COPD患者机体中β-内啡肽被激活后可结合阿片受体，进而造成呼吸抑制，下调脑干神经对CO_2的敏感性，并促使$PaCO_2$水平增高，导致高碳酸血症潴留加剧，引发呼吸衰竭，造成电解质紊乱及中毒。但当前临床尚未见关于肠道菌群和血气状态的关联性的系统性研究。本研究结果显示：研究组PaO_2水平低于对照组，$PaCO_2$水平高于对照组，双歧杆菌、乳酸杆菌水平与PaO_2水平呈正相关，与$PaCO_2$水平呈负相关；粪肠球菌、屎肠球菌水平与PaO_2水平呈负相关，与$PaCO_2$水平呈正相关(P<0.05)，故推测肠道菌群可能也会影响血气状态。分析其原因可能在于：COPD患者随气流受限程度持续加剧，缺氧加重，而缺氧可引发多个脏器功能损伤、肠道瘀血，致使肠道菌群改变，肠道菌群紊乱加剧，导致肠源性内毒素含量增加、炎症递质生成过度，进而引发慢性炎症，造成血清炎症因子表达过度，间接或直接促使COPD气道重塑及肺功能改变、血气异常，进而形成恶性循环。

综上所述，AECOPD患者存在一定程度的肠道微生态环境紊乱，且肠道微生态环境紊乱程度和肺功能、血气状态存在密切关联性，故在AECOPD患者治疗期间可注重调节肠道微生态环境，将其作为疾病治疗的新的靶点与思路，从而进一步提升疾病治疗效果，保证患者良好转归。

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